The THAI Journal of SURGERY 2022;43(2):70-77.
Official Publication of The Royal College of Surgeons of Thailand

Original Article

Five-Year Survival and Prognostic Factors of Patients with Periampullary Carcinoma Who Underwent Pancreaticoduodenectomy

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Abstract

Objective: Periampullary carcinomas are defined as tumors that arise within 2 cm of the major papilla. The pancreaticoduodenectomy is the standard curative treatment for these tumors. However, the long-term survival may vary due to many factors. This study aimed to identify prognostic factors and 5-year survival of periampullary carcinoma; and to evaluate the surgical outcomes of a pancreaticoduodenectomy.

Patients and Methods: We conducted a retrospective review of the medical records of patients with periampullary carcinoma who underwent pancreaticoduodenectomy from January 2010 to December 2014 in a tertiary hospital. Patient characteristics, perioperative data and pathological data were analyzed. Univariate and multivariate analysis of prognostic factors for survival was analyzed by the Cox proportional hazard model. The Kaplan-Meier survival curve was used to describe survival rate. The *P*-value less than 0.05 was considered as statistically significant.

Results: Of 61 patients (with a median age of 58 years), cancer of the ampulla of Vater was the most common tumor. The 3-year and 5-year overall survival rates were 52.5% and 34.4%, respectively. The 30-day postoperative mortality rate was 4.9%. Median overall survival time is 37.4 months. The independent prognostic factors were lymphovascular invasion (hazard ratio (HR): 9.10, 95% confidence interval (95% CI): 2.51 to 32.96, $p = < 0.001$) and moderate or poor tumor differentiation (HR: 2.28, 95% CI: 1.08 to 4.84, $p = 0.03$).

Conclusion: In this study, the 5-year overall survival rate was 34.4%. Poor prognostic factors of periampullary carcinoma after pancreaticoduodenectomy included the presence of lymphovascular invasion and poor to moderate tumor differentiation.

Keywords: Periampullary carcinoma, Pancreaticoduodenectomy, Survival rate

Introduction

Periampullary carcinoma is defined as a tumor arising within 2 cm of the major papilla. It comprises cancer of the ampulla of Vater, distal common bile duct cancer, cancer presented in the second portion of the duodenum, and tumor of the pancreatic head.[1] The standard curative treatment for this condition is pancreaticoduodenectomy or its variation. Although these tumors have similar clinical presentations, anatomical location, and therapeutic approaches,[2,3] their long-term outcomes may vary.[2,4] Few studies in Thailand have reported the long-term survival and prognostic factors of these tumors.[5-7] This study aimed to investigate the 5-year survival and determine the factors affecting survival in patients who underwent pancreaticoduodenectomy for periampullary carcinoma at a tertiary hospital.

Received for publication 18 November 2021; Revised 13 May 2022; Accepted 17 May 2022

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Patients And Methods

Approval was obtained from the institutional review board. We proceeded to review the medical and surgical records of patients with periampullary carcinoma who underwent either pancreaticoduodenectomy or pyloric preserving pancreaticoduodenectomy from January 1, 2010 to December 31, 2014 in Maharat Nakhon Ratchasima Hospital.

We targeted the following data: patient characteristics (age, sex, comorbid diseases, history of cholangitis, preoperative biliary drainage, clinical signs and symptoms); laboratory data (total bilirubin, serum CA19-9, serum albumin); waiting time to surgery, postoperative chemotherapy, tumor characteristics (size, regional lymph node status, paraaortic lymph node status, margin status, superior mesenteric vein resection, histologic grade, lymphovascular invasion); type of surgery, estimated blood loss, operative time, recurrence rate, in-hospital and 30-day mortality rate, 3- and 5-year survival rates. The in-hospital mortality was defined death at any time during admission after surgery and 30-day mortality was defined as death within 30 days after surgery.

All the data were analyzed using the RStudio program version 1.2.5033 with R version 3.6.3. Continuous variables were presented as mean and standard deviation (SD), or as medians and ranges where appropriate. Categorical variables were presented as frequency and percentages. Survival time was defined as time between the day of surgery and the day of death from any cause, or last day of contact entered in the medical records. Univariate and multivariate analyses of survival prognostic factors were conducted via the Cox proportional hazard model. Kaplan-Meier survival estimation was used to describe survival rates. A *p*-value of less than 0.05 was considered statistically significant.

Results

Table 1 presents patient characteristics. This study included a total of 61 patients, all of whom underwent a pancreaticoduodenectomy. There were 32 men and 29 women, and the median age at the time of surgery was 58 years (range 34 to 78 years). Twenty-three patients (38%) were diagnosed with cholangitis prior to definitive treatment. These patients (with cholangitis) received preoperative drainage, mostly via endoscopic trans papillary stents. The most common comorbid diseases encountered were hypertension and diabetes mellitus in 15 patients (25%) and 12 patients (20%), respectively. A history of smoking was found in 14 patients (23%).

Table 1 Patient characteristics

Patient characteristics	Summary (n = 61)
Age (years): median (range)	58 (34 – 78)
Sex: n (%)	
Male	32 (53)
Female	29 (47)
Cholangitis before surgery: n (%)	23 (38)
Preoperative biliary drainage: n (%)	
Trans papillary stent	21 (34)
PTBD	3 (5)
T-tube	1 (2)
No drainage	36 (59)
Comorbid disease: n (%)	
DM	12 (20)
HT	15 (25)
DLP	6 (10)
Gout	3 (5)
Cardiac disease	4 (7)
Pulmonary disease	4 (7)
CKD	2 (3)
Other	6 (10)
Smoking: n (%)	
Yes	14 (23)
No	47 (77)
Presenting symptom: n (%)	
Obstructive jaundice	55 (90)
Abdominal pain	3 (5)
GI bleeding	1 (2)
Gastric outlet obstruction	2 (3)
Serum CA 19-9 (U/mL): median (range)	108.6 (0.8 - 63,542.6)
Elevated CA 19-9 (> 37 U/mL): n (%)	42 (70)
Total bilirubin (mg/dL): median (range)	12.4 (0.5 – 39.6)
Total bilirubin ≥ 2: n (%)	54 (89)
Serum albumin (mg/dL): n (%)	
< 3.5	37 (61)
≥ 3.5	24 (39)
Waiting time (days): median (range)	30 (4 – 95)
Adjuvant Chemotherapy: n (%)	27 (44)

Abbreviations: PTBD = Percutaneous Transhepatic Biliary Drainage, DM = Diabetes Mellitus, HT = Hypertension, DLP = dyslipidemia, CKD = Chronic kidney disease, GI bleeding = Gastrointestinal bleeding, CA = Cancer

The most common symptom was obstructive jaundice, which was found in 55 (90%) patients. The median total bilirubin was 12.9 mg/dL, which ranged between 0.5 to 39.6 mg/dL. Median serum CA19-9 level was 108.6 U/mL (range 0.8 to 63,542.6 U/mL) and there was 42 patients (69%) with elevated CA 19-9 (> 37 U/mL). Hypoalbuminemia (albumin < 3.5 mg/dL) was found in 37 (61%) patients. The median waiting time (time from the diagnosis to the surgery) was 30 days (range 4 to 95 days). Only 27 patients (44%) received adjuvant chemotherapy.

The primary tumor location in descending order of occurrence were ampulla of Vater in 39 patients (64%), pancreatic head in 17 patients (28%), distal common bile duct in 4 patients (7%), and duodenum in 1 patient (2%). The median tumor size was 2 cm for those located at the ampulla of Vater, 3.5 cm for the pancreatic head, 2.8 cm for the duodenum, and 5 cm for the distal common bile duct. Regional lymph node metastasis was found in 26 patients (43%). The median number of lymph nodes retrieved was 6 (range 0 to 43 lymph nodes). Concomitant superior mesenteric vein or portal vein resection was performed in 3 patients (5%). Regarding the histological grading of the tumors, the following was observed: 31 (51%) were well-differentiated, 27 (44%) were moderately differentiated, and 3 (5%) were poorly differentiated. Lymphovascular invasion was reported in 34 patients (56%). Negative resected margins were identified in 59 patients (97%). The pathological data of the tumors are displayed in Table 2.

The perioperative outcomes and survival data are summarized in Table 3. Forty-five patients (74%) underwent classical pancreaticoduodenectomy and 16 patients (26%) underwent pylorus-preserving pancreaticoduodenectomy. The median intra-operative blood loss was 1,000 mL (range 200 to 8,000 mL) and the median operative time was 335 minutes (range 180 to 645 minutes). Overall, postoperative complications occurred in 25 patients (41%). The occurrence of pancreatic fistulas was encountered in 5 patients (8%). Three patients (5%) underwent re-exploratory laparotomy for the treatment of intra-abdominal collection or postoperative bleeding. The median hospital stay was 19 days (range 10 to 102 days). Four patients died on the 2nd, 24th, 28th and 56th postoperative day respectively. The in-hospital mortality was 6.6% and the 30-day mortality rate was 4.9%.

The 3- and 5-year overall survival rates for patients were 52.5% and 34.4%, respectively. The median overall survival time for the cohort was 37.4 months, as presented in Figure 1. Patients diagnosed with ampullary carcinoma exhibited better survival rates compared to those with other types of cancer, with 3-year survival rates of 64.1% and 5-year survival rates of 46.1%.

Table 2 Pathological characteristics

Pathological characteristics	Summary (n = 61)
Tumor location: n (%)	
Ampulla of Vater	39 (65)
Pancreatic head	17 (28)
Duodenum	4 (5)
Distal CBD	1 (2)
Tumor size (cm) : median (range)	
Ampulla of Vater	2 (1 – 5)
Pancreatic head	3.5 (2 – 6)
Duodenum	2.75 (2 – 3)
Distal CBD	5 (5 – 5)
Total lymph node retrieved : median (range)	6 (0 – 43)
Positive regional lymph node: n (%)	26 (43)
Positive paraaortic lymph node: n (%)	1 (2)
SMV resection: n (%)	3 (5)
Histological grade: n (%)	
Well-differentiated	31 (51)
Moderately differentiated	27 (44)
Poorly differentiated	3 (5)
Lymphovascular invasion: n (%)	
No	27 (44)
Yes	34 (56)
Resection margin: n (%)	
Negative	59 (97)
Positive	2 (3)
Pathologic T staging: n (%)	
pT1	9 (15)
pT2	18 (30)
pT3	2 (3)
pT4	31 (51)
Pathologic N staging: n (%)	
pN0	34 (56)
pN1	17 (28)
pN2	10 (16)

Abbreviations: CA = Cancer, CBD = common bile duct, SMV resection = Superior Mesenteric Vein resection

The recurrence rate was 50.8% and the median time-to-recurrence was 14.4 months (range 3.6 to 42.4 months), as shown in Table 3. Figure 1 shows the overall 5-year survival curve of the 61 patients.

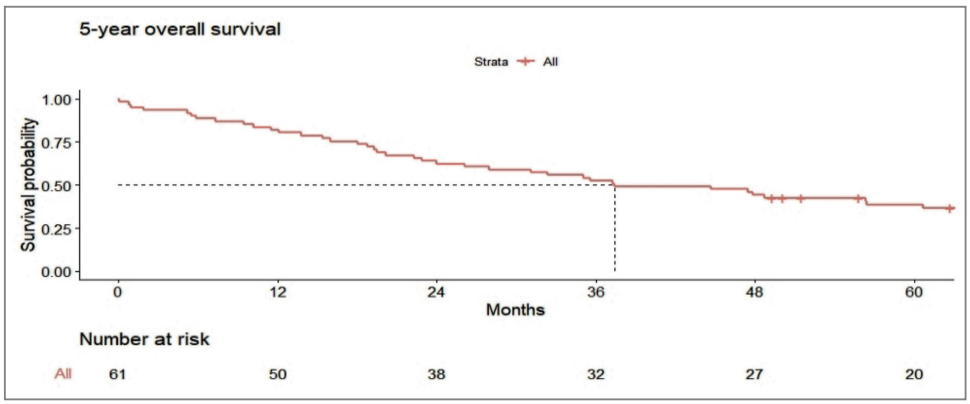

Figure 1 Overall survival rates at 5 years

Table 3 Perioperative outcomes and survival rates

Perioperative outcomes	Summary (n = 61)
Type of surgery: n (%)	
Classical pancreaticoduodenectomy	45 (74)
Pylorus-preserving pancreaticoduodenectomy	16 (26)
Estimated blood loss (ml) : median (range)	1,000 (200 – 8,000)
Operative time (min) : median (range)	335 (180 – 645)
Postoperative complication: n (%)	
Pancreatic fistula	5 (8)
Wound complications	4 (7)
Intra-abdominal collection	4 (7)
Enterocutaneous fistula	2 (3)
Post-pancreatectomy hemorrhage	1 (2)
Delayed gastric emptying	1 (2)
Respiratory complications	5 (8)
Renal complications	3 (5)
Hospital stays (days): median (range)	19 (10 – 102)
In-hospital mortality: n (%)	4 (7)
30-day mortality: n (%)	3 (5)
Median overall survival (months): median (range)	37.4 (0 – 60)
3-year survival: n (%)	
Overall	32 (53)
Ampullary cancer	25 (78)
Non ampullary cancer	7 (22)
5-year survival: n (%)	
Overall	21 (34)
Ampullary cancer	18 (86)
Non ampullary cancer	3 (14)
Recurrence: n (%)	
No	30 (49)
Yes	31 (51)
Time to recurrence (months) : median (range)	14.36 (3.58 – 42.35)

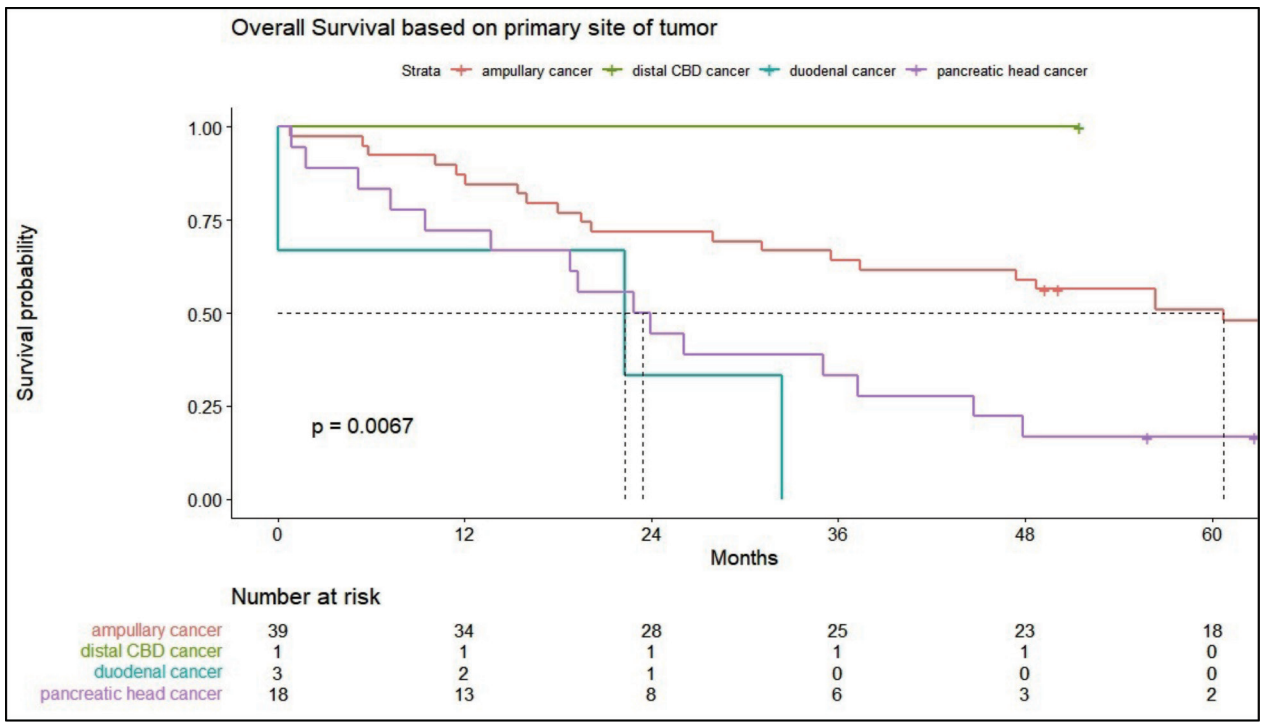

Figure 2 Overall survival based on primary site of tumor

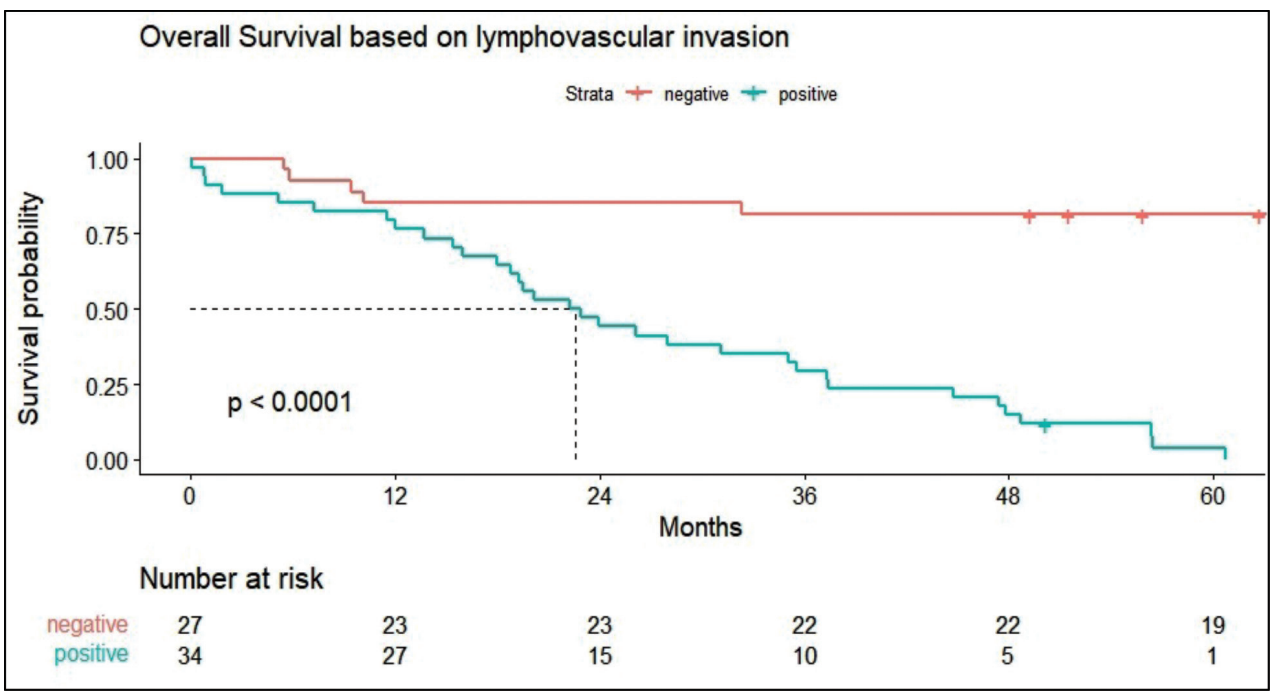

Figure 3 Overall survival based on lymphovascular invasion

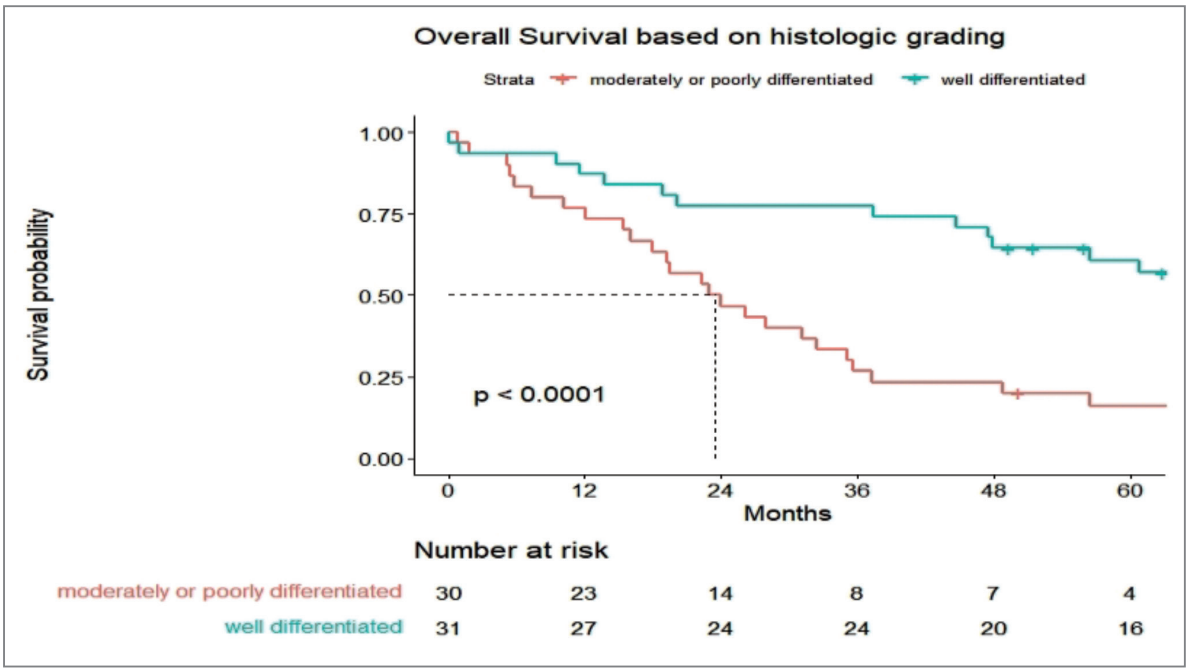

Figure 4 Overall survival based on histological grading

Table 4 Univariate analysis of prognostic factors

Factors	Crude HR (95% CI)	*P*-value
Age ≥ 65 years	1.12 (0.55, 2.30)	0.749
Male	1.36 (0.73, 2.55)	0.327
Smoking	1.22 (0.59, 2.50)	0.598
Cholangitis before surgery	1.23 (0.66, 2.30)	0.513
Preoperative biliary drainage	0.78 (0.41, 1.47)	0.4
Primary tumor location		
Ampulla of Vater	0.40 (0.21, 0.77)	0.006
Other locations	1	
Tumor size ≥ 2 cm	1.12 (0.55, 2.30)	0.749
Regional LN metastasis, Positive	7.38 (3.55, 15.34)	< 0.001
SMV resection (Yes)	2.92 (0.88, 9.72)	0.127
Positive resection margin	6.56 (1.47 – 29.25)	< 0.001
Lymphovascular invasion positive	12.43 (4.59 – 33.68)	< 0.001
Histological grade		
Well-differentiated	1	
Moderate or poorly differentiation	3.54 (1.83 – 6.87)	< 0.0001
Serum CA 19-9 (> 37 U/mL)	1.49 (0.73, 3.05)	0.258
Total bilirubin ≥ 2 mg/dL	0.72 (0.28, 1.83)	0.501
Serum albumin < 3.5 mg/dL	1.29 (0.67, 2.45)	0.441
Adjuvant chemotherapy (Yes)	1.54 (0.82, 2.89)	0.174

Abbreviations: LN = Lymph Node, SMV resection = Superior Mesenteric Vein resection

Table 5 Multivariate analysis of prognostic factors

Factors	Adjusted HR (95%CI)	*P*-value
Ampullary cancer	0.56 (0.28 – 1.13)	0.09
Regional lymph node positive	1.65 (0.68 – 4.02)	0.27
Margin positive	31.2 (0.67 – 15.11)	0.14
Lymphovascular invasion positive	9.10 (2.51 – 32.96)	< 0.001
Moderately or poorly differentiation	2.28 (1.08 – 4.84)	0.03
Adjuvant chemotherapy (Yes)	0.52 (0.25 – 1.07)	0.08

Several clinicopathological factors influenced the survival rates as revealed by the univariate and multivariate analyses shown in Tables 4 and 5. Based on univariate analyses; primary tumor location, nodal status, positive resection margin, lymphovascular invasion, and histological grading were identified as significant prognostic factors for survival. The independent prognostic factors identified from the multivariate analyses were the presence of lymphovascular invasion (HR: 8.11, 95% CI: 2.18 to 30.19, $p < 0.001$) and moderate or poorly differentiated tumors (HR: 2.18, 95% CI: 1.99 to 4.82, $p < 0.001$).

Figures 2 to 4 demonstrate the overall 5-year survival rate based on the primary tumor site, lymphovascular invasion, and histologic grading, respectively.

Discussion

In our study, the median age was 58 years with the male gender slightly predominating, with a male-to-female ratio of 1.1 : 1. Ampullary cancer (64%) occurred most commonly, followed by pancreatic head cancer (28%); our results differed from a study conducted in Western countries that reported pancreatic cancer as the most commonly occurring periampullary cancer.[8–11] The overall 5-year survival rate for periampullary cancer in this study was 34.4%. Ampullary cancer had a more favorable 5-year survival rate than that of other periampullary cancers (46.1% vs 13.6%). The lower survival rate in the second group might have been due to the fact that 77% of cancer in the second group was pancreatic head cancer, which is known to be more aggressive. The higher proportion of resectable ampullary cancer might be due to ampullary cancer usually causing symptom, e.g., obstructive jaundice, at the earlier stage of disease compared to pancreatic cancer. In patients with pancreatic cancer, the early stage of tumor may be asymptomatic[12]. However, there is no screening program for pancreatic cancer in Thailand. Therefore, symptomatic pancreatic cancer patient is usually at a more advanced stage with lower resectability than asymptomatic patients.

The 34.5% 5-year overall survival observed in the present study was higher than the 24% 5-year survival from a similar but larger American study based on the Surveillance, End Results and Epidemiology (SEER) database,[13] and higher than the 16% in a study from single tertiary hospital in Thailand.[6] The better 5-year overall survival than those reported in previous studies was found possibly because of the higher proportion of ampullary carcinoma in the present study.[6,7,13]

Pancreaticoduodenectomy or pylorus-preserving pancreaticoduodenectomy are curative surgical treatments for these tumors. In the present study, the hospital mortality rate was 6.6% and 30-day mortality rate was 4.9%. We also found that the lymphovascular invasion and histological grading of moderately or poorly differentiated tumors were significant prognostic factors. Chen et al. proposed that the total number of harvested lymph nodes and lymph node metastasis are significant prognostic factors.[14,15] However the present study did not demonstrate significant difference in survival by lymph node status. This might be explained by the relatively low number of lymph nodes harvested in the present study, as 21 out of 35 negative lymph nodes patients (60%) had the total number of harvested lymph nodes less than 10 lymph nodes. The recommended minimal number of harvested lymph nodes for optimal staging in periampullary carcinoma and pancreatic cancer is at least 10 lymph nodes.[16,17]

There were several limitations in the present study. Due to the small number of patients, we were unable to demonstrate significant differences in outcomes in terms of lymph node metastasis, margin status, tumor

size, primary tumor site, and adjuvant chemotherapy, as reported in other studies.[8–10,18,19] There were no data regarding perineural invasion, which could have been investigated as a prognostic factor for survival.[20] Only 44% of patients in the present study received adjuvant chemotherapy, the outcome after which could have significantly changed their survival rates.

Conclusion

The present study showed that the 3- and 5-year average overall survival rates were 52.5% and 34.4%, respectively, and lymphovascular invasion and higher histologic grading of tumors were independent poor prognostic factors, for periampullary cancer after pancreaticoduodenectomy.

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