RESEARCH ARTICLE

Prognostic Factors and Survival of Patients with Carcinoma of the Ampulla of Vater after Pancreaticoduodenectomy

Sunhawit Junrungsee*, Ekkapope Kittivarakul, Wasana Ko-iam, Worakitti Lapisatepun, Trichak Sandhu, Anon Chotirosniramit

Abstract

Background: Although carcinoma of the ampulla of Vater (CAV) is a rare tumor, accounting for just 0.2% of gastrointestinal cancers, the survival of CAV patients is unfavorable. The five-year rates have ranged from 36.8-75.2% in previous reports but there is a lack of data relating to Thai people. Also prognostic factors are controversial. **Objectives:** This study aimed to determine survival outcomes and to identify prognostic factors for a positive outcome for CAV patients after surgery. **Methods:** In this retrospective cohort study, data were collected from CAV patients who underwent surgery in Chiang Mai University Hospital from 2005 to 2012 for time to event analysis, the log rank test and univariate and multivariate Cox's regression analysis. **Results:** There were 72 CAV patients recruited, 45.8% being male. The mean age was 65.1 ± 10.5 years and the median waiting time for surgery was 56.5 days (24.5-91.5). The 30 day mortality rate was 5.6%., while 5-yr survival was 33.3%. The average disease free survival was 14.6 months. Prognostic factors relating to recurrence were positive lymph nodes (50% VS 19.6% p = 0.015) and advanced stage (44.1% VS 18.4% p = 0.023). Multivariate analysis showed that the potential prognostic factors for CAV patients included recurrence, moderate and poor differentiation, comorbidities and a tumor size > 2.0 cm. **Conclusions:** The findings of the study indicate that the overall survival of CAV patients after surgery is quite fair, with a tendency for better outcome with early as compared to advanced lesions. The key prognostic factors were recurrence, moderate and poor differentiation, comorbidity and tumor size > 2.0 cm.

Keywords: Ampulla of Vater carcinoma- pancreaticoduodenectomy- survival

Asian Pac J Cancer Prev, **18 (1)**, 225-229

Introduction

In Thailand, cancers are the commonest cause of death, being higher than cardiovascular events and trauma. Cancer of the ampulla of Vater is one of the periampullary cancers (cancer of ampulla of Vater, distal common bile duct, pancreas and duodenum). Cancer of the ampulla of Vater is uncommon, accounting for 0.2% of gastrointestinal malignancies and 6% of periampullary cancers.(Jemal et al., 2008) Although it has the best survival compared to other periampullary cancers the five year survival rate ranges from 36.8 to 78.8% and has not improved for the past two decades.(Talamini et al., 1997; Howe et al., 1998; Duffy et al., 2003; Bettschart et al., 2004; Brown et al., 2005; Di Giorgio et al., 2005; Riall et al., 2005; Yoon et al., 2005; Kim et al., 2006)

A recent study from China reported survival rate and prognostic factors which affect the survival rate of ampulla of Vater carcinoma in patients after pancreaticoduodenectomy.(Zhou et al., 2014) The prognostic factors identified are pancreatic invasion, lymph node metastasis and elevated CA19-9 level. There are several studies revealed T stage, tumor differentiated and chemotherapy also identified as prognostic factors(Talamini et al., 1997; Howe et al., 1998; Duffy et al., 2003; Di Giorgio et al., 2005; Kim et al., 2006; Woo et al., 2007; O'Connell et al., 2008) but there is no reported data in Thai people.

The primary aim of this study was to report the survival rate of ampulla of Vater carcinoma patients in Thailand and the secondary aim was to investigate prognostic factors which influenced the survival rate.

Material and Methods

All patients diagnosed with ampulla of Vater carcinoma at Chiang Mai University Hospital from 2005 to 2012 were retrospectively analyzed (72 patients included). Radical resection (Whipple's operation or pyloric preserving pancreaticoduodenectomy) was done in all patients. The area of lymph node dissection was performed by removal of all tissue around hepatoduodenal ligament (station 12), along common hepatic artery (station 8) and highest peri-pancreatic lymph node (station 13). The specimens were sent to pathologists for confirmation of the diagnosis and TNM staging was identified according to the American

*Division of Hepatobiliarypancreas Surgery, Department of Surgery, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand. *For Correspondence: sunhawit.j@cmu.ac.th*

Joint Committee on Cancer (AJCC) 7th Ed. staging system. The patients who had received palliative bypass, resection or had distant metastasis were excluded from the study. The data analysis included survival rate, tumor size, T staging, lymph node metastasis, tumor staging, free margin, tumor differentiation, elevated CA19-9, jaundice, waiting time for surgery, time to recurrence and chemotherapy. Almost of the patients who were jaundiced (total bilirubin more than 3 mg/dl) underwent percutaneous transhepatic biliary drainage (PTBD) or endoscopic retrograde cholangiopancreatography(ERCP) with internal stent before surgery.

Statistical analysis

A t-test/Mann Whitney U test were used to analyze the quantitative variables, Fisher's exact test was used for the analysis of qualitative variables. The time to event analysis was performed for survival comparisons. Cox's proportional hazard, univariate and multivariate analysis were performed to identify prognostic factors. A p-value of < 0.005 was regarded as statistically significant.

Results

There were 72 CAV patients included in the study. 12 out of 72 patients (16.7%) were lost to follow up in one year after surgery. Four patients (5.6%) were dead within 30 days after surgery; two from anastomosis bleeding, one from pneumonia and one from sepsis. There were more female patients than male (54.2% vs. 45.8%). Mean age was 65.2 years old. Patients usually presented with elevated CA 19-9 (61.1%), jaundice (66.7%) and without comorbidities (59.3%) regards to Charlson comorbidity index. (Quan et al., 2011) Median waiting time for surgery was 56.5 days (Interquartile range (IQR) 24.5-91.5). There was no difference in waiting time in jaundiced and none-jaundiced patients. Overall recurrence rate was 30.6% (22 patients). 36.3% of patients with recurrence received chemotherapy treatment (8 out of 22 patients) (Table 1).

Nearly three quarters of patients had a tumor size of more than 2 cm (72.2%). Using TNM staging, the distribution of patients was stage IA 11.1%, stage IB 29.2%, stage IIA 12.5%, stage IIB 25% and stage III 22.2%. 36.2% of patients had lymph node metastasis. The majority of tumors were well differentiated (83.3%). Only one patient was margin positive (R1 resection) (Table 1).

There were 22 patients who had recurrence of disease. In this group,13 patients (50%) had lymph node metastasis and 15 patients (44.1%) had advanced TNM staging (stage IIB and III). These two groups had a statistically significant higher rate of recurrence (50% ($p = 0.015$) and 44.1% ($p = 0.023$)). While T staging showed no statistical significance.

Baseline characteristics and tumor factors had been analyzed to know the distribution of number in dead and alive patients. These had shown the possible prognostic factors in the next step of data analysis (Table 2).

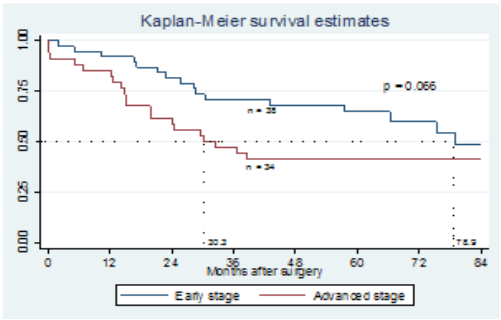
From the univariate analysis, the prognostic factors that effected survival were comorbidities (HR 2.62, 95% CI 1.36-5.06, $p = 0.004$), tumor size more than 2 cm (HR 3.11, 95% CI 1.21-8.02, $p = 0.019$), lymph node metastasis (HR 2.65, 95% CI 1.37-5.13, $p = 0.004$) and recurrence (HR 5.71, 95% CI 2.76-11.80, $p < 0.001$) (Table 3).

According to the multivariate analysis, recurrence (HR 5.90, 95% CI 2.71-12.84, $p < 0.001$), moderate and poor differentiation (HR 4.88, 95% CI 2.08-11.48.65, $p < 0.001$), comorbidity (HR 3.98, 95% CI 1.94-8.18,

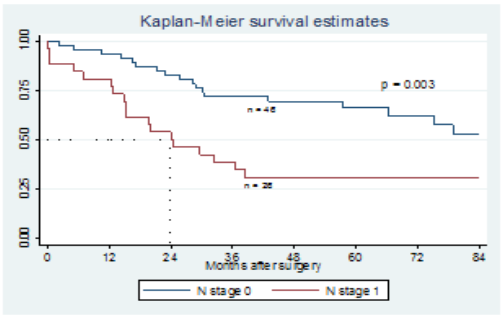
Table 1. Baseline Characteristics and Overall Descriptive Data of CAV Patients

Baseline characteristics	N = 72
Gender, n (%)	
Male	33 (45.8)
Female	39 (54.2)
Age, mean + SD	65.1 + 10.5
Tumor size (cm), n (%)	
< 2.0	20 (27.8)
≥ 2.0	52 (72.2)
T staging, n (%)	
Stage 1	8 (11.1)
Stage 2	31 (43.1)
Stage 3	17 (23.6)
Stage 4	16 (22.2)
N staging, n (%)	
Stage 0	46 (63.9)
Stage 1	26 (36.1)
TNM Stage, n (%)	
IA	8 (11.1)
IB	21 (29.2)
IIA	9 (12.5)
IIB	18 (25.0)
III	16 (22.2)
Free margin, n (%)	
Yes	71 (98.6)
No	1 (1.4)
Tumor differentiation, n (%)	
Well differentiated	60 (83.3)
Moderately	11 (15.3)
Poorly differentiated	1 (1.4)
CA19-9 (μ/mL), n (%)	
0–37	28 (38.9)
> 37	44 (61.1)
Total bilirubin (mg/dL), n (%)	
< 3	24 (33.3)
≥ 3	48 (66.7)
Waiting time (min), median (IQR)	56.5 (24.5-91.5)
30-day mortality, n (%)	4 (5.6)
Recurrence, n (%)	22 (30.6)
Chemotherapy, n (%)	8 (11.1)
Median survival time (month)	75.3
5-year survival, n/N (%)	24/72 (33.3)

N stage 0, No lymph node metastasis; N stage 1, Lymph node metastasis; IQR, Interquartile range



A. Survival Analysis of Patients with CAV after Surgery, by Stages



B. Survival Analysis of Patients with CAV after Surgery, by N Staging

Figure 1 A, B. Survival Analysis of Patients with CAV after Surgery, by Potential Clinical Factors

Table 2. Prognostic Factors for CAV Patients after Surgery

Prognostic factors	Dead (N = 36)	Alive (N = 36)	p value
Gender, n (%)			1
Male	16 (48.5)	17 (51.5)	
Female	20 (51.3)	19 (48.7)	
Age (mean + SD)	66.3 + 10.9	63.9 + 10.1	0.333
Comorbidity, n (%)			0.023
Yes	17 (70.8)	7 (29.2)	
No	19 (39.6)	29 (60.4)	
Waiting time (day), median (IQR)	43 (17-88)	65.5 (30.5-96)	0.253
Loss FU, n (%)			0.343
Yes	8 (66.7)	4 (33.3)	
No	28 (46.7)	32 (53.3)	
Tumor size (cm), n (%)			0.017
< 2.0	5 (25)	15 (75)	
≥ 2.0	31 (59.6)	21 (40.4)	
T staging, n (%)			0.477
Stage 1	2 (25)	6 (75)	
Stage 2	17 (54.8)	14 (45.2)	
Stage 3	8 (47.1)	9 (52.9)	
Stage 4	9 (56.3)	7 (43.7)	
N staging, n (%)			0.026
Stage 0	18 (39.1)	28 (60.9)	
Stage 1	18 (69.2)	8 (30.8)	
TNM stage, n (%)			0.238
Early stage	16 (42.1)	22 (57.9)	
Advanced stage	20 (58.8)	14 (41.2)	
Margin, n (%)			1
Negative	35 (49.3)	36 (50.7)	
Positive	1 (100)	0	

Table 2. Continued

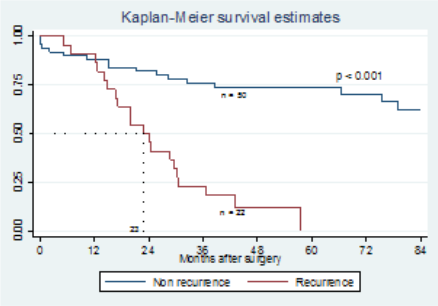
Prognostic factors	Dead (N = 36)	Alive (N = 36)	p value
Tumor differentiation, n (%)			0.111
Well differentiated	27 (45)	33 (55)	
Moderately differentiated	8 (72.7)	3 (27.3)	
Poorly differentiated	1 (100)	0	
CA19-9 (μ/mL), n (%)			1
0–37	14 (50)	14 (50)	
> 37	22 (50)	22 (50)	
Total bilirubin (mg/dL), n (%)			0.211
< 3	15 (62.5)	9 (37.5)	
≥ 3	21 (43.7)	27 (56.3)	
Chemotherapy, n (%)			0.26
Yes	6 (75)	2 (25)	
No	30 (46.9)	34 (53.1)	
Recurrence, n (%)			< 0.001
Yes	20 (90.9)	2 (9.1)	
No	16 (32)	34 (68)	

p < 0.001) and tumor size > 2.0 cm (HR 2.75, 95% CI 1.04-7.25, p = 0.041) were potential prognostic factors for the survival of CAV patients (Table 4).

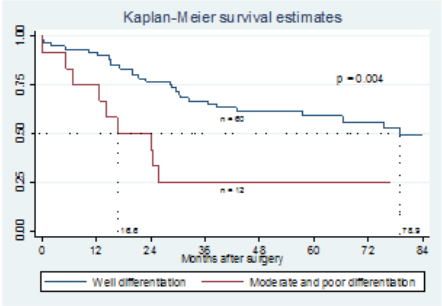
Overall 5 year survival rate of CAV patients was 33.3 months. Although overall median survival time was 75.3 months (Figure 1). The trend was that the early stages (stage IA, IB and IIA) had a higher median survival time than the advanced stages (stage IIB and III) (78.9 vs. 30.3 months, p = 0.066) (Figure 1A). Median survival times for patients with lymph node metastasis was 24 months which was significantly poorer than lymph node negative group (p = 0.003) (Figure 1B). Median survival times for patients with recurrence was 23 months (Figure 2A), patients with moderate or poor differentiation was 16.6 months (Figure 2B), patients with comorbidities was 21.3 months (Figure 2C) and a tumor size of more than 2 cm patients was 38.5 months (Figure 2D).

Discussion

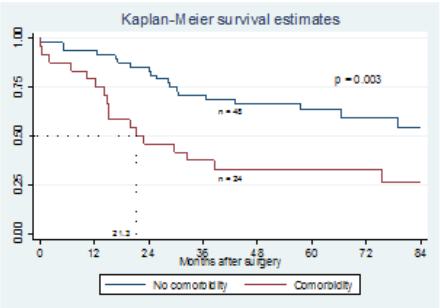
For many decades the outcomes for patients with carcinoma of the ampulla of Vater were unimpressive. The complete removal of the tumor by surgery was a key to prolonging the survival of patients. From the 1980s, local resection for early CAV patients was interesting topic but it had 10% of lymph node metastasis in early stage. (Clary



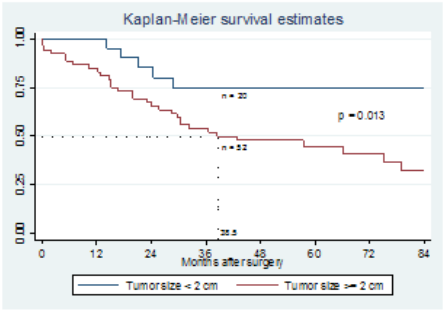
A. Survival Analysis of Patients with CAV after Surgery, by Recurrence



B. Survival analysis of patients with CAV after surgery, by tumor differentiation



C. Survival Analysis of Patients with CAV after Surgery, by Comorbidity



D. Survival Analysis of Patients with CAV after Surgery, by Tumor Size

Figure 2A, B, C, D. Survival Analysis of Patients with CAV After Surgery, by Prognostic Factors

Table 3. Univariate Analysis for Prognostic Factors for CAV Patients after Surgery

Factors	Crude Hazard ratio	95% CI	p-value
Comorbidity	2.62	1.36-5.06	0.004
Tumor size ≥ 2.0 cm	3.11	1.21-8.02	0.019
T staging	1.28	0.90-1.81	0.165
N Stage 1	2.65	1.37-5.13	0.004
TNM advanced stage	1.84	0.95-3.56	0.07
Positive margin	13.69	1.60-117.21	0.017
Moderate and poor differentiation	2.97	1.38-6.42	0.006
Elevated CA19-9 (>37 μ/mL)	1.02	0.52-1.99	0.957
Jaundice (total bilirubin ≥ 3 mg/dL)	0.71	0.37-1.38	0.311
Chemotherapy	1.94	0.80-4.73	0.144
Recurrence	5.71	2.76-11.80	< 0.001

Table 4. Multivariate Analysis for Potential Prognostic Factors for CAV Patients after Surgery

Factors	Adjusted Hazard ratio	95% Confidence interval	p value
Recurrence	5.9	2.71-12.84	< 0.001
Moderate and poor differentiation	4.88	2.08-11.48	< 0.001
Comorbidity	3.98	1.94-8.18	< 0.001
Tumor size > 2.0 cm	2.75	1.04-7.25	0.041

et al., 2000; Dixon et al., 2005; Demetriades et al., 2006; Lee et al., 2006; Yoon et al., 2007) Then, the risks and benefits might be adjusted for individual patients. In this study, the median overall survival time was 75.3 months which was comparable to a study from Di Giorgio(Di Giorgio et al., 2005) The postoperative mortality was higher than a recent study from China (5.6% vs. 4.32%) (Zhou et al., 2014).

In this study, all CAV patients with jaundice had the procedure preoperative PTBD or ERCP with internal stent performed and the bilirubin was checked until it was within normal limits before surgery(Abdullah et al., 2009). The waiting time in both jaundiced and none jaundiced patients were no different. This means that the preoperative biliary drainage procedure did not delay surgery and also that the waiting time was too long. One way to improve the outcome for the non-jaundiced patients would be to reduce the waiting time.

After surgery, there was no adjuvant chemotherapy. Again a possibility for the improvement of survival rates may be to use chemotherapy in high risk patients. (Narang et al., 2011) The high risk patients from this study refers

to the patients who had poor prognostic factors such as moderate or poor differentiation, large tumor size of more than 2 cm and lymph node metastasis which related to dead. Recurrence of tumor is obviously a key factor for poor survival. Once the patients had recurrence, the survival couldn't reach five years. It would be useful for a future study to focus on this.

Chemotherapy treatment in this study was restricted to recurrent patients. The surgeons sent recurrent patients to an oncologist who made the decision regarding chemotherapy treatment. Only 36.3% (8 of 22) of recurrent patients can receive chemotherapy. Majority of recurrent patients had poor performance status after recurrence was detected. There are rooms for improvement in follow up care. If it is possible to detect recurrence more earlier, we might achieve better survival in recurrent group.

There were many limitations in this study. First, this was a retrospective study, secondly, there was loss to follow up a significant number of patients (12 of 72, 16.7%) which meant this data was collected by phone, thirdly, the study had fewer CAV patients than the previous study and lastly the chemotherapy was only offered to some recurrent patients. If adjuvant chemotherapy was used the survival rate might be better.

The findings of this study indicate that the overall survival rate of CAV patients after surgery was quite fair (5 year survival rate = 33.3%), and the trend to better survival is in early stages when compared to advanced stages especially in lymph node negative group. The key prognostic factors were recurrence, moderate and poor differentiation, comorbidity and tumor size > 2.0 cm.

Disclosure: none

Grant or Financial support: none

Acknowledgments

The authors thank for many respected professors and research units of the Department of Surgery, Faculty of Medicine, Chiang Mai University, for helping in this study.

References

Abdullah SA, Gupta T, Jaafar KA, et al (2009). Ampullary carcinoma: effect of preoperative biliary drainage on surgical outcome. *World J Gastroenterol*, **15**, 2908-12.

Bettschart V, Rahman MQ, Engelken FJ, et al (2004). Presentation, treatment and outcome in patients with ampullary tumours. *Br J Surg*, **91**, 1600-7.

Brown KM, Tompkins AJ, Yong S, et al (2005). Pancreaticoduodenectomy is curative in the majority of patients with node-negative ampullary cancer. *Arch Surg*, **140**, 529-32.

Clary BM, Tyler DS, Dematos P, et al (2000). Local ampullary resection with careful intraoperative frozen section evaluation for presumed benign ampullary neoplasms. *Surgery*, **127**, 628-33.

Demetriades H, Zacharakis E, Kirou I, et al (2006). Local excision as a treatment for tumors of ampulla of Vater. *World J Surg Oncol*, **4**, 14.

Di Giorgio A, Alfieri S, Rotondi F, et al (2005). Pancreatoduodenectomy for tumors of Vater's ampulla: report on 94 consecutive patients. *World J Surg*, **29**, 513-8.

Dixon E, Vollmer CM Jr, Sahajpal A, et al (2005). Transduodenal resection of peri-ampullary lesions. *World J Surg*, **29**, 649-52.

Duffy JP, Hines OJ, Liu JH, et al (2003). Improved survival for adenocarcinoma of the ampulla of Vater: fifty-five consecutive resections. *Arch Surg*, **138**, 941-8.

Howe JR, Klimstra DS, Moccia RD, et al (1998). Factors predictive of survival in ampullary carcinoma. *Ann Surg*, **228**, 87-94.

Jemal A, Siegel R, Ward E, et al (2008). Cancer statistics, 2008. *CA Cancer J Clin*, **58**, 71-96.

Kim RD, Kundhal PS, McGilvray ID, et al (2006). Predictors of failure after pancreaticoduodenectomy for ampullary carcinoma. *J Am Coll Surg*, **202**, 112-9.

Lee SY, Jang KT, Lee KT, et al (2006). Can endoscopic resection be applied for early stage ampulla of Vater cancer?. *Gastrointest Endosc*, **63**, 783-8.

Narang AK, Miller RC, Hsu CC, et al (2011). Evaluation of adjuvant chemoradiation therapy for ampullary adenocarcinoma: the Johns Hopkins Hospital-Mayo Clinic collaborative study. *Radiat Oncol*, **6**, 126.

O'Connell JB, Maggard MA, Manunga J Jr, et al (2008). Survival after resection of ampullary carcinoma: a national population-based study. *Ann Surg Oncol*, **15**, 1820-7.

Quan H, Li B, Couris CM, et al (2011). Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*, **173**, 676-82.

Riall TS, Cameron JL, Lillemoe KD, et al (2005). Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma part 3: update on 5-year survival. *J Gastrointest Surg*, **9**, 204-6.

Talamini MA, Moesinger RC, Pitt HA, et al (1997). Adenocarcinoma of the ampulla of Vater. A 28-year experience. Ann Surg, 225, 590-9.

Woo SM, Ryu JK, Lee SH, et al (2007). Recurrence and prognostic factors of ampullary carcinoma after radical resection: comparison with distal extrahepatic cholangiocarcinoma. *Ann Surg Oncol*, **14**, 3195-201.

Yoon SM, Kim MH, Kim MJ, et al (2007). Focal early stage cancer in ampullary adenoma: surgery or endoscopic papillectomy?. *Gastrointest Endosc*, **66**, 701-7.

Yoon YS, Kim SW, Park SJ, et al (2005). Clinicopathologic analysis of early ampullary cancers with a focus on the feasibility of ampullectomy. *Ann Surg*, **242**, 92-100.

Zhou J, Zhang Q, Li P, et al (2014). Prognostic factors of carcinoma of the ampulla of Vater after surgery. *Tumour Biol*, **35**, 1143-8.