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Original Article

A comprehensive clinicopathological analysis and survival outcome of periampullary cancer following pancreatoduodenectomy

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Abstract: Background: The study was to elucidate the relationships between 20 clinicopathologic factors and survival of patients with periampullary cancer receiving pancreatoduodenectomy (PD) or pylorus-preserving partial pancreatoduodenectomy (PPPD). Methods: The retrospective study recruited 224 patients with periampullary cancer, including duodenal papilla, bile duct and ampullary cancers between January 2000 and August 2010. Twenty clinicopathological variables were considered for univariate and multivariate analysis to identify significant predictive factors of survival. Results: Overall survival rates at 3 and 5 years were 52% and 47%, respectively. Preoperative jaundice, preoperative CA199, lymph node metastasis, site of origin, differentiation, size of tumor, depth of infiltration, pancreatic invasion, peripancreatic soft tissue invasion, UICC pT factor, lymphovascular invasion, and stage (UICC) significantly predicted survival on univariate analysis. PPPD was a marginal significant factor (P = 0.063) for better survival. CA19-9 level, lymph node metastasis, histologic differentiation, size of tumor and UICC pT factor were independent predictors of survival on multivariate analysis. Conclusions: CA19-9, lymph node metastasis, histologic differentiation, size of tumor and UICC pT factor were independent prognostic factors. Biological behavior may be an important prognostic indicator in periampullary cancers amenable to resection, regardless of origin site. Pylorus preservation, not extended pancreatoduodenectomy has marginal benefit for survival.

Keywords: Clinicopathologic factors, survival, periampullary cancer, biological behavior, pancreatoduodenectomy

Introduction

Pancreatoduodenal cancer mainly encompasses tumors originating in or adjacent to duodenal papilla, distal bile duct, pancreatic head and ampulla of Vater [1]. Among these cancers, ampullary cancer, duodenal cancer and distal bile duct cancer have better prognosis than pancreatic head cancer. Pancreatoduodenal cancer is divided into periampullary cancer (including duodenal papilla cancer, bile duct and ampullary cancer) and pancreatic head cancer.

For patients with a resectable periampullary cancer and without radiologic evidence of metastasis, surgery is the treatment of choice [2]. Pancreatoduodenectomy (PD) or pylorus-preserving partial pancreatoduodenectomy (PPPD) are usually the operation choices for pancreatoduodenal cancer [3]. In the majority of high-volume centers, the surgical morbidity rate still remains as high as 30-40% [4]. An important observation is that despite similar perioperative outcomes, the long-term survival of patients varies greatly. Therefore, increasing studies have been conducted to identify the clinicopathologic factors that might significantly influence survival of patients after resection for periampullary cancers [5-7]. Nevertheless, previous studies focus on relatively less factors, and an agreement has not been reached on the criteria used to decide when local excision is suitable for certain patients in different studies and are generally not well addressed. Therefore, a more comprehensive analysis of clinicopathologic factors was needed for identification of predictive factors of survival in patients with periampullary cancer treated by PD or PPPD.

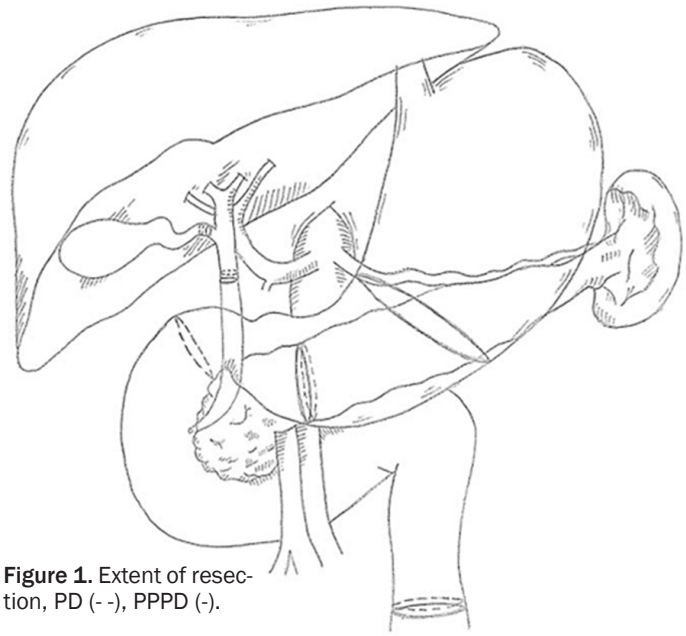

Figure 1. Extent of resection, PD (- -), PPPD (-).

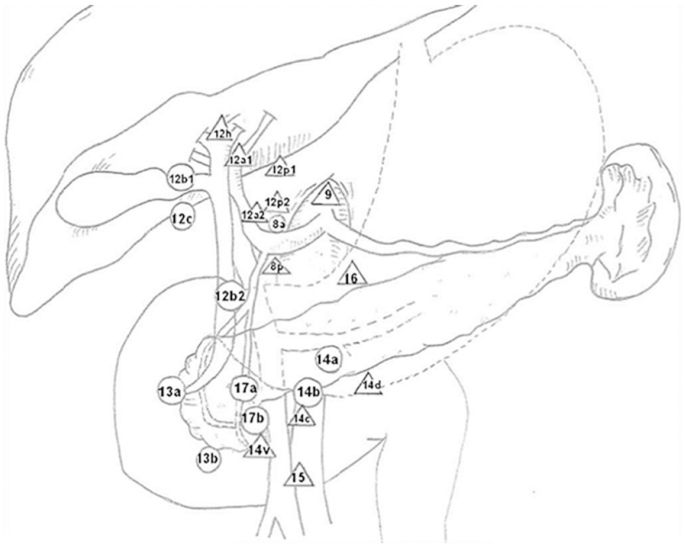

Figure 2. Extent of lymphadenectomy according to the type of resection (3): standard (○), extended (○eΔ) (adapted from Pedrazzoli (3)). Lymph node stations: standard: 12b1, 12c, lymph nodes of the right side of the hepatoduodenal ligament; 13a and 13b, posterior pancreaticoduodenal nodes; 14a and 14b, nodes to the right side of the superior mesenteric artery (SMA) from the origin of the SMA at the aorta to the inferior pancreaticoduodenal artery; 17a and 17b, anterior pancreaticoduodenal nodes; 8a, lymph nodes of the anterior superior region of the common hepatic artery. Extended: all 8, skeletonization of the common and proper hepatic artery lymph nodes; 9, celiac axis nodes; all 12, lymph nodes of the left and right side of the hepatoduodenal ligament; all 14, circumferential skeletonization of the SMA between the aorta and the inferior pancreaticoduodenal artery; all 16, clearance of all lymphatic and connective tissue, starting from 3 cm to the right of the duodenum and extending to the mid portion of the left kidney, and from the inferior margin of the liver across the diaphragmatic hiatus, above the origin of the celiac trunk to the origin of the common iliac arteries.

The retrospective study investigated 20 clinicopathologic factors (age, sex, preoperative serum total bilirubin, preoperative serum carbohydrate antigen (CA) 19-9 level, preoperative biliary drainage, operative procedures (PD or PPPD), extend of lymph node dissection, intraoperative blood loss, operative curability (R0 or R1 resection), site of origin of tumor, size of tumor, UICC pT factor, lymph node metastasis, UICC stage, differentiation, pancreatic invasion, depth of infiltration, peripancreatic soft tissue invasion, perineural invasion and lymphovascular invasion) from preoperative clinical and histological data, treatment data, and survival outcome of 224 patients undergoing PD or PPPD for periampullary adenocarcinoma with a view to identifying significant prognostic factors.

Materials and methods

Subjects

The retrospective study was performed on patients with periampullary cancer, who were treated with PD or PPPD at Department of Hepatobiliary Surgery of the General Hospital of Chinese People's Liberation Army (PLA) between January 2000 and August 2010. Periampullary cancers including duodenal papilla cancer, bile duct cancer (cholangiocarcinoma) and ampullary cancer were defined according to WHO classification of tumors [8]. All patients were diagnosed histopathologically. Histopathologic diagnosis and assessment was made by two experienced pathologists.

To allow the study to accurately identify predictors of survival associated with the malignancy itself rather than the risk of the surgery, pathologic and operative notes were carefully reviewed to exclude any patient with a tumor arising from duodenum, intrapancreatic distal bile duct, exocrine pancreatic tissue or the endocrine pancreas. Besides, patients

Table 1. Result of univariate analysis (20 variables)

Variable	Cutoff	Number	Median survival (month)	Survival rate (%)		*P*-value
				3 year	5 year	
Age (year)	≥ 60	103	36 (7-107.2)	51	45	0.7966
	< 60	121	36 (6-95)	52	45	
Sex	Male	146	36 (7-113.25)	55	48	0.2293
	Female	78	33 (6-85.55)	46	46	
TB (mg/dl)	< 10	168	36.5 (8.4-118.9)	57	52	0.0031
	≥ 10	56	24 (3-70)	35	34	
CA19-9 (U/ml)	< 111	133	39 (7.6-102.4)	60	56	0.034
	≥ 111	91	26 (6-101.5)	40	34	
Biliary drainage	No	157	35 (6-106.4)	48	45	0.1419
	Yes	67	40 (10-100)	60	52	
P-P	PD	151	36 (5-121.5)	50	45	0.0633
	PPPD	73	36 (9.2-70.4)	55	52	
ELND	SPD	177	36 (7-116.2)	52	47	0.3497
	EPD	47	36 (6-73.7)	49	45	
Intraoperative blood loss (mL)	< 600	171	36 (6-97.5)	52	48	0.1757
	≥ 600	53	36 (9-106.8)	51	45	
Site of origin	Ampullar	42	36 (12-85.85)	57	57	0.0017
	Distant Bile	68	24 (3.35-71.95)	38	34	
	Duodenal papilla	114	39.5 (8-110.45	58	51	
Size (cm)	< 3	147	40 (9-119.9)	62	57	0.0003
	≥ 3	77	24 (4-78)	32	27	
Differentiation	Well	24	53 (10.3-139.55)	66	56	0.0094
	Moderate	125	36 (8-99)	54	49	
	Poor	75	31 (5.4-70.9)	43	39	
Depth	muscular layer	42	53 (12.1-136.5)	67	60	0.0002
	Overall	182	35 (6-85.85)	48	43	
PI	NO	103	42 (10-121.3)	65	64	0.0000
	YES	121	28 (4-73)	40	32	
PNI	NO	196	36 (7.75-101.5)	55	50	0.0552
	YES	28	19 (4.7-108.75)	29	0	
PPSI	No	209	36 (7-107.2)	54	49	0.0310
	Yes	15	18 (3-56.4)	26	20	
UICC pT factor	I and II	74	53.5 (18-119.2)	73	73	0.0000
	III and IV	150	30 (4.9-88.75)	41	34	
LVI	No	205	36 (6-107.6)	55	49	0.0067
	Yes	19	18 (7-50.2)	27	21	
LNM	No	182	38 (7-114.65)	59	55	0.0000
	Yes	42	21 (4-55)	17	14	
R Status	R0	220	36 (6-106.1)	53	48	0.1537
	R1	4	21 (12.9-24)	0	0	
Stage (UICC)	I and II	154	40 (8.65-106.7)	62	57	0.0001
	III and IV	70	22.5 (4.9-84.65)	29	25	

CA19-9, serum carbohydrate antigen (CA) 19-9, TB: Total bilirubin, P-P: pylorus-preserving, PD, pancreatoduodenectomy, PPPD, pylorus-preserving partial pancreatoduodenectomy, ELND: Extent of lymph node dissection, SPD: standard pancreatoduodenectomy, EPD: pancreatoduodenectomy, PI: Pancreatic invasion, PNI: Perineural invasion, PPSI: peripancreatic soft tissue invasion, LVI: Lymphovascular invasion, LNM: Lymph node metastasis.

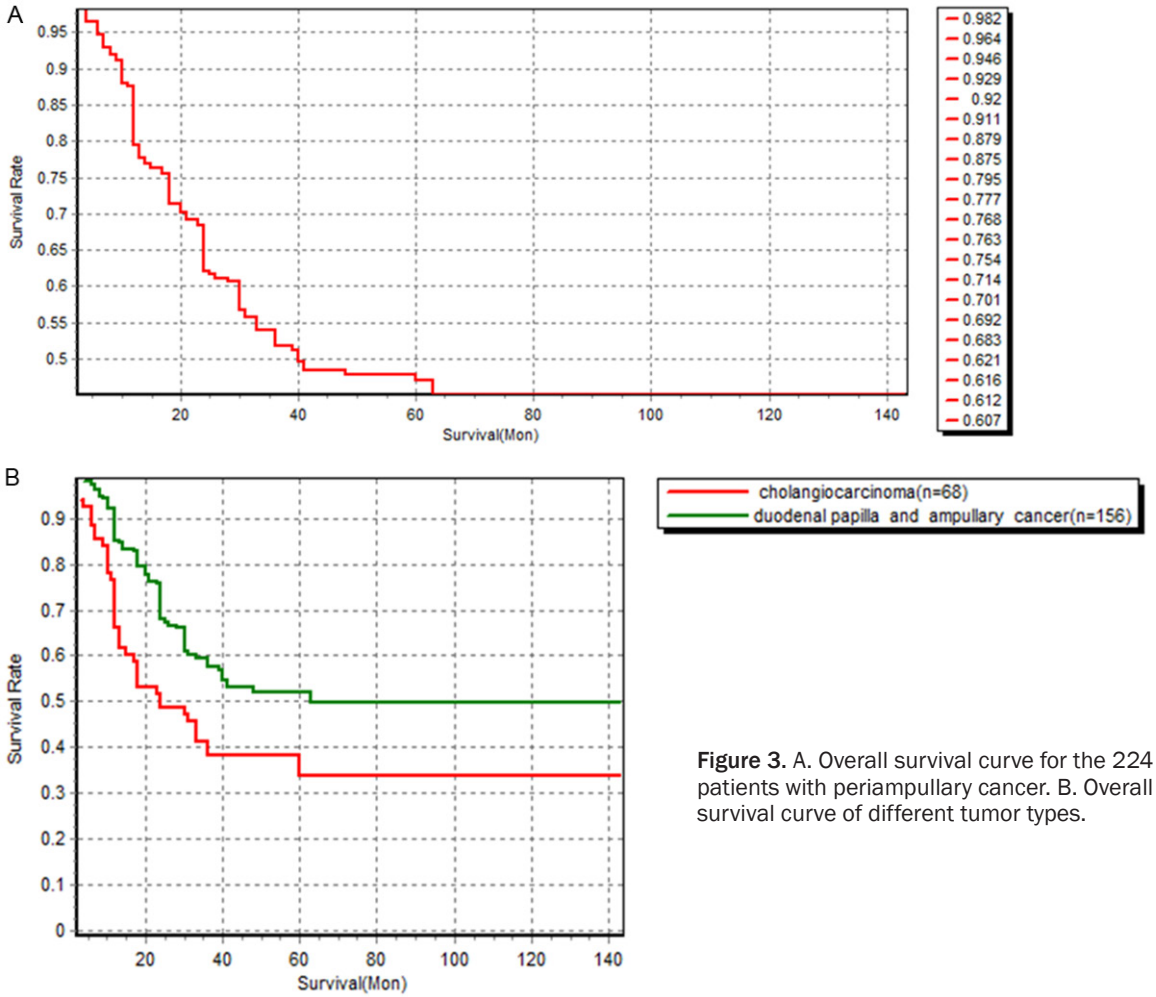

Figure 3. A. Overall survival curve for the 224 patients with periampullary cancer. B. Overall survival curve of different tumor types.

surviving less than 2 months after the operation were also excluded. Finally, 224 eligible patients were included in the study.

This study was conducted with the approval of the Committee for the Ethical of the General Hospital of Chinese PLA. All patients provided written informed consent prior to the study.

Surgical strategy

All patients underwent PD or PPPD for malignant disease (**Figure 1**). As shown in **Figure 2**, the lymph-node dissection in all cases was performed in pursuance of standard pancreatoduodenectomy (SPD) or extended pancreatoduodenectomy (EPD).

Evaluation of clinicopathological data

The clinical characteristics, laboratory data, treatment including surgical procedure, tumor pathological histology, and long-term outcome of patients were obtained from the database. Twenty clinicopathological variables (age, sex, preoperative serum total bilirubin, preoperative serum carbohydrate antigen (CA) 19-9 level, preoperative biliary drainage, operative procedures (PD or PPPD), lymph node dissection (SPD or EPD), intraoperative blood loss, operative curability (R0 resection: no residual cancer; R1 resection: microscopic residual cancer), site of origin of tumor, size of tumor, UICC pT factor, lymph node metastasis, UICC stage, histologic differentiation, pancreatic invasion, depth of infiltration, peripancreatic soft tissue invasion, perineural invasion and lymphovascular invasion) were reviewed. Histopathologic factors were evaluated using routine examination [9]. Tumor was staged in pursuance with the International Union Against Cancer (UICC) classification [10-12], and differentiation grades was defined based on the criteria proposed by

Table 2. Results of multivariate analysis

Variable	Regression coefficient	Standard error	U-value	*P*-value	Relative risk	95% Confidence interval
Biliary drainage	-0.106	0.239	0.443	0.6580	0.90	0.563~1.437
CA19-9	0.490	0.210	2.332	0.0197	1.63	1.081~2.465
Differentiation	0.446	0.181	2.466	0.0137	1.56	1.096~2.226
PPSI	0.644	0.369	1.745	0.0809	1.90	0.924~3.925
Depth	-0.182	0.333	0.548	0.5838	0.83	0.434~1.600
LNM	0.844	0.235	3.600	0.0003	2.33	1.469~3.685
LVI	0.504	0.304	1.658	0.0973	1.66	0.912~3.006
PI	-0.430	0.328	1.310	0.1900	0.65	0.342~1.238
PNI	0.610	0.336	1.818	0.0691	1.84	0.953~3.557
Pylorus-preserving	-0.248	0.220	1.128	0.2592	0.78	0.507~1.201
R Status	0.931	0.558	1.669	0.0950	2.54	0.850~7.568
Site of origin	0.118	0.137	0.866	0.3866	1.13	0.861~1.471
Size	0.653	0.214	3.052	0.0023	1.92	1.263~2.923
Stage	-0.262	0.292	0.898	0.3692	0.77	0.434~1.363
TB	0.261	0.234	1.116	0.2645	1.30	0.821~2.055
Blood lose	-0.121	0.226	0.537	0.5915	0.89	0.569~1.380
UICC pT factor	1.267	0.410	3.089	0.0020	3.55	1.589~7.934

χ^2 = 1109.2323. P = 0.0000. CA19-9, serum carbohydrate antigen (CA) 19-9, TB: Total bilirubin, PI: Pancreatic invasion, PNI: Perineural invasion, PPSI: peripancreatic soft tissue invasion, LVI: Lymphovascular invasion, LNM: Lymph node metastasis.

Albores-Saavedra *et al.* [13]. Overall survival was defined from the date of operation until the date of death by any cause, as recorded in hospital records of August, 20, 2013.

Statistical analysis

Statistical analysis was conducted using SPSS 17.0 (SPSS Inc, Chicago, III). The categorical variables were compared by means of chi-square test or Fisher's exact test. Survival was assessed through Kaplane-Meier analysis, and significance was ascertained using log rank test. Univariate analysis was assessed by means of analysis of variance (ANOVA). The factors most likely to impact survival on univariate analysis were entered into multivariate analysis using the Cox proportional hazards model. Statistical significance was accepted at $P < 0.05$.

Results

Demographic and clinical information

The demographic, clinic and pathological data of the 224 patients were shown in **Table 1**. Average age of these patients (male/female: 146/78) was 58 years (range from 34 to 77). Fifty-six (25%) patients were presented with total bilirubin level more than 10 mg/dl, and 91 (40.6%) patients were presented with preoperative serum CA19-9 level more than 111 U/ml. Preoperative biliary drainage was performed in 67 patients (29.9%), including endoscopic nasobiliary drainage in 6 patients, endoscopic retrograde biliary drainage in 50 patients, and percutaneous transbiliary drainage in 11 patients. PPPD was performed in 73 patients and classic PD was performed in the other 151 patients. SPD was performed in 177 patients and EPD was conducted in the other 47 patients.

R0 resections were achieved in 220 (98.2%) patients with a respectability rate of 90%, and R1 resections were achieved in the other 4 (1.8%) patients. All patients had a single tumor. Seventy-seven (34.4%) patients had the tumor size more than 3 cm. Site of origin of tumor was identified to be ampullary cancer in 42 patients, duodenal papillary cancer in 114 patients and distal bile duct cancer in 68 patients. Tumor was well differentiated in 24 (10.7%) patients, moderately differentiated in 125 (55.8%) patients and poorly differentiated in 75 (33.5%) patients. Perineural invasion was detected in 28 patients (12.5%). According to UICC TNM staging, T1 or T2 lesions were found in 74

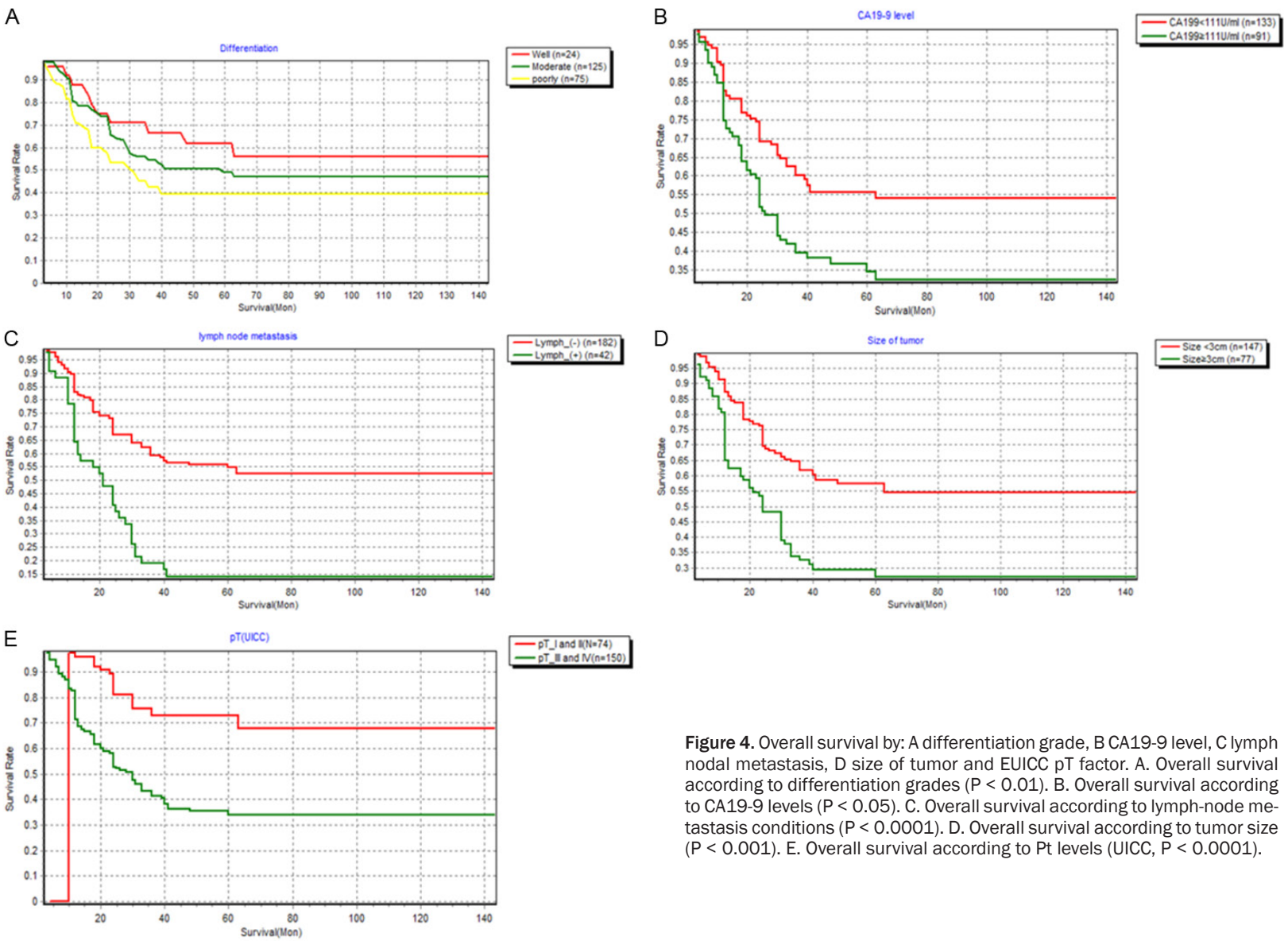

Figure 4. Overall survival by: A differentiation grade, B CA19-9 level, C lymph nodal metastasis, D size of tumor and EUICC pT factor. A. Overall survival according to differentiation grades ($P < 0.01$). B. Overall survival according to CA19-9 levels ($P < 0.05$). C. Overall survival according to lymph-node metastasis conditions ($P < 0.0001$). D. Overall survival according to tumor size ($P < 0.001$). E. Overall survival according to Pt levels (UICC, $P < 0.0001$).

Table 3. Analysis of tumor stage of different tumor types

Variable	Cutoff	Ampulla	Distant biliary	Duodenal papilla	χ^2	*P*-value
Stage	I and II	34	36	84	12.1128	0.0023
	III and IV	8	32	30		

Table 4. Relationships between clinicopathologic factors and lymph node metastasis

		Lymph-node metastasis			
Variable	Cutoff	(-)	(+)	χ^2	P
PI	(-)	90	13	3.9859	0.0459
	(+)	92	29		
Size (cm)	< 3	126	21	4.7744	0.0289
	≥ 3	56	21		
LVI	(-)	169	36	1.4171	0.2339
	(+)	13	6		
Stage	I and II	132	22	5.5433	0.0186
	III and IV	50	20		

PI: Pancreatic invasion, LVI: Lymphovascular invasion.

patients (33%), T3 in 149 (66.5%) patients, and T4 in only one patient. Lymph node metastasis was present in 42 patients (18.6%). Additionally, 154 patients (68.8%) belonged to stage I-II, and the other 70 (31.2%) patients belonged to stage III-IV.

Overall survival rates

As shown in **Figure 3**, the average follow-up of all patients was 36 months (range: 3-143 months). The overall survival rates were 52% at 3 years and 47% at 5 years, respectively.

Univariate and multivariate survival analysis

As shown in **Table 1**, univariate analysis revealed that age, sex, biliary drainage, pylorus preservation, extent of lymph-node dissection, intraoperative blood loss, perineural invasion, and R status were not significant predictors of survival (P > 0.05). By contrast, serum total bilirubin (P = 0.0031), CA19-9 (P = 0.034), site of origin of tumor (P = 0.0017), size of tumor (P = 0.0003), differentiation (P = 0.0094), depth of infiltration (P = 0.0002), pancreatic invasion (P = 0.0000), peripancreatic soft tissue invasion (P = 0.031), UICC pT factor (P = 0.0000), lymphovascular invasion (P = 0.0067), lymph node metastasis (P = 0.0000), and tumor stage (UICC, P = 0.0000) were significantly associated with survival. In addition, PPPD is a marginal significant factor (P = 0.063) for better survival, while perineural invasion was marginal significant factor for poor survival (P = 0.055).

Furthermore, multivariate Cox regression analysis (**Table 2**) found that CA19-9 level, differentiation, lymph node metastasis, size of tumor and UICC pT factor were independent predictors of survival (P < 0.05, **Figure 4**).

Associations between clinicopathologic factors

The associations between clinicopathologic factors were further analyzed. As shown in **Table 3**, the percentage of T3-T4 distant cholangiocarcinoma was significantly elevated than that of T3-T4 ampullary cancers and duodenal papilla cancers. This indicates that site of origin might be associated with tumor stage. However, neither site of origin nor tumor stage was an independent predictive factor of survival on multivariate analysis.

As shown in **Table 4**, positive lymph nodes were found in 28.6% (20/70) of patients with T3-T4 carcinoma, whereas it was only in 14.2% of patients in patients with T1-T2 periampullary carcinoma. Lymph node metastasis was significantly associated with pancreatic invasion (P = 0.0459), tumor size (P = 0.0289) and tumor stage (P = 0.0186), rather than lymphovascular invasion (P = 0.2339). However, neither pancreatic invasion nor tumor stage was identified as an independent predictor of survival on multivariate analysis. Tumor differentiation did not appear to be influenced by lymph node metastasis and perineural invasion (**Table 5**).

Furthermore, ampullary cancers, distant cholangiocarcinoma and duodenal papilla cancers did not significantly differ in CA19-9 level, differentiation degree and lymph node metastasis when they presented at the same stage (**Tables 6** and **7**). Different types of periampullary cancers at the same stage had similar biologic behavior, indicating that biologic behavior may an important predictor of survival regardless of site of origin. Additionally, duodenal papilla cancer showed a favorable trend for lymphovascular invasion (P < 0.05), and distant cholangiocarcinoma showed a favorable trend for lym-

Table 5. Relationships between clinicopathologic factors and tumor differentiation grade

Variable	Cut-off	Differentiation grade			χ^2	*P*-value
		Well differentiation	Moderately differentiation	Poorlydifferentiation		
LNM	(-)	18	105	59	1.5644	0.4574
	(+)	6	20	16		
PNI	(-)	23	109	64	1.856	0.3953
	(+)	1	16	11		

LNM: Lymph node metastasis, PNI: Perineural invasion.

Table 6. Biologic behavior of different tumor types at the same stage (Stage I and II)

Variable	Cutoff	Ampulla	Distant biliary	Duodenal papilla	χ^2	*P*-value
CA19-9 (U/ml)	< 111	20	19	54	1.4399	0.4868
	≥ 111	14	17	30		
Differentiation	Well	3	2	18	8.3291	0.0802
	Moderately	21	18	43		
	Poorly	10	16	23		
LNM	(-)	28	34	70	2.9434	0.2295
	(+)	6	2	14		
LVI	(-)	31	36	84	10.7986	0.0045
	(+)	3	0	0		
PNI	(-)	33	36	84	3.5525	0.1693
	(+)	1	0	0		

PNI: Perineural invasion, LVI: Lymphovascular invasion, LNM: Lymph node metastasis.

Table 7. Biologic behavior of different tumor types in the same stage (Stage III and IV)

Variable	Cutoff	Ampulla	Distant biliary	Duodenal papilla	χ^2	*P*-value
CA19-9 (U/ml)	< 111	3	20	17	1.6382	0.4408
	≥ 111	5	12	13		
Differentiation	Well	0	0	1	2.0015	0.7355
	Moderately	4	20	19		
	Poorly	4	12	10		
LNM	(-)	7	23	20	1.3490	0.5094
	(+)	1	9	10		
LVI	(-)	8	27	19	6.5642	0.0375
	(+)	0	5	11		
PNI	(-)	5	13	25	11.9242	0.0026
	(+)	3	19	5		

PNI: Perineural invasion, LVI: Lymphovascular invasion, LNM: Lymph node metastasis.

phovascular invasion and perineural invasion ($P < 0.01$).

Discussion

Long-term survival of patients with periampullary cancer varies considerably. Previous studies attempting to identify significant predictors of survival focus on relatively less risk factors. In order to extend the research in this field, a comprehensive analysis of 20 clinicopathological variables for identification of significant prognostic factors was conducted in 224 patients with periampullary cancer treated by PD or PPPD using univariate and multivariate analysis. The overall actuarial survival rates at 3 and 5 years were 52% and 47%, respectively. The univariate analysis revealed that preoperative jaundice, preoperative CA199 level, lymph node metastasis, site of origin, histologic differentiation, size of tumor, depth of infiltration, pancreatic invasion, peripancreatic soft tissue invasion, UICC pT factor, lymphovascular invasion and stage (UICC) were potential predictors of survival. On multivariate analysis, preoperative CA19-9 level, lymph node metastasis, histologic differentiation, size of the tumor and UICC pT factor were significant independent prognostic factors. Biological behavior may be an important prognostic factor in periampullary cancers amenable to resection regardless of site of origin.

Serum CA19-9 has emerged as a clinically valuable biomarker of pancreatic cancer, and it has proved that higher preoperative serum CA19-9 level predicts poorer survival of pancreatic cancer [14, 15]. However, there were few studies on the prognostic value of CA19-9 in periampullary cancer. Gao Z *et al*. have suggested that periampullary cancer patients with preop-

erative serum CA19-9 > 35 U/ml are prone to have a poorer survival [16]. In the present study, both univariate analysis and multivariate analysis unraveled that preoperative serum CA19-9 level more than 111 U/ml significantly predicted a poorer survival of periampullary carcinoma. It suggests that more studies are needed to clarify the relation between CA19-9 and survival.

Lymph node metastasis has been reported to be an important prognostic factor [17-20]. As well, in the present study, lymph node metastasis was confirmed to be an independent predictor of survival, and significantly associated with pancreatic invasion, tumor size and tumor stage. There is evidence that patients without pancreatic invasion had significantly longer survival than those with pancreatic invasion [17]. Likewise, in the present study, pancreatic invasion was significantly related to survival on univariate analysis. Some studies report that lymphovascular invasion is closely related tolymph node metastasis [2, 21, 22]. Hatzaras I *et al.* have found that lymphovascular invasion is closely associated with nodal metastasis, but not a significant predictor of survival [6]. Similarly, results of this study suggested that lymphovascular invasion was not an independent predictor of survival on multivariate analysis. But it was not associated with lymph node metastasis, which might be ascribed to the limited sample size of our study. Additionally, in this study, the frequency of lymph node metastasis is 19% in patients with ampulla of Vater cancers, which is much lower than previous reports (38%-70%) [2, 18, 20, 21]. This might be due to the higher rate of duodenal papilla cancer.

There are controversial viewpoints regarding whether poor differentiation is a predictor of survival. Gamagami RA *et al.* have reported that tumor differentiation is an independent prognostic factor in periampulary neoplasms [23]. Nonetheless, in the study of Hatzaras I *et al.*, tumor differentiation is not selected as a independent predictor of survival on multivariate analysis [6]. In the present study, both univariate analysis and multivariate analysis unveiled that tumor differentiation significantly predicted survival. The inconsistent results might be due to the relative subjectivity in determining differentiation grade of tumor. Limited sample size might be another reason. Moreover, the study found that tumor differentiation was not significantly associated with lymph node metastasis or perineural invasion. Furthermore, as noteworthy is the observation that ampullary cancers, distant cholangiocarcinoma and duodenal papilla cancers at the same stage were not significantly different in terms of differentiation grade and lymph node metastasis in the present study. It indicates that biological behavior may be an important predictive factor of survival in periampullary cancers amenable to resection regardless of site of origin. Although Hatzaras I *et al*. also have reported that biological behavior is the most important prognostic indicator, only neural invasion and nodal metastasis are identified to independent prognostic factors in their study [6]. These findings call for more studies to elucidate the prognostic value of biological behavior in patients with periampullary cancer.

Jaundice is reported as an indicator of advanced disease with a dismal prognosis in periampullary cancers [2]. The present study suggested that preoperative total bilirubin level more than 10 mg/dl significantly predicted poorer survival on univariate analysis, but not a significant independent risk factor for poor outcome on multivariate analysis. It is speculated that jaundice may reflect the bile duct invasion and hepatoduodenal ligament infiltration. The routine use of preoperative biliary drainage in jaundiced patients is debated, but preoperative biliary drainage is performed more frequently in jaundiced patients. Some scholars report that routine preoperative biliary drainage before surgery for pancreatic head cancer increases the rate of complications [24]. However, previous studies of our department show that preoperative biliray drainage don't decrease the rate of complications [25]. In this study, preoperative biliary drainage did not appear to benefit the long-term outcome of the patients undergoing pancreatoduodenectomy.

Although the prognosis of extensive lymph node metastasis was dismal, Shirai *et al.* have reported that application of radical lymph node dissection appears to be justified in patients with lymph node metastasis [26]. At present, there is a lack of controlled clinical data on the impact of extended lymph node dissection on long-term survival, therefore, two kinds of lymph-node dissection (EPD and SPD) were performed in the study. Our data showed there

was no significantly difference in survival between the two kinds of lymph-node dissection. It revealed no survival benefit of extended lymphadenectomy with pancreaticoduodenectomy, suggesting that standard pancreaticoduodenectomy is the procedure of choice for periampullary neoplasm.

Various studies have compared PD with PPPD and have found no significantly difference in survival between them [27]. However, published literature has revealed that there is a better postoperative gastrointestinal QOL in patients undergone PPPD in terms of appetite, nausea and diarrhea [28], and some studies have shown that patients gain better nutritional recovery [29], better weight gain postoperatively [28, 30], more postoperative exocrine function as well as glucose metabolism function reservation [30] when the whole stomach is preserved. Our data herein showed PPPD is a marginal significant factor (P = 0.063) for better survival. PPPD might be a better choice than PD.

The study is underpowered by some weaknesses. It is a retrospective analysis with a limited sample size. Additionally, there might be a selection bias because patients were selected from one institution. Thus, better designed and adequately powered studies, including prospective studies, are necessary to validate the findings of this study.

Conclusions

Preoperative CA19-9 level, lymph node metastasis, differentiation, size of tumor and UICC pT factor were independent predictors of survival. Biological behavior was an important prognostic factor in patients with periampullary cancer treated by PD or PPPD, regardless of site of origin. It is pylorus preservation but not extended pancreatoduodenectomy that might has marginal benefit for survival.

Disclosure of conflict of interest

None.

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References

[1] Pancreatic S. Guidelines for the management of patients with pancreatic cancer periampullary and ampullary carcinomas. Gut 2005; 54: v1.

[2] Yokoyama N, Shirai Y, Wakai T, Nagakura S, Akazawa K and Hatakeyama K. Jaundice at presentation heralds advanced disease and poor prognosis in patients with ampullary carcinoma. World J Surg 2005; 29: 519-523.

[3] Kondo S, Takada T, Miyazaki M, Miyakawa S, Tsukada K, Nagino M, Furuse J, Saito H, Tsuyuguchi T and Yamamoto M. Guidelines for the management of biliary tract and ampullary carcinomas: surgical treatment. J Hepatobiliary Pancreat Surg 2008; 15: 41-54.

[4] Asari S, Matsumoto I, Ajiki T, Shinzeki M, Goto T, Fukumoto T and Ku Y. Perioperative management for pancreatoduodenectomy following severe acute pancreatitis in patients with periampullary cancer: our experience with six consecutive cases. Surgery Today 2015; 45: 1-8.

[5] Bronsert P, Kohler I, Werner M, Makowiec F, Kuesters S, Hoeppner J, Hopt UT, Keck T, Bausch D and Wellner UF. Intestinal-type of differentiation predicts favourable overall survival: confirmatory clinicopathological analysis of 198 periampullary adenocarcinomas of pancreatic, biliary, ampullary and duodenal origin. BMC Cancer 2013; 13: 428.

[6] Hatzaras I, George N, Muscarella P, Melvin WS, Ellison EC and Bloomston M. Predictors of survival in periampullary cancers following pancreaticoduodenectomy. Ann Surg Oncol 2010; 17: 991-997.

[7] Winter JM, Cameron JL, Olino K, Herman JM, Jong MCD, Hruban RH, Wolfgang CL, Eckhauser F, Edil BH and Choti MA. Clinicopathologic analysis of ampullary neoplasms in 450 patients: implications for surgical strategy and long-term prognosis. J Gastrointest Surg 2010; 14: 379-387.

[8] Bosman FT, Carneiro F, Hruban RH and Theise ND. WHO classification of tumours of the digestive system. World Health Organization 2010.

[9] Westgaard A, Tafjord S, Farstad IN, Cvancarova M, Eide TJ, Mathisen O, Clausen OP and Gladhaug IP. Pancreatobiliary versus intestinal histologic type of differentiation is an independent prognostic factor in resected periampullary adenocarcinoma. BMC Cancer 2008; 8: 170.

[10] Sobin LH, Gospodarowicz MK and Wittekind C. TNM classification of malignant tumours. John Wiley & Sons 2011.

[11] Sobin L and Wittekind C. International Union Against Cancer (UICC): TNM classification of

malignant tumors 6th edition. New York: Willey-Liss; 2002.
[12] Edge SB and Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010; 17: 1471-1474.
[13] Albores-Saavedra J, Henson DE and Klimstra DS. Tumors of the gallbladder, extrahepatic bile ducts, and ampulla of vater. Armed Forces Institute of Pathology 2000.
[14] Waraya M, Yamashita K, Katagiri H, Ishii K, Takahashi Y, Furuta K and Watanabe M. Preoperative serum CA19-9 and dissected peripancreatic tissue margin as determiners of long-term survival in pancreatic cancer. Ann Surg Oncol 2009; 16: 1231-1240.
[15] Humphris J, Chang D, Johns A, Scarlett C, Pajic M, Jones M, Colvin E, Nagrial A, Chin V and Chantrill L. The prognostic and predictive value of serum CA19. 9 in pancreatic cancer. Ann Surg Oncol 2012; 23: 1713-1722.
[16] Gao Z, Wang H and Cai Z. Diagnostic and prognostic values of CA 19-9 and CEA in periampullary cancers. J Am Coll Surg 1999; 188: 415-420.
[17] Qiao Ql, Zhao YG, Ye MI, Yang YM, Zhao JX, Huang YT and Wan YI. Carcinoma of the ampulla of Vater: factors influencing long-term survival of 127 patients with resection. World J Surg 2007; 31: 137-143.
[18] Klempnauer J, Ridder GJ, Maschek H and Pichlmayr R. Carcinoma of the ampulla of Vater: determinants of long-term survival in 94 resected patients. HPB Surgery 1998; 11: 1-11.
[19] Sudo T, Murakami Y, Uemura K, Hayashidani Y, Hashimoto Y, Ohge H, Shimamoto F and Sueda T. Prognostic impact of perineural invasion following pancreatoduodenectomy with lymphadenectomy for ampullary carcinoma. Dig Dis Sci 2008; 53: 2281-2286.
[20] Sakata J, Shirai Y, Wakai T, Yokoyama N, Sakata E, Akazawa K and Hatakeyama K. Number of positive lymph nodes independently affects long-term survival after resection in patients with ampullary carcinoma. Eur J Surg Oncol 2007; 33: 346-351.
[21] Moriya T, Kimura W, Hirai I, Mizutani M, Ma J, Kamiga M and Fuse A. Nodal involvement as an indicator of postoperative liver metastasis in carcinoma of the papilla of Vater. J Hepatobiliary Pancreat Surg 2006; 13: 549-555.
[22] Duffy JP, Hines OJ, Liu JH, Ko CY, Cortina G, Isacoff WH, Nguyen H, Leonardi M, Tompkins RK and Reber HA. Improved survival for adenocarcinoma of the ampulla of Vater: fifty-five consecutive resections. Arch Surg 2003; 138: 941-950.
[23] Gamagami RA, Gilpin EA and Romeo O. Factors influencing survival after resection for periampullary neoplasms. Am J Surg 2000; 180: 13-17.
[24] van der Gaag NA, Rauws EA, van Eijck CH, Bruno MJ, van der Harst E, Kubben FJ, Gerritsen JJ, Greve JW, Gerhards MF and de Hingh IH. Preoperative biliary drainage for cancer of the head of the pancreas. N Engl J Med 2010; 362: 129-137.
[25] Feng J, Huang Z, Chen Y, Dong J, Chen M, Wang Y, Liu Z, Xiao M, Li L and Xin X. [Influence of obstructive jaundice on postoperative complications and mortality after pancreaticoduodenectomy: analysis of the 25-year single-center data]. Zhonghua Wai Ke Za Zhi 2012; 50: 294-298.
[26] Shirai Y, Ohtani T, Tsukada K and Hatakeyama K. Patterns of lymphatic spread of carcinoma of the ampulla of Vater. Br J Surg 1997; 84: 1012-1016.
[27] Iqbal N, Lovegrove R, Tilney H, Abraham A, Bhattacharya S, Tekkis P and Kocher H. A comparison of pancreaticoduodenectomy with pylorus preserving pancreaticoduodenectomy: a meta-analysis of 2822 patients. Eur J Surg Oncol 2008; 34: 1237-1245.
[28] Wenger F, Jacobi C, Haubold K, Zieren H and Müller J. [Gastrointestinal quality of life after duodenopancreatectomy in pancreatic carcinoma. Preliminary results of a prospective randomized study: pancreatoduodenectomy or pylorus-preserving pancreatoduodenectomy]. Chirurg 1999; 70: 1454-1459.
[29] Di Carlo V, Zerbi A, Balzano G and Corso V. Pylorus-preserving pancreaticoduodenectomy versus conventional Whipple operation. World J Surg 1999; 23: 920-925.
[30] Klinkenbijl J, Van der Schelling G, Hop W, Van Pel R, Bruining H and Jeekel J. The advantages of pylorus-preserving pancreatoduodenectomy in malignant disease of the pancreas and periampullary region. Ann Surg 1992; 216: 142.