Original Article

Outcome and Prognostic Factors for Periampullary Carcinoma after Pancreaticoduodenectomy: A Single Tertiary Center Experience

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Objective: Pancreaticoduodenectomy (PD) remains the standard treatment in achieving long-term outcome for periampullary carcinoma. This study aims to evaluate outcome and prognostic factors of PD in a large tertiary center in Thailand.

Materials and Methods: This study is a single-center, retrospective study including patients who underwent PD for periampullary carcinoma at Siriraj Hospital from 2011 to 2015. Univariate and multivariate analyses were performed to identify poor clinico-pathological prognostic factors for survival after PD.

Results: A total of 128 patients who underwent PD for periampullary carcinoma at Siriraj Hospital between 2011 and 2015 were included. Five-year overall survival was 16% with median survival time of 23 months. Patients with ampullary cancer (25.7%) and duodenal cancer (21.1%) had longer 5-year survival than pancreatic cancer (13.3%) and distal cholangiocarcinoma (0%) ($p<0.001$). Multivariate analysis showed that independent adverse prognostic factors were perineural invasion (HR: 3.94, 95% CI: 1.90 to 6.40, $p<0.01$), N2 nodal status (HR: 2.98, 95% CI: 1.16 to 7.64, $p = 0.02$), positive resection margin (HR: 1.93, 95% CI: 1.19 to 3.14, $p = 0.047$), lymphovascular invasion (HR: 1.73, 95% CI: 1.03 to 2.90, $p = 0.03$) and pre-operative albumin <3.5 g/dl (HR 1.71, 95% CI: 1.09 to 2.67, $p = 0.02$). Tumors with perineural invasion also had higher rate of lymphovascular invasion. Patients with low albumin level had higher proportion of T3 and T4 staging, and poorly differentiated tumors. Notably, pre-operative biliary drainage and total bilirubin were not significant predictive factors.

Conclusion: Poor prognostic factors for periampullary carcinoma after PD included N2 nodal status, perineural invasion, lymphovascular invasion, positive resection margin and low albumin level. Therefore, radical surgical resection and pre-operative improvement of nutritional status should be considered.

Keywords: Periampullary carcinoma, Pancreaticoduodenectomy

Periampullary carcinoma encompasses tumors arising from four areas surrounding major duodenal papillae including: pancreatic head ductal adenocarcinoma, ampullary adenocarcinoma, distal cholangiocarcinoma and duodenal adenocarcinoma. While the incidence of pancreatic ductal adenocarcinoma continues to increase, the survival rate remains the lowest among all types of cancer[1]. With advances in treatment and improvements in outcomes of other cancers, periampullary cancer is predicted to be the second leading cause of death within the next decade. There were various studies performed in order to identify the predictive factors for outcome of patients and multiple attempts were made to establish better therapeutic options including better adjuvant treatment, neoadjuvant treatment or targeted therapy[2,3].

The main effective treatment of periampullary cancer is surgical resection. There is a paucity of the detailed clinicopathological data and outcome for periampullary cancer patients in Thailand. Only one study reported overall survival for pancreatic cancer treatment in Thailand[4], and predictive factor analysis remains scarce. This study aims to determine the outcome and prognostic factors in patients who underwent pancreaticoduodenectomy for periampullary carcinoma in a single-tertiary center in Thailand.

Materials and Methods

The medical records of patients who underwent pancreaticoduodenectomy for periampullary carcinoma at Siriraj Hospital from January 2011 to December 2015 were obtained using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), code

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527 for radical pancreaticoduodenectomy, and International Statistical Classification of Diseases and Related Health problems, Tenth Revision (ICD-10) code C23 to C25 for periampullary carcinoma. Patients with two primary tumors were excluded.

Standard pre-operative evaluation included routine laboratory testing, serum tumor markers (CEA and CA 19-9), chest radiography, computed tomographic and/or magnetic resonance imaging. The surgically fit patients with resectable or borderline resectable disease according to National Comprehensive cancer network (NCCN) criteria were scheduled for curative resection[5]. Pre-operative biliary drainage was performed based on surgeons and gastro-enterologists treatment plan. Either pancreatico-duodenectomy or pylorus-preserving pancreaticoduo-denectomy was selected according to the extent of tumor and surgeon preference. Tumors were classified according to 8th edition of AJCC staging systems[6-9]. Lymph node ratio (LNR) was defined as ratio of number of positive lymph nodes to total examined lymph nodes.

Adjuvant therapy was decided on by a multidisciplinary team including surgeons, medical and radiation oncologists. The patients were followed-up with computed tomography and tumor markers (CEA and CA19-9) every 4 to 6 months. Patient outcome including 5-year overall survival and recurrence rate was monitored. The study was approved by Human Research Protection Unit (Institutional Review Board), Faculty of Medicine Siriraj Hospital, Mahidol University. The present study was approved by the Siriraj Institutional Review Board (023/2561(EC1)).

Statistical analysis

Continuous variables were expressed using mean and standard deviation (SD) or median with range as appropriate. Independent t-test, was used to compare means between independent groups. Categorical variables were expressed with percentage and compared between independent groups using Pearson's Chi-square test or Fisher test where appropriate.

Overall survival was calculated from the date of surgery to the date of death from any cause or the date of last contact with the hospital. Overall survival curves were estimated according to the Kaplan-Meier method and compared using the log-rank test. A multivariate Cox regression model was used to calculate hazard ratios with 95% confidence intervals (95% CI). The *p*-value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS software version 18.0 for Windows.

Results
Patient demographics and perioperative variables

A total of 128 patients underwent pancreaticoduo-denectomy during the study period. The patient characteristics and perioperative data are presented in Table 1. There were 63 men and 65 women, and the median age at surgery was 63 years (range 37 to 91 years). Median

Table 1. Patient characteristics and perioperative status

Variable	n = 128
Patient demographic data	
Sex, n (%)	
Male	63 (49.2)
Female	65 (50.8)
Age at surgery (years), median (min, max)	63.6 (37 to 91)
Preoperative status	
Hemoglobin (g/dl), mean ± SD	11.01±1.59
Albumin (mg/dl) mean ± SD	3.54±0.55
<3.5	56 (43.8%)
≥3.5	72 (56.3%)
Total bilirubin (mg/dl), median (min-max)	7.95 (0.2 to 38.9)
<2	45 (35.2%)
≥2	83 (64.8%)
Pre-operative biliary drainage, n (%)	
No	90 (70.3)
Yes	38 (29.7)
Operative status	
Vessel resection	
No	108 (84.3%)
Yes	20 (15.6%)
Blood loss (ml), median (min-max)	625 (100 to 3,000)
Operative time (min), mean ± SD	369±85.10
Postoperative status	
In-hospital mortality, n (%)	5 (3.6)
Received adjuvant chemotherapy, n (%)	48 (37.5)
Received adjuvant radiotherapy, n (%)	13 (10.2)
Median survival time (month), median (min-max)	23 (0.26 to 60)
5-year overall survival rate (%)	21 (16)
3-year overall survival rate (%)	55 (43)
Recurrent rate, n (%)	65 (48)

pre-operative bilirubin level was 7.95 mg/dl (range 0.2 to 38.9 mg/dl), and 38 patients (29.7%) underwent pre-operative biliary drainage, mostly due to cholangitis.

Regarding pathological diagnosis, the most common cancer was pancreatic ductal adenocarcinoma with 60 (46.8%) patients. The remaining patients had non-pancreatic ductal adenocarcinoma, including: 35 (27.3%) with ampullary carcinoma, 14 (10.9%) with distal cholangiocarcinoma and 19 (14.8%) with duodenal adenocarcinoma. Patients with pancreatic ductal adenocarcinoma and ampullary carcinoma had a significantly higher pre-operative total bilirubin level compared to other cancers (12.95 and 15.7 mg/dl, respectively, *p* = 0.001). Mean pre-operative albumin level was 3.54 mg/dl with SD of 0.55 mg/dl, the difference of pre-operative albumin level was not significant between tumor types but tended to be higher in ampullary carcinoma (*p* = 0.053).

Median intra-operative blood loss was 625 ml (range 100 to 3,000 ml) and mean operative time was 369 minutes with SD of 85.1 minutes. Venous resection was performed in 20 (15.6%) patients, mostly associated with pancreatic adenocarcinoma (15 patients (25.4%), *p* = 0.027).

Pathology

The size of tumor of pancreatic ductal

adenocarcinoma and duodenal adenocarcinoma was significantly larger than ampullary carcinoma and distal cholangiocarcinoma ($p<0.001$). Free resection margin (R0 resection) was achieved in 92 patients (71.9%). The median number of obtained lymph nodes was 8 nodes (range 0 to 32) with 48% negative lymph node (N0). Median LNR was 0.11 (range 0 to 0.8). Forty-six (35.8%) patients had positive lymphovascular invasion, and 84 (65.6%) patients had positive perineural invasion. The pathological features of the tumors are described in Table 2.

Survival analysis

The overall 3-year and 5-year survival rates for all patients was 43% and 16%, respectively. Median overall survival for the cohort was 23 months (Figure 1). There was no difference in 5-year survival in terms of age or gender. Ampullary carcinoma patients had the longest survival, with 5-year survival rates of 25.7% and median survival of 37 months. On the other hand, pancreatic cancer and distal cholangiocarcinoma patients had worse prognosis (Figure 2). Several clinicopathologic factors were associated with survival on univariate and multivariate analyses as shown in Table 3 and Figure 3. Based on univariate analyses, pre-operative total bilirubin level ≥ 2 mg/dl, preoperative albumin level <3.5 g/dl, nodal status, LNR >0.2, positive resection margin, lymphovascular invasion and perineural invasion were demonstrated as significant prognostic factors for overall

Table 2. Tumor characteristics and staging

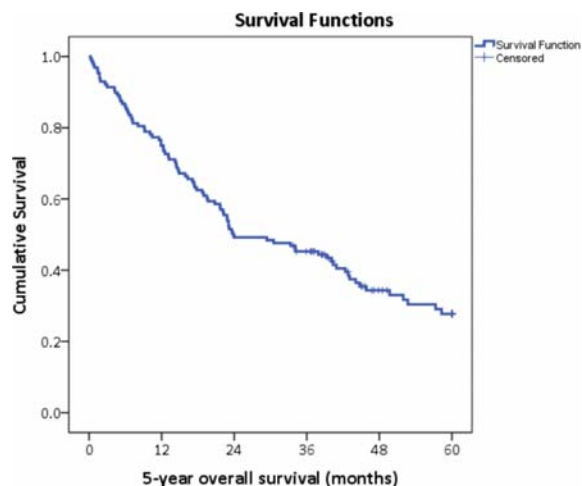| Variable	
Tumor location, n (%)	
Pancreatic ductal adenocarcinoma (head, uncinate process)	60 (46.8)
Ampullary carcinoma	35 (27.3)
Distal cholangiocarcinoma	14 (10.9)
Duodenal adenocarcinoma	19 (14.8)
Tumor size (cm), median (min-max)	2.5 (1 to 9)
Differentiation, n (%)	
Well	8 (6.3)
Moderate	113 (88.3)
Poor	6 (4.7)
Lymph node status	
Total node positive, median (min-max)	1 (0 to 17)
Node positive, n (%)	76 (52)
Node 8a positive, n (%)	4 (3)
Distant node positive, n (%)	6 (5)
Number of lymph node dissected, median (min-max)	8 (0 to 32)
Lymph node ratio (LNR), median (mix-max)	0.11 (0 to 0.8)
LNR <0.15	68 (53.1%)
LNR $\geq$0.15	58 (45.3%)
Lymphovascular invasion, n (%)	
No	82 (64.1)
Yes	43 (33.6)
Extensive	3 (2.3)
Perineural invasion, n (%)	
No	44 (34.4)
Yes	68 (53.1)
Extensive	16 (12.5)
Resection margin, n (%)	
R0	92 (71.9)
R1	33 (25.8)
R2	3 (2.3)
pT staging, n (%)	
T1	23 (17.9)
T2	54 (42.2)
T3	41 (32.0)
T4	10 (7.8)
pN staging, n (%)	
N0	52 (40.6)
N1	52 (40.6)
N2	24 (18.8)

Figure 1. 5-year overall survival rates of patients underwent pancreaticoduodenectomy
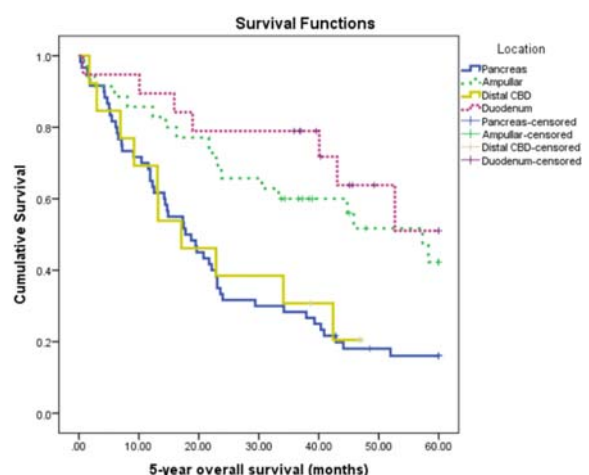

Figure 2. 5-year survival rates based on location of cancer.

Table 3. Predictors of overall survival

Variable	Crude HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Pre-operative biliary drainage, n (%)				
No				
Yes	1.147 (0.90 to 1.45)	0.26		
Total bilirubin (mg/dl), n (%)				
<2				
≥2	1.629 (1.02 to 2.59)	0.04	1.32 (0.79 to 2.20)	0.28
Tumor size (cm), n (%)				
Size <2 cm				
Size ≥2 cm	0.72 (0.04 to 1.3)	0.32		
pT staging, n (%)				
T1 T2				
T3 T4	0.75 (0.48 to 1.15)	0.19		
pN staging, n (%)				
N0	1.00		1.00	
N1	1.525 (0.93 to 2.49)	0.09	1.21 (0.61 to 2.43)	0.57
N2	2.58 (1.45 to 4.57)	0.001	2.98 (1.16 to 7.64)	0.02
LNR, n (%)				
LNR <0.15	1.00			
LNR ≥0.15	1.833 (1.19 to 2.82)	0.006	0.59 (0.28 to 1.26)	0.174
Total lymph node resected				
<12	1			
≥12	0.85 (0.53 to 1.36)	0.50		
Albumin (mg/dl), n (%)				
<3.5	1.92 (1.25 to 2.93)	0.03	1.71 (1.09 to 2.67)	0.02
≥3.5	1.00		1.00	
Resection margin, n (%)				
Negative	1.00		1.00	
Positive	2.54 (1.62 to 3.98)	<0.001	1.93 (1.19 to 3.14)	0.07
Lymphovascular invasion, n (%)				
No	1.00		1.00	
Yes + extensive	2.31 (1.49 to 3.58)	<0.001	1.73 (1.03 to 2.90)	0.03
Perineural invasion, n (%)				
No	1.00		1.00	
Yes	4.034 (2.32 to 7.00)	<0.001	3.49 (1.90 to 6.40)	<0.001

HR = hazard ratio, 95% CI = confidence interval

survival. By multivariate analysis, the significant independent factors were perineural invasion (HR: 3.94, 95% CI: 1.90 to 6.40, $p<0.01$), N2 nodal status (HR: 2.98, 95% CI: 1.16 to 7.64, $p = 0.02$), positive resection margin (HR: 1.93, 95% CI: 1.19 to 3.14, $p = 0.047$), lymphovascular invasion (HR: 1.73, 95% CI: 1.03 to 2.9, $p = 0.03$) and pre-operative albumin <3.5 g/dl (HR 1.71, 95% CI: 1.09 to 2.67, $p = 0.02$). Perineural invasion appears to be the strongest prognostic factor. Notably, pre-operative biliary drainage was not associated with overall survival in both univariate and multivariate analysis, as well as tumor size, operative time and intra-operative blood transfusion.

Discussion

This is a retrospective study for survival outcomes and prognostic factors of resected periampullary adenocarcinoma patients in a single tertiary university hospital. The patient demographic data was comparable to other reports from Western countries in terms of age and gender. However, the incidence of anatomical subtype of patients undergoing surgical resection was different[10,11]. In Thailand, the proportion of pancreatic head cancer patient was 46.9%, while the United States national cancer registry reported 68% of pancreatic head cancer patients. Pancreaticoduodenectomy rates for ampullary and duodenal adenocarcinoma in Thailand are slightly higher (27.3% and 20%, 14.7% and 9%, respectively)[12,13].

The overall 5-year survival rate was 16% and the median survival time was 23 months. Significantly, ampullary carcinoma had the most favorable outcome, with 5-year survival rate of 25.7%, while distal cholangiocarcinoma and pancreatic cancer patients had 5-year survival rate of 0% and 13.3%, respectively. The result of survival outcome is similar to the previous large population-based study in the United States[11].

Nodal involvement has been associated with unfavorable outcomes in various studies, specifically the number of lymph nodes examined and number of lymph
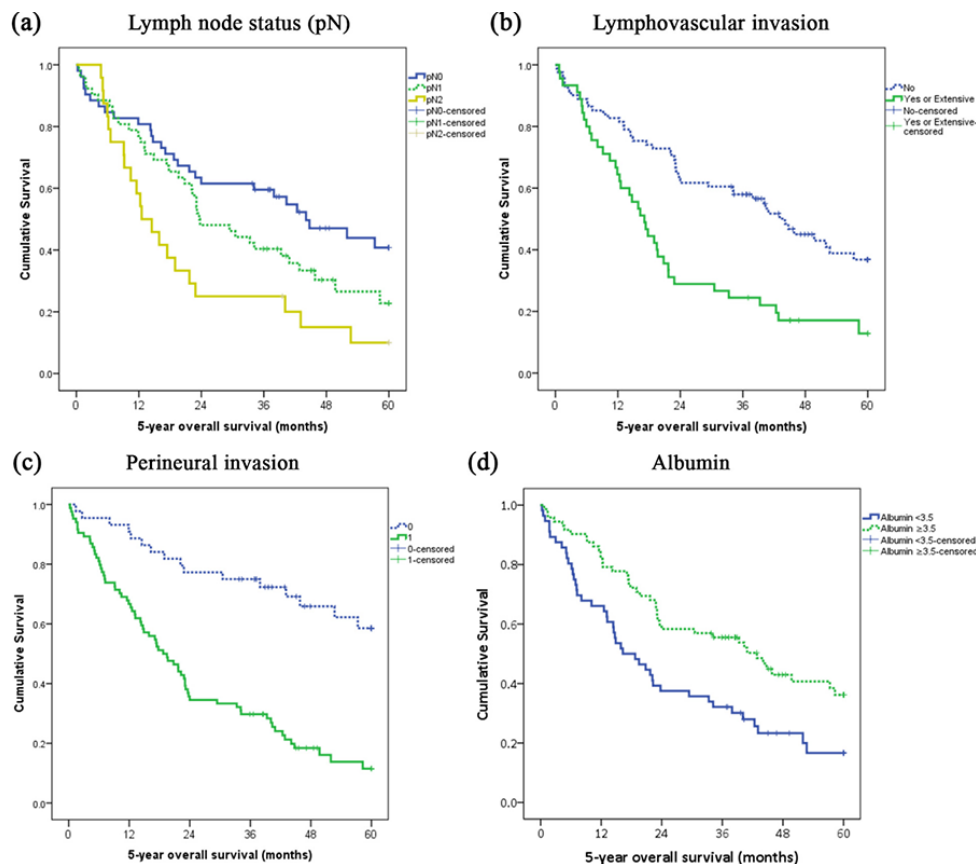
Figure 3.　5-year survival rates based on selected significant prognostic factors. (a) Lymph node status, (b) lymphovascular invasion, (c) Perineural invasion, (d) Serum albumin level.

node involvement. Recent investigations also suggest lymph node ratios (LNR) as strong prognostic predictors[14-16]. There is no consensus on adequacy of lymph node harvested, Gutierrez et al demonstrated 10 to 15 lymph node obtained as an important predictor for patient outcome[17]. According to this study, there was a relatively low number yield for ampullary and duodenal cancer[11], but the total number of nodes examined is not prognostically significant from univariate analysis. Pathological N2 status and LNR >0.15 was confirmed to be independent prognostic factors.

Perineural growth and lymphovascular invasion have been proposed to be important prognostic factors despite not being included in 8th edition of AJCC staging system[18-21]. This study showed perineural infiltration as the strongest independent prognostic factor. Median survival time in tumors with perineural invasion and extensive perineural invasion was 14.7 and 21.7 months, respectively ($p<0.05$). More than half of patients without perineural invasion survived after 5 years of follow-up. Lymphovascular invasion was also proved to be associated with survival ($p = 0.07$), and also significantly associated with perineural invasion.

Pre-operative nutritional status is also associated with patient outcome[22]. Almost half of patients in this study revealed pre-operative albumin level of less than 3.5 mg/dl. Compared with the patients with good nutritional status, those who had poorer nutritional status had larger tumor size, poor differentiation on histologic examination and the shorter median survival. These findings stress the importance of nutritional status evaluation and preoperative nutrition improvement.

There were numerous concerns on T staging category in 7th AJCC system, which categorized 80% patients as T3 lesion because of tumors extending beyond the pancreas. Therefore, 8th AJCC system stratified T category based on size alone[23,24]. Nevertheless, the study was unable to demonstrate T category as a prognostic factor for survival in neither univariate nor multivariate analysis (crude HR 0.72, 0.04 to 1.3, $p = 0.32$).

The survival benefit of preoperative biliary drainage remains unclear. Different studies reported diverse results[25,27]. Selective drainage is supported in the indicated cases including presence of cholangitis or postponement of surgery due to malnutrition. There was no significant

difference of survival outcome in terms of pre-operative biliary drainage in this study.

Conclusion

Poor prognostic factors for periampullary carcinoma after pancreaticoduodenectomy included lymph node status, perineural invasion, lymphovascular invasion and positive resection margin. Furthermore, a low albumin level was also associated with poor outcome. Therefore, radical surgical resection and pre-operative improvement of nutritional status should be of concern.

What is already known on this topic?

Survival rate of periampullary carcinoma may depend on various factors including primary tumor location, lymph node status, resection margin, perineural and lymphovascular invasion.

What this study adds?

Low serum albumin level also affects periampullary carcinoma outcome, therefore pre-operative evaluation and improvement of nutritional status in selected patients should be considered.

Potential conflicts of interest

The authors declare no conflicts of interest.

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การศึกษาอัตราการรอดชีวิตและปัจจัยพยากรณ์โรคของผู้ป่วย periampullary carcinoma ที่ได้รับการผ่าตัด pancreaticoduodenectomy ใน โรงพยาบาลศิริราช

ประวัฒน์ โฆสิตะมงคล, ธันยพร กำจรกิจบวร, ประเวช มหาวิทัตวงศ์, ชุติวิชัย โตวิกกัย, เวธิต ดำรงกิตติกุล, พลสิทธิ์ แสงเสริสถิตย์, สมชัย ลิ้มศรีจำเริญ, ยงยุทธ ศิริวัฒนอักษร

ภูมิหลังและวัตถุประสงค์: การผ่าตัด pancreaticoduodenectomy ถือเป็นการผ่าตัดรักษามาตรฐานในกลุ่มผู้ป่วย periampullary carcinoma ที่ได้ผลลัพธ์เป็นที่น่าพอใจ ในระยะยาว การศึกษานี้มีวัตถุประสงค์เพื่อประเมินผลลัพธ์ของการรักษาและปัจจัยพยากรณ์โรคในกลุ่มผู้ป่วยที่ได้รับการผ่าตัด pancreaticoduodenectomy ในโรงพยาบาล ระดับตติยภูมิ

วัสดุและวิธีการ: การวิจัยนี้จัดขึ้นเพื่อศึกษาอัตราการรอดชีวิตและปัจจัยพยากรณ์โรคคนไข้ periampullary carcinoma ที่ได้รับการผ่าตัด pancreaticoduodenectomy ในโรงพยาบาลศิริราช โดยเก็บข้อมูลย้อนหลังจากเวชระเบียนผู้ป่วยที่ได้รับการผ่าตัดตั้งแต่ ปี พ.ศ. 2554 ถึง ปี พ.ศ. 2558 วิเคราะห์ข้อมูลแบบหลายตัวแปร

ผลการศึกษา: พบว่ามีคนไข้จำนวน 128 คน ได้รับการผ่าตัด pancreaticoduodenectomy มีอัตราการรอดชีวิตโดยรวม 5 ปี ร้อยละ 16 และมี median survival time ที่ 23 เดือน ผู้ป่วยโรคมะเร็ง ampulla และ duodenum มีอัตราการรอดชีวิตโดยรวม 5 ปี สูงกว่าผู้ป่วยมะเร็งตับอ่อนและทางเดินน้ำดีส่วนปลายอย่างมีนัยสำคัญทางสถิติ ($p<0.01$) พบปัจจัยที่มีผลต่อการรอดชีพหลายตัวแปร ได้แก่ perineural invasion (HR: 3.94, 95% CI: 1.90 ถึง 6.40, $p<0.01$) การลุกลามไปยังต่อมน้ำเหลืองระยะ N2 (HR: 2.98, 95% CI: 1.16 ถึง 7.64, $p = 0.02$) การผ่าตัดโดยยังมีมะเร็งหลงเหลือ (positive margin) (HR: 1.93, 95% CI: 1.19 ถึง 3.14, $p = 0.047$) lymphovascular invasion (HR: 1.73, 95% CI: 1.03 ถึง 2.9, $p = 0.03$) และค่า albumin ก่อนผ่าตัดที่น้อยกว่า 3.5 mg/dl (HR 1.71, 95% CI: 1.09 ถึง 2.67, $p = 0.02$) คนไข้ที่มีภาวะทุพโภชนาการก่อนผ่าตัดมีแนวโน้มที่จะมีขนาดมะเร็งที่ใหญ่ (T3, T4) และมีการเจริญของมะเร็งแบบ poorly differentiated ส่วนค่า total bilirubin และการระบายน้ำดีก่อนผ่าตัดนั้นไม่มีผลต่ออัตราการรอดชีวิต

สรุป: ปัจจัยที่มีผลต่อการรอดชีพหลังผ่าตัด pancreaticoduodenectomy ในกลุ่มผู้ป่วย periampullary carcinoma ได้แก่ การลุกลามของต่อมน้ำเหลืองระยะ N2 perineural invasion lymphovascular invasion การผ่าตัดโดยยังมีมะเร็งหลงเหลือ และค่า albumin ในเลือดที่ต่ำ ดังนั้นการประเมินและแก้ไขภาวะทุพโภชนาการเป็นปัจจัยหนึ่ง ที่สำคัญที่ต้องคำนึงถึงก่อนพิจารณาผ่าตัด