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BRIEF ARTICLE

Prognosis and feasibility of *en-bloc* vascular resection in stage Ⅱ pancreatic adenocarcinoma

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Abstract

AIM: To establish the prognosis and feasibility of *en-bloc* vascular resection of stage Ⅱ pancreatic adenocarcinoma of the head and uncinate process.

METHODS: We retrospectively analyzed 87 patients with stage Ⅱ pancreatic adenocarcinoma, who were subjected to pancreaticoduodenectomy (PD) and pylorus-preserving PD (PPPD) between 1996 and 2006 in Chang Gung Memorial Hospital, Taiwan. Twelve and 75 patients underwent PD/PPPD with and without resection of portal vein/superior mesenteric vein (PV/SMV), respectively.

RESULTS: The overall 1- and 3-year survival rates of patients undergoing PD/PPPD with and without vascular resection were 50.0% and 16.7%, and 44.4% and 12.2%, respectively. Morbidity and mortality rates in the PV/SMV resection *vs* non-resection group were 50.0% and 0.0%, and 40.0% and 2.7%, respectively. In multivariate analysis, serum bilirubin, histological differentiation and adjuvant chemotherapy were independent prognostic factors that influenced survival.

CONCLUSION: In stage Ⅱ adenocarcinoma of the pancreatic head and uncinate process, serum bilirubin, histological differentiation and adjuvant chemotherapy were independent prognostic factors, and *en-bloc* vascular resection is a feasible option in carefully selected patients.

Key words: Pancreatic neoplasms; Adenocarcinoma; Portal vein; Superior mesenteric vein; Pancreaticoduodenectomy; Chemotherapy

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INTRODUCTION

Pancreaticoduodenectomy (PD) combined with vascular resection in locally advanced pancreatic malignancies was initially associated with high morbidity and mortality rates[1]. However, with improvement in surgical techniques and postoperative care, more aggressive *en-bloc* resection of pancreatic malignancies, along with portal vein/superior mesenteric vein (PV/SMV) is being

carried out at present, without any increase in surgical complications[2]. Unexpected tumor invasion to the lateral or posterolateral wall of the confluence of the PV/SMV is a common finding during PD for pancreatic malignancies[3]. The 5-year survival rate following PD or pylorus-preserving PD (PPPD) is 10%-15%, and the reported survival for > 5 years is less[4-6]. Mortality associated with PD has decreased dramatically to 0%-5% over the past two decades, but morbidity remains as high as 35%-60%[7-11]. Few studies are available regarding stage Ⅱ pancreatic adenocarcinoma with special attention to adenocarcinoma located in the pancreatic head and uncinate process, which is more likely to invade the PV/SMV because of its close proximity to these vessels. The aim of the present study was to establish the prognostic factors and feasibility of *en-bloc* vascular resection in patients with stage Ⅱ adenocarcinoma of the pancreatic head and uncinate process following PD/PPPD.

MATERIALS AND METHODS

Patient population

From January 1996 to December 2006, 129 consecutive patients with stage Ⅰ to Ⅲ adenocarcinoma of the pancreatic head and uncinate process were subjected to surgery at Chang Gung Memorial Hospital, Taipei, Taiwan. We included only stage Ⅱ adenocarcinoma of the pancreatic head and uncinate process [87 patients; stage ⅡA (n = 14) and ⅡB (n = 73)], as there is more possibility of vascular encasement in stage Ⅱ pancreatic cancers located in the head and uncinate process. The tumors were staged according to the 6th edition of the American Joint Committee on Cancer Staging System (2002). Survival duration was calculated from the time of surgery to death or the last follow-up date (December 31, 2007), irrespective of the cause of death.

Surgical procedure

PD and PPPD were considered as standard procedures. Resection margins from the common bile duct, pancreatic neck, retropancreatic tissue, and from the PV or SMV (in PV/SMV resection) were sent routinely for frozen sectioning, and in cases with positive resection margins, wider resection was performed until a negative resection margin was achieved. Lymph nodes around the hepaticoduodenal ligament, common hepatic artery, celiac trunk, PV, SMV and retropancreatic area were routinely dissected and removed. Reconstruction was performed by pancreaticojejunostomy. In case of PV/SMV encasement, segmental resection and reconstruction by end-to-end anastomosis (n = 9) or a vascular graft (n = 3; one autologous and two ePTFE grafts) were performed. Ten patients had segmental resection of the PV and two had combined PV/SMV segmental resection, and the splenic vein was anastomosed to the main portal trunk in both cases. All the patients who underwent vascular reconstruction were treated with a single dose of heparin intraoperatively and postoperatively; heparin was not used routinely. These patients were monitored by Doppler study for vascular graft patency in the early postoperative period.

Statistical analysis

Clinical records were compared by either Fischer's exact test or Pearson's χ^2 test, as appropriate. Age was analyzed using Student's t test. Patient survival rate was calculated by the methods of Kaplan-Meier and log-rank test to determine univariate significance. Factors that were deemed of potential importance on the univariate analysis ($P < 0.05$) were included in the multivariate analysis. Cox's regression was used for the multivariate analysis of these factors. $P < 0.05$ was regarded as significant. Statistical analyses were performed with SPSS for windows, version 11.5 (SPSS, Inc., Chicago, IL, USA).

RESULTS

Patient demographics

Twelve of 87 (13.8%) patients underwent PD (n = 8) or PPPD (n = 4) with PV/SMV resection (group Ⅰ) and 75/87 (86.2%) patients underwent PD (n = 57) or PPPD (n = 18) without vascular resection (group Ⅱ). Tumor location was in the pancreatic head (n = 80), uncinate process (n = 1), and in both (n = 6).

Patient outcome

Analysis of clinicopathological features (Table 1) revealed predominantly male patients aged > 60 years old, and common symptoms were jaundice, abdominal pain and weight loss. Most common findings were jaundice and anemia. Preoperative biliary drainage was performed (in case of total bilirubin levels > 15 mg/dL) in six (50.0%) and 44 (58.7%) patients in group Ⅰ and Ⅱ, respectively. Curative resection was possible in all 12 (100.0%) patients in group Ⅰ and in only 48 (64.0%) in group Ⅱ. Adjuvant chemotherapy (5-fluorouracil, gemcitabine and cisplatin) was given to eight (66.7%) and 41 (54.7%) patients in group Ⅰ and Ⅱ, respectively. Surgical mortality rate (within 1 mo) was 0.0% and 2.7% in group Ⅰ and Ⅱ, respectively. The two deaths in group Ⅱ were due to sepsis and multiorgan failure. The overall surgical complication rate was 41.4% and the complication rate was higher in group Ⅰ (50.0% *vs* 40.0%) (Table 2).

Survival period

The median period of follow-up was 10.36 mo (range: 1.18-61.68 mo), and the last follow up date was December 31, 2007. The overall survival rate at 1 year and 3 years for stage Ⅱ adenocarcinoma of the pancreatic head and uncinate process, with PV/SMV resection, was 50.0% and 16.7%, respectively in group Ⅰ and 44.4% and 12.2% in group Ⅱ (Figure 1A). Two patients in group Ⅰ survived for > 3 years; one patient died after 4 years and the other survived for 4.5 years and is still

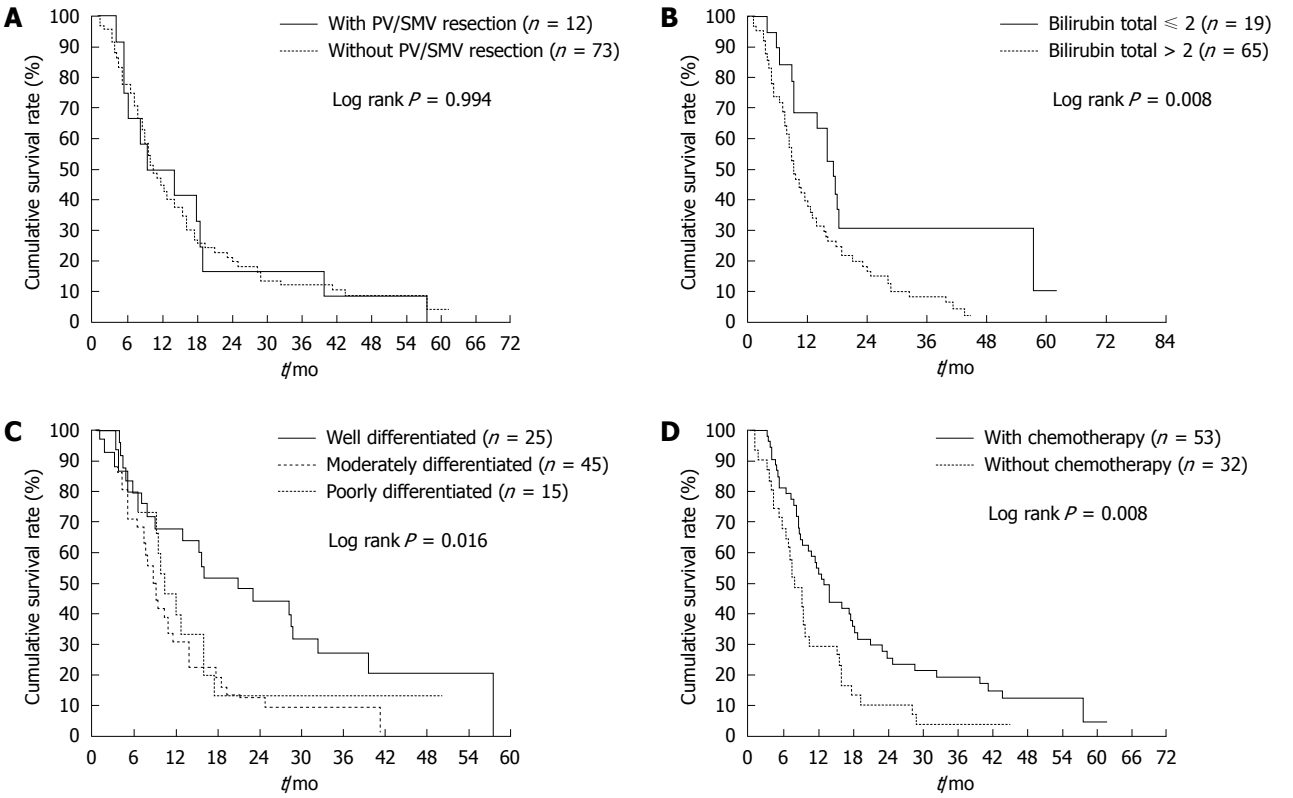

Figure 1 Overall survival in stage Ⅱ adenocarcinoma of pancreatic head and uncinate process after pancreaticoduodenectomy (PD)/pylorus-preserving PD (PPPD). A: With and without PV/SMV resection; B: With preoperative total bilirubin level ≤ or > 2 mg/dL; C: In terms of histological differentiation; D: Treated with and without adjuvant chemotherapy.

under follow-up. Univariate (Table 3) and multivariate (Table 4) analyses revealed that serum bilirubin, histological differentiation and adjuvant chemotherapy were significant prognostic factors ($P < 0.05$).

The 1- and 3-year survival rate in patients with and without elevation of serum bilirubin (> or ≤ 2 mg/dL) was 39.1% and 8.2%, and 68.4% and 30.7%, respectively (Figure 1B). In analysis of tumor factors, that is, histological differentiation, the 1-year survival rates in well, moderately well and poorly differentiated groups were 68.0%, 31.8% and 46.7%, respectively. The 3-year survival rates in these three categories were 24.0%, 8.8% and 6.7%, respectively. Better survival was found in the well-differentiated group (Figure 1C). The 1- and 3-year survival in patients treated with or without adjuvant chemotherapy was 54.7% and 18.8%, and 29.0% and 3.2%, respectively (Figure 1D).

DISCUSSION

In our study, the overall 1- and 3-year survival was comparable to that in the study by Fukuda *et al*[12], which had a survival rate of 47% and 26.8%, respectively, in group Ⅰ, and 63.4% and 28.4% in group Ⅱ patients. However, van Geenen *et al*[13] have reported 55% and 6%, respectively, Ye *et al*[14] have reported 37.7% and 5.6%, respectively, and Launois *et al*[15] have reported 42.4% and 11.9% in group Ⅰ, which is slightly less than the survival rates in our study. The 3-year survival in the studies of Aramaki *et al*[16] and Carrère *et al*[17] was 21.3% and 20.0%, and 22.0% and 25.0%, in group Ⅰ and Ⅱ, respectively. All the above studies included all stages of pancreatic cancer, irrespective of location in the pancreas. This differs from our study, in which we focused only on stage Ⅱ adenocarcinoma localized in the pancreatic head and uncinate process, where there is more probability of vascular encasement.

In our study, the mean survival time in patients undergoing curative PV/SMV resection was 16.28 mo. There was not much difference in the mortality rate in PD/PPPD with or without vascular resection, but the associated morbidity was higher in the vascular resection group. This is in contrast to earlier studies that have found that PV/SMV resection does not greatly influence morbidity and mortality in PD[12,18]. In our study, all 12 patients in group Ⅰ had negative resection margins. Previous studies have reported that the resectability rate is high in PD with vascular resection[14]. PD/PPD with *en-bloc* vascular resection potentially provides an opportunity to achieve negative resection margins, and thus might be beneficial in achieving better survival rates in carefully selected patients with pancreatic adenocarcinoma[19,20]. Hence, in patients who were subjected to palliative treatment alone, based on their preoperative evaluation that showed PV/SMV encasement, some carefully selected patients, as determined by preoperative CT [length and severity (complete *vs* partial circumference) of vascular involvement], may be suitable candidates for *en-bloc* resection

Table 1 Clinicopathological features of patients with stage Ⅱ pancreatic adenocarcinoma (mean ± SD) *n* (%)

Parameters	With vascular resection (*n* = 12)	Without vascular resection (*n* = 75)	*P* value
Age (yr)	62.9 ± 11.0	62.9 ± 9.8	0.994
Gender			0.745
Male	7 (58.3)	50 (66.7)	
Female	5 (41.7)	25 (33.3)	
Symptoms			
Jaundice	6 (50.0)	55 (73.3)	0.171
Abdominal pain	6 (50.0)	35 (46.7)	0.830
Body weight loss	6 (50.0)	31 (41.3)	0.573
Anorexia	3 (25.0)	17 (22.7)	1.000
Signs			
Anemic	4 (33.3)	38 (50.7)	0.265
Icterus	6 (50.0)	54 (72.0)	0.178
Abdominal tenderness	3 (25.0)	15 (20.0)	0.707
Albumin (g/dL)	3.9 ± 0.6	3.7 ± 0.5	0.205
Total bilirubin (mg/dL)	6.8 ± 7.0	8.9 ± 7.1	0.333
Pre-op biliary drainage			0.573
Yes	6 (50.0)	44 (58.7)	
No	6 (50.0)	31 (41.3)	
CEA (ng/mL)			1.000
≤ 5	5 (62.5)	36 (62.1)	
> 5	3 (37.5)	22 (37.9)	
CA19-9 (U/mL)			0.411
≤ 37	3 (33.3)	13 (21.0)	
> 37	6 (66.7)	49 (79.0)	
Operation time (min)	473.9 ± 185.2	461.6 ± 110.4	0.826
Blood transfusion (mL)	396 ± 588	304 ± 590	0.618
Tumor size (cm)	3.6 ± 1.6	3.3 ± 1.4	0.526
Lymph node metastases			0.097
Yes	8 (66.7)	65 (86.7)	
No	4 (33.3)	10 (13.3)	
Curability			0.015
Yes	12 (100.0)	48 (64.0)	
No	0 (0.0)	27 (36.0)	
Postoperative chemotherapy			0.436
Yes	8 (66.7)	41 (54.7)	
No	4 (33.3)	34 (45.3)	

CA19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen.

Table 2 Morbidity and mortality in patients with stage Ⅱ pancreatic adenocarcinoma *n* (%)

Parameters	With vascular resection (*n* = 12)	Without vascular resection (*n* = 75)
Morbidity	6/12 (50.0)	30/75 (40.0)
Pancreatic leakage	2 (16.7)	9 (12.0)
Pancreatic fistula	0 (0.0)	8 (10.7)
Gastrointestinal bleeding	1 (8.3)	6 (8.0)
Pleural effusion	2 (8.3)	4 (5.3)
Delayed gastric emptying	1 (8.3)	3 (4.0)
Wound infection	0 (0.0)	4 (4.0)
Intra-abdominal abscess	0 (0.0)	4 (5.3)
Bile leakage	1 (8.3)	3 (4.0)
Sepsis	0 (0.0)	3 (4.0)
Intra-abdominal bleeding	1 (8.3)	2 (2.7)
Mortality	0 (0.0)	2 (2.7)

of PV/SMV, thus achieving better survival rates. Earlier studies have suggested that encasement of PV or SMV is a function of tumor location rather than more aggressive

Table 3 Univariate analyses of predictive factors for survival of patients with stage Ⅱ adenocarcinoma of the pancreas after PD or PPPD, with or without vascular resection

Parameters	Median (mo)	95% CI of median	3-yr survival (%)	*P* value
Age (yr)				0.852
≤ 70 (*n* = 62)	11.51	7.78-15.25	12.0	
> 70 (*n* = 23)	9.40	9.15-9.65	16.3	
Sex				0.191
Male (*n* = 55)	9.76	7.61-11.91	9.6	
Female (*n* = 30)	14.01	3.20-24.82	19.4	
Albumin (g/dL)				0.107
≤ 3.5 (*n* = 21)	7.40	3.86-10.94	12.7	
> 3.5 (*n* = 47)	11.67	5.96-17.38	12.8	
Total bilirubin (mg/dL)				0.008
≤ 2 (*n* = 19)	17.39	15.23-19.55	30.7	
> 2 (*n* = 65)	9.40	7.66-11.14	3.5	
Serum CA 19-9 (U/L)				0.167
≤ 37 (*n* = 16)	16.11	1.47-30.75	25.0	
> 37 (*n* = 54)	11.51	8.17-14.85	12.3	
Serum CEA (ng/mL)				0.455
≤ 5 (*n* = 40)	16.08	10.78-21.38	13.4	
> 5 (*n* = 24)	7.82	5.18-10.46.	16.7	
Blood transfusion				0.491
Yes (*n* = 47)	10.88	7.17-14.59	14.9	
No (*n* = 38)	9.24	5.59-12.89	9.8	
Tumor size (cm)				
≤ 3 (*n* = 43)	13.97	10.77-17.18	13.3	0.508
> 3 (*n* = 41)	9.27	8.82-9.72	12.5	
Nodal metastases				0.557
Yes (*n* = 71)	9.76	7.69-11.83	13.6	
No (*n* = 14)	12.16	0.00-28.36	8.3	
Pre-op biliary drainage				0.262
Yes (*n* = 49)	9.24	7.80-10.68	12.0	
No (*n* = 36)	13.97	9.44-18.50	14.3	
PV/SMV resection				0.994
Yes (*n* = 12)	9.27	0.00-19.54	16.7	
No (*n* = 73)	10.36	7.87-12.86	12.2	
Resection margin[1]				0.071
Negative (*n* = 58)	11.51	6.46-16.56	16.1	
Positive (*n* = 27)	9.27	7.46-11.08	5.1	
Differentiation				0.016
Well (*n* = 25)	20.98	9.02-32.94	24.0	
Moderately (*n* = 45)	8.81	7.81-9.81	8.8	
Poorly (*n* = 15)	10.49	7.01-13.97	6.7	
Adjuvant chemotherapy				0.008
Yes (*n* = 53)	12.99	10.44-12.74	18.8	
No (*n* = 32)	7.96	5.74-10.19	3.2	

Two cases of mortality were not included in survival analysis. [1]Resection margin was negative in all 12 patients who underwent vascular resection.

behavior, and almost equal or even better survival rates can be achieved by *en-bloc* resection of PV/SMV[12,19]. Our study shows that *en-bloc* vascular resection in stage Ⅱ pancreatic adenocarcinoma is a feasible option in carefully selected patients. Hence, vascular encasement should not be considered as a contraindication for surgery; risk must be balanced against the benefit by case to case evaluation.

Serum bilirubin, histological differentiation and adjuvant chemotherapy were significant prognostic factors in our series. Previous studies have focused on the significance of depth of PV invasion[18], lymph node metastasis[21], tumor size[22], negative resection margin[23], and adjuvant chemotherapy[24] in pancreatic adenocarcinoma. These preoperative and intraoperative factors

Table 4 Multivariate analysis in stage Ⅱ pancreatic adenocarcinoma of the head and uncinate process

Parameters	Hazard ratio (95% CI)	*P* value
Bilirubin (mg/dL)		
≤ 2/> 2	2.024 (1.613-3.774)	0.026
Differentiation		0.005
Moderately/well	2.412 (1.379-4.217)	0.002
Poorly/well	2.091 (1.034-4.225)	0.040
Adjuvant chemotherapy		
No/yes	2.068 (1.270-3.366)	0.003
PV/SMV resection		
Yes/no		0.591

help in deciding the extent of resection, proper planning of adjuvant therapy, and predicting the survival outcome in these patients. In our study, preoperative biliary drainage has no statistical significance in the outcome of stage Ⅱ pancreatic adenocarcinoma, similar to an earlier study[25]. Few studies have reported the potential advantages of preoperative biliary drainage, which include improved nutritional, metabolic and immune function, and the possibility of reduced postoperative morbidity and mortality[26,27]. In contrast, one study has reported that the biliary stents induce bacterial contamination and enhance the risk of cholangitis because of clogging. Biliary stenting also generates a severe inflammatory response adjacent to the wall of the bile duct, which is probably a factor that is responsible for increased risk of bile leakage and infection after biliodigestive reconstruction[28]. An experimental study has indicated that a period of 4-6 wk is necessary to recover metabolic and immune functions so that some benefit may be achieved by preoperative biliary drainage[29].

Histological differentiation was found to be significant in our study in determining survival outcome. Patients with well-differentiated adenocarcinoma had better survival than those with moderately well and poorly differentiated adenocarcinoma. Earlier studies by Sohn *et al*[22], Riediger *et al*[23] and Yamaguchi *et al*[30] have highlighted the significance of histological differentiation as a prognostic factor in pancreatic adenocarcinoma.

Adjuvant chemotherapy was also found to be statistically significant. In our study, patients who received adjuvant chemotherapy had better survival than those without chemotherapy. Adjuvant chemotherapy in pancreatic cancer substantially improved the disease-free survival and overall increase in survival rate, as shown by our study and an earlier one[31]. The drawback of our study is that it was a retrospective analysis. However, it still gives information about the prognostic factors and feasibility of *en-bloc* vascular resection in stage Ⅱ adenocarcinoma of the pancreatic head and uncinate process.

In summary, our study concludes that serum bilirubin, histological differentiation and adjuvant chemotherapy are independent prognostic factors that influence survival in patients with stage Ⅱ adenocarcinoma of the pancreatic head and uncinate process. PD/PPPD along with *en-bloc* vascular resection is a technically feasible option in carefully selected patients.

COMMENTS

Background

Unexpected tumor invasion to the lateral or posterolateral wall of the confluence of the portal vein/superior mesenteric vein (PV/SMV) is a common finding during pancreaticoduodenectomy for pancreatic malignancies. This study was designed to establish the prognostic factors and feasibility of *en-bloc* vascular resection in stage Ⅱ adenocarcinoma of the pancreatic head and uncinate process.

Research frontiers

With improvement in surgical techniques and postoperative care, more aggressive *en-bloc* resection of pancreatic malignancies, along with PV/SMV is being carried out at present, without any increase in surgical complications.

Innovations and breakthroughs

Only a few studies have investigated stage Ⅱ pancreatic adenocarcinoma, with special attention to adenocarcinoma in the head and uncinate process, which is more likely to invade the PV/SMV because of its close proximity to these vessels.

Applications

En-bloc vascular resection is a feasible option in carefully selected patients with stage Ⅱ adenocarcinoma of the pancreatic head and uncinate process. Serum bilirubin, histological differentiation and adjuvant chemotherapy are the independent prognostic factors.

Peer review

This is a very well-focused paper that reports a single-center experience with *en-bloc* venous resection of stage Ⅱ pancreatic adenocarcinoma.

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