

## Randomized Controlled Trial

**Outcome of curative resection for perihilar cholangiocarcinoma in Northeast Thailand**

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## Abstract

**AIM:** To examine survival outcomes of perihilar cholangiocarcinoma (PCCA) resection including mortality, morbidity and prognostic factors.

**METHODS:** Multivariate analyses were carried out based on the survival data of all patients with histologically confirmed PCCA who underwent curative resection at Srinagarind Hospital from January 2006 to December 2011.

**RESULTS:** There were 29 (19%) cases of intrahepatic CCA that involved hilar and 124 (81%) with hilar bile-duct cancer. R0 resection was carried out on 66 (43.1%) patients of whom 50 (32.7%) also had lymph node metastasis. The other patients underwent R1 resection. The overall 5-year survival rate was 20.6% (95%CI: 13.8-28.4) and median survival time was 19.9 mo. Postoperative mortality was 2%, and 30% of patients had complications. Patients without lymph node metastasis were 60% less likely to die than those with metastasis. Achieving R0 led to a 58% reduction in the chance of mortality as compared to R1.

**CONCLUSION:** To achieve a better survival outcome, focus should center on performing radical surgery and detection of patients with early stage cancer.

**Key words:** Perihilar cholangiocarcinoma; Thailand; Curative resection; Five-year survival; Prognostic factors

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**Core tip:** Cholangiocarcinoma is usually fatal because detection most commonly occurs during late stage disease. Early detection leads to a substantially better survival outcome. Thus, priority should be placed on early stage detection allowing curative radical surgery.

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## INTRODUCTION

Cholangiocarcinoma (CCA) is the most common primary liver cancer in the northeast of Thailand where it has its highest incidence worldwide<sup>[1,2]</sup> and where it is one of the major causes of death. CCA is divided into three types according to the location of the primary tumor. Perihilar cholangiocarcinoma (PCCA) is the most common type. It occurs when the tumor originates or includes the confluence of the

hepatic duct and accounts for 67% of all cases. It is followed by distal cholangiocarcinoma and intrahepatic cholangiocarcinoma which account for 27% and 6% of cases, respectively<sup>[3]</sup>.

PCCA requires a major hepatectomy with bile duct resection, caudate lobectomy and regional lymphadenectomy to achieve a free margin resection and the best survival outcome<sup>[4-6]</sup>. Due to the anatomical complexity of the hepatic hilum, early lymphatic metastasis and vascular invasion, various techniques have been used to achieve margin negative resection (R0) to improve survival outcome and to reduce operative mortality<sup>[7]</sup>.

Because caudate bile ducts are open to hepatic duct confluence, most PCCA have microscopic tumor invasion to the caudate lobe<sup>[8]</sup>. Caudate lobectomy is necessary to achieve margin negative resection and better survival without increasing post-operative mortality<sup>[9,10]</sup>. Preoperative biliary drainage (PBD) is performed to relieve suffering from jaundice or cholangitis as it reduces postoperative morbidity and mortality in patients who undergo right hepatectomy, who have a future liver remnant volume of  $\leq 30\%$ <sup>[11,12]</sup> and a preoperative total bilirubin of  $\geq 170 \mu\text{mol/L}$  (10 mg/dL)<sup>[13]</sup>. It is not recommended that PBD be performed systemically due to potential complications such as sepsis, vascular injuries, and tumor seeding. Preoperative portal vein embolization (PVE) is widely used for pre-operative preparation to induce hypertrophy of remnant liver. It has resulted in minimized post-operative complications especially in cirrhotic patients<sup>[14]</sup> or future liver remnant volume (FLR)  $< 25\%$  in normal liver<sup>[15]</sup>. Right or left trisectionectomy is performed for Bismuth IV PCCA and patients show an increasing number of margin negative resections and also improved long-term survival<sup>[16-18]</sup>. Combined major hepatectomy with portal vein and hepatic artery resection have high R0 resection with acceptable mortality<sup>[19,20]</sup>.

Although outcomes of curative resection for PCCA have continuously been improving over the last decade, the 5-year survival rate is unsatisfactorily low. This has also been the case for Thailand where there are few studies on the outcome of curative resection for PCCA and 5-year survival, even though advances have been made in early stage diagnosis and surgical procedures. This study addresses this limitation in Thailand. It is based on a large cohort size and examines survival outcomes of PCCA liver resection including mortality, morbidity and prognostic factors.

## MATERIALS AND METHODS

Between January 2006 and December 2011, 153 patients from northeast Thailand received curative hepatic resection for PCCA at Srinagarind Hospital, Khon Kaen, the tertiary referral center for northeast Thailand. Data relating to patient survival are examined and compared. We excluded patients who had gross residual tumor and required palliative procedures. Patient

**Table 1** Characteristics of the 153 of patients with perihilar cholangiocarcinoma presented as number and percentage unless specified otherwise

Characteristics	n (%)
Gender	
Male	113 (73.9)
Female	40 (26.1)
Mean $\pm$ SD of age (yr)	56.8 $\pm$ 8.22
Symptoms	
Median (min-max) duration (d)	60 (3-300)
Abdominal discomfort	92 (60.1)
Jaundice	90 (58.8)
Weight loss	37 (24.2)
Fever	18 (11.8)
Co-morbidity	32 (20.9)
Hypertension	14 (9.1)
Diabetes mellitus	15 (9.8)
Renal failure	2 (1.3)
Chronic obstructive pulmonary disease	4 (2.6)
Hepatitis	3 (1.9)
Others	6 (3.9)

survival was measured from the day of operation until death or the end of the study on 19 September 2014 so that there was a minimum follow-up of 33 mo. This study was approved by Institutional Ethics Committee, Khon Kaen University, No. 571283.

We report continuous data as mean  $\pm$  SD, and range. Categorical variables were reported as percentages. Median survival time and the 5-year survival were estimated using Kaplan-Meier methods. Log-rank test was used to compare survival experience between selected groups of patients. Cox proportional hazard model was used to determine factors affecting the overall survival. Initially we explored the effect of each factor, independently, on the survival. Based on the results from these bivariate models, all variables with a p-value of less than 0.2 were included into the full model as the starting of the model fitting using backward elimination processes. The least significant factor was removed from the full model, one at a time, where its effect on the model was assessed using a likelihood ratio test. In the final model that contained all factors that were statistically significant survival was used as the basis to estimate the hazard ratios and their 95%CI. Tests for proportional hazard model assumptions and model's goodness-of-fit were also implemented. A P value of  $\leq$  0.05 was considered statistically significant. All statistical analyses were done using Stata version 13 (Stata Corp, College Station, TX, United States).

## RESULTS

Of the 153 patients included in the analysis, 113 (73.9%) were male and 40 (26.1%) were female with a combined mean age of 56.8  $\pm$  8.2 years (Table 1). Most of the patients presented with abdominal discomfort 92 (60.1%) and jaundice 90 (58.8%). Thirty seven patients showed weight loss (24.3%) and 18 had fever (11.8%). The median duration of symptoms was 60 d

**Table 2** Type and staging of perihilar cholangiocarcinoma

Characteristics	n (%)
Type	
Bismuth I	5 (3.3)
Bismuth II	9 (5.9)
Bismuth IIIa	65 (42.5)
Bismuth IIIb	41 (26.8)
Bismuth IV	4 (2.6)
Right intrahepatic mass involving hilar	22 (14.4)
Left intrahepatic mass involving hilar	7 (4.6)
Staging	
Stage 0	9 (5.9)
Stage I	9 (5.9)
Stage II	65 (42.5)
Stage IIIa	17 (11.1)
Stage IIIb	47 (30.7)
Stage IVa	4 (2.6)
Stage IVb	2 (1.3)

(range 3-300 d). Thirty two patients had co-morbidity that included hypertension, diabetes, renal failure, pulmonary disease and hepatitis.

### Classification of resected tumors

Most tumors originated from the hepatic hilum, namely, 5 patients (3.3%) with Bismuth type I, 9 (5.9%) Bismuth type II, 65 (42.5%) Bismuth type IIIa, 41 (26.8%) Bismuth type IIIb, and 4 (2.6%) Bismuth type IV. There were 29 patients who had intrahepatic mass with hilar invasion (Table 2).

According to the American Joint Cancer Committee (AJCC) staging for perihilar bile duct tumors 7<sup>th</sup> edition patients were group as carcinoma in situ ( $n = 9$ , 5.9%), stage I ( $n = 9$ , 5.9%), stage II ( $n = 65$ , 42.5%), stage IIIa ( $n = 17$ , 11.1%), stage IIIb ( $n = 47$ , 30.7%), stage IVa ( $n = 4$ , 2.6%), and stage IVb ( $n = 2$ , 1.3%), patients who had intrahepatic tumor were also included in this staging system. Four patients with stage IVa, Bismuth type IV were classified as T4, and all underwent curative trisectionectomy. Two patients with stage IVb had celiac lymph node metastasis all of whom underwent curative resection with extensive lymphadenectomy.

Patients who had co-morbidity were group as carcinoma in situ ( $n = 3$ , 9.4%), stage I ( $n = 1$ , 3.1%), stage II ( $n = 18$ , 56.2%), stage IIIa ( $n = 3$ , 9.4%), stage IIIb ( $n = 7$ , 21.8%) and none were in stage IV.

Histological findings showed 91 papillary adenocarcinoma (59.4%), 58 tubular adenocarcinoma (37.9%), 1 adenocarcinoma with squamous metaplasia (0.6%), 2 poorly differentiated adenocarcinoma (1.3%), and 1 undifferentiated carcinoma (0.6%).

### Preoperative preparation

The 90 patients who presented with jaundice had a mean total bilirubin level of 17.6 mg/dL. A total of 37 patients (41%) underwent preoperative percutaneous biliary drainage with a decrease in total serum bilirubin to 3.9 mg/dL on the day before surgery. Fifty-three

**Table 3** Preoperative biliary drainage in jaundice patients (*n* = 90)

	<b>Biliary drainage 37 (41%)</b>	<b>Non-biliary drainage 53 (59%)</b>	<b><i>P</i> value</b>
TB at presentation (mean ± SD)	19.4 ± 10.5	12.1 ± 15.8	0.06
TB at day before surgery (mean ± SD)	3.9 ± 4.1	17.1 ± 14.3	0.04
Post-operative complication	35%	37.70%	0.80
Length of hospital stay (mean ± SD)	15.6 ± 9.7	16.3 ± 7.6	0.56
Mortality (%)	0	2 (3.7)	-
Median survival time, mo (95%CI)	30.4 (16.3-58.7)	17 (12.2-26.6)	0.02
5-year survival rate, %(95%CI)	29.5 (14.1-46.7)	7.3 (0.9-22.4)	0.02

TB: Serum total bilirubin.

patients (59%) underwent surgery without preoperative drainage. These had a total serum bilirubin of 17.1 on the day before surgery (Table 3).

Combined preoperative portal vein embolization (PVE) was performed on 10 patients (6.5%) who had an estimated small FLR, right hepatectomy on 4 patients, extended right hepatectomy on 5 patients and one patient underwent left hepatectomy.

### Operative procedure

Major hepatectomy was carried out on 145 patients comprising 63 patients who underwent right hepatectomy, 35 patients who underwent extended right hepatectomy including trisectionectomy and 47 patients who had a left hepatectomy. Extrahepatic bile duct resection alone was performed in 8 patients due to limited tumor involvement. Mean operative time was 326 ± 125 min, blood loss was 1274.2 ± 1312.5 mL and length hospital stay was 15 ± 8.2 d.

Post-operative complications occurred in 70.3%, 37.1%, 29.8% of right hepatectomy, right extended hepatectomy and left hepatectomy patients, respectively. There were no significant differences in operative time, blood loss or length of hospital stay between the major hepatectomy procedures.

Combined portal vein resection was performed in 12 patients (7.8%). Mean operative time was 463.3 ± 101.1 min, blood loss was 1804.2 ± 1664.6 mL and length hospital stay was 17.7 ± 8.7 d.

R0 resection was achieved 31.7%, 37.5%, 51.4% and 53.2% of right hepatectomy, bile duct resection, right extended hepatectomy and left hepatectomy patients, respectively. Overall R0 resection was achieved in 66 (43.1%) of patients and R1 (indicated by microscopic residual tumor) in 87 (56.6%) of patients (Table 4).

### Operative morbidity and mortality

Mortality at 30 d was 2% with 1 patient dying of postoperative bleeding, renal failure and myocardial infarction, and 2 patients dying after being discharged from hospital. Post-operative complications occurred in

46 patients (30%). Four patients had post-operative bleeding (2.6%) and all underwent re-operation. There were 13 patients who had bile leakage (8.5%) all of whom received conservative treatment. Eleven patients had intra-abdominal collection, 7 of whom underwent percutaneous drainage. There were pleural effusions in 12 patients (7.8%), 9 (5.9%) had wound infection, 7 (1.2%) developed pneumonia, and 2 (1.3%) had urinary tract infection. Jaundice patients who underwent preoperative biliary drainage had comparable post-operative complications, mortality and length of hospital stay to non-biliary drainage patients (Table 3).

### Survival analysis

Median survival time after curative resection was 19.9 mo (95%CI: 14.2-23.8; Figures 1 and 2A). Patients with R0 had the longest median survival time of 40.2 (95%CI: 22.4-57.9) mo. The overall survival rate was 68% (95%CI: 60%-74.7%) after 1 year, 33.7% (95%CI: 26.3%-41.2%) after 3 years, and 20.6% (95%CI: 13.8%-28.4%) after 5 years (Figure 3).

### Survival according to stage

Following are survival rates according to the AJCC staging for perihilar bile duct tumor 7<sup>th</sup> edition 2010, including all 153 patients. Stage 0, 5-year survival rate was 71.1% (95%CI: 23.3%-92.3%); Stage I, 5-year survival rate was 51.8% (95%CI: 16.4%-78.8%); Stage II, 5-year survival rate was 25.3% (95%CI: 15%-37%); Stage IIIa, 5-year survival rate was 17.6% (95%CI: 4.3%-38.3%); Stage IIIb, 5-year survival rate was 2.68% (95%CI: 0.2%-11.8%); Stage IVa and stage IVb had no 5-year survival rate. The patient groups with an early stage showed significantly better long-term survival (*P* < 0.001).

Twenty-nine patients who had intrahepatic tumor all had tumor with periductal invasion or nodal metastasis, according to AJCC staging for intrahepatic bile duct tumor 7<sup>th</sup> edition 2010, they were in stage IVa. The 5-year survival rate was 20.1%, median survival time was 14.9 mo comparable to overall survival (*P* = 0.39)

### Survival according to residual tumor status

R0 resection resulted in a significantly better survival with 5-year survival rate of 35.6% (95%CI: 23.1%-48.3%) compared to R1 resection which resulted in a 5-year survival rate of 6.4% (95%CI: 0.9%-20.3%; *P* < 0.001) (FigureS 2B and 3).

### Survival according to histopathology

Lymph node metastasis had a major influence on the patient's survival. The 5-year survival rate of lymph node negative (N0) patients was 29.7% (95%CI: 20%-40%), while for lymph node metastasis (N1) patients it was 2.5% (95%CI: 0.2%-11.1%; *P* < 0.001) (Figures 2C and 3).

There was very good long-term survival in the lymph node negative patients within the R0 group. The 5-year survival rate was significantly higher in the R0N0

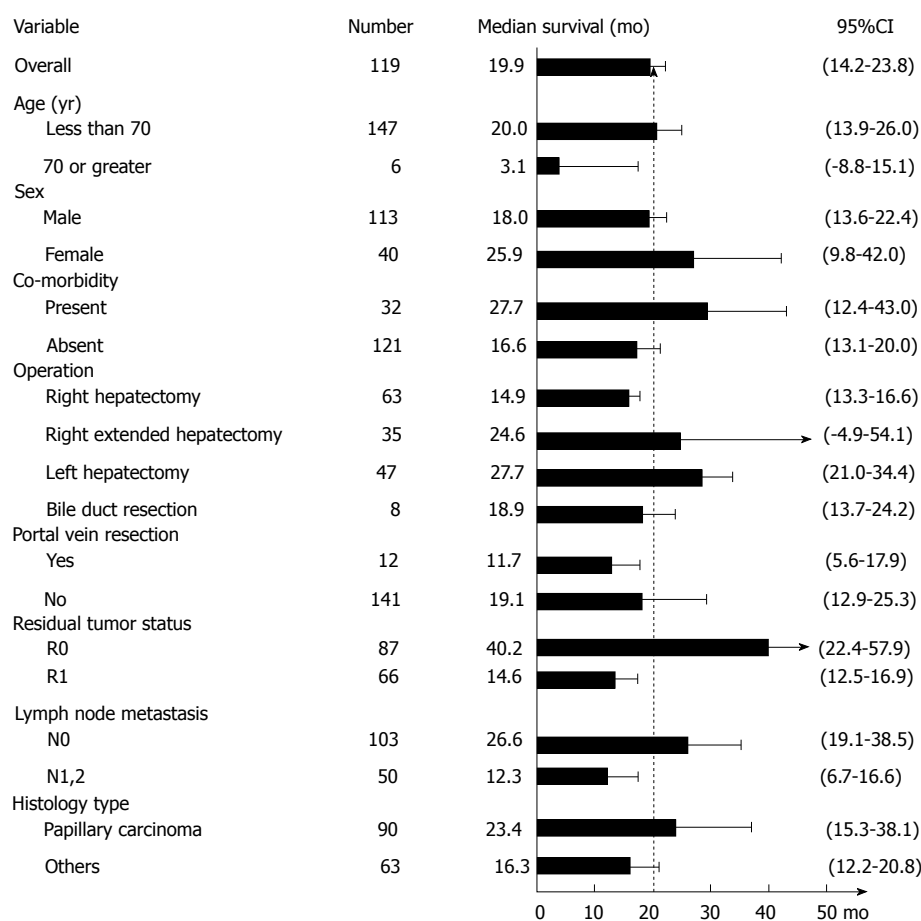


Figure 1 Median survival (mo) of clinico-pathological parameters.

group 47% (95%CI: 31.2%-61.3%) compared with the R1 or N1 groups 6.9% (95%CI: 2%-16.3%;  $P < 0.001$ ) (Figure 2D).

### Bivariate and multivariable survival analyses

The results of our bivariate analysis are shown in Table 5. There are 4 significant parameters associated with long-term survival: age  $< 70$  ( $P = 0.003$ ), residual tumor status ( $P < 0.001$ ), lymph node metastasis ( $P < 0.001$ ), and papillary histology type ( $P = 0.012$ ). In the multivariable model, where the effect of age was taken into account, however, only the 3 factors excluding age were significantly associated with overall survival (Table 6). Achieving R0 resulted in a 58% (HR = 0.42; 95%CI: 0.28-0.62;  $P < 0.001$ ) reduction in the chance of mortality as compared to R1. Likewise, patients without lymph node metastasis were 60% (HR = 0.40; 95%CI: 0.27-0.59;  $P < 0.001$ ) less likely to die than those who had metastasis.

Patients with other types of invasive cholangiocarcinoma had a 58% (HR = 1.58; 95%CI: 1.08-2.30;  $P = 0.018$ ) higher chance of mortality as compared to papillary carcinoma.

## DISCUSSION

Results from this study showed that curative resection

of PCCA in Srinagarind hospital, Khon Kaen, Thailand had low perioperative morbidity, mortality and a 5-year survival rate comparable to recent studies. Five-year survival after curative resection for PCCA in Asia ranges from 0% to 64%<sup>[7,10,17-19,21-26]</sup> and in North America and Europe from 10% to 38%<sup>[4,27-29]</sup>, post-operative morbidity was 26.3%-75% and mortality rates were 0%-11% (Table 7). There are only two previous studies from Thailand<sup>[23,26]</sup>, and one review article by Khuntikeo *et al*<sup>[30]</sup>, which found a 5-year survival of 0%-10.8%. The substantial improvements shown in our northeast Thailand cohort are most likely to be due to better, more radical surgical procedures, patient selection, and preoperative care.

This study did not show that preoperative biliary drainage in jaundice patients reduced post-operative complications, mortality or length of hospital stay. Preoperative biliary drainage patients showed a better rate of survival, but this was not significant in multivariate analysis.

A small number of patients underwent preoperative PVE because CT was not used to estimate remnant liver volume. The benefit of PVE could not be evaluated due to lack of clear indications.

We found that patients who had co-morbidity had a better survival outcome because these patients regularly had medical attention that increased the

**Table 4 Operative procedure**

Procedures	n (%)	Operative time; min (mean ± SD)	Blood loss; mL (mean ± SD)	Hospital stay; d (mean ± SD)	Morbidity	RO
Overall	153	326 ± 125	1274.2 ± 1312.5	15 ± 8.2	30%	43.1%
Right hepatectomy	63 (41.2)	334.3 ± 118.6	1480.2 ± 1644.9	15.4 ± 9	70.3%	31.7%
Right extended hepatectomy <sup>1</sup>	35 (22.9)	365.4 ± 133.7	1200.6 ± 881.5	15.6 ± 8.2	37.1%	51.4%
Left hepatectomy	47 (30.7)	319.4 ± 112	1180.5 ± 1082.9	15.2 ± 7.2	29.8%	53.2%
Extra hepatic duct resection	8 (5.2)	150.6 ± 55.4	481.2 ± 380.7	8.6 ± 5	0	37.5%
Portal vein resection	12 (7.8)	463.3 ± 101.1	1804.2 ± 1664.6	17.7 ± 8.7	50%	50%

<sup>1</sup>Included right trisectionectomy.

**Table 5 Bivariate analysis of clinico-pathological parameters**

Variable	Number (person-months)	IRR/100	HR	95%CI	P value
Age (10 yr added)	153 (4026.8)	2.96	0.99	(0.97-1.01)	0.743
Age (yr)					0.003
Less than 70	147 (3984.4)	2.84	1		
70 or greater	6 (42.4)	14.15	4.71	(2.02-10.97)	
Sex					0.066
Male	113 (2729.4)	3.33	1		
Female	40 (1297.4)	2.16	0.68	(0.44-1.04)	
Co-morbidity					0.281
Present	32 (1009.3)	2.48	0.79	(0.51-1.23)	
Absent	121 (3017.5)	3.12	1		
Operation					0.061
Right hepatectomy	63 (1389.1)	3.89	1		
Right extended hepatectomy	35 (1059.3)	2.36	0.63	(0.39-1.03)	
Left hepatectomy	47 (1412.6)	2.27	0.6	(0.39-0.93)	
Bile duct resection	8 (165.8)	4.83	1.12	(0.53-2.36)	
Portal vein resection					0.259
Yes	12 (3909.8)	2.92	1.49	(0.77-2.86)	
No	141 (117.0)	4.27	1		
Residual tumor status					< 0.001
R1	87 (2386.8)	4.63	1		
R0	66 (1640.0)	1.8	0.40	(0.27-0.59)	
Lymph node metastasis					< 0.001
N1, 2	103 (3248.6)	6.17	1		
N0	50 (778.2)	2.19	0.38	(0.26-0.55)	
Histology type					0.012
Papillary carcinoma	90 (2687.4)	2.38	1		
Others	63 (1339.4)	4.11	1.61	(1.11-2.33)	

IRR: Incidence rate per 100 person-months.

chance of detecting an early stage tumor. Early stages (stages 0, I and II) were found in 68.7% of patients who had co-morbidity compare to 50.4% of patients who did not.

This study validates John Hopkin’s definition of perihilar cholangiocarcinoma<sup>[3]</sup>. *i.e.*, that any tumor involving hepatic duct bifurcation should be treated and staged like perihilar tumor, because there are no differences in the prognosis and treatment strategy.

**Table 6 Multivariable analysis of clinico-pathological parameters**

Variable	IRR/100	Unadjusted HR	Adjusted HR <sup>1</sup>	95%CI	P value
Residual tumor status					< 0.001
R1	4.63	1	1		
R0	1.8	0.40	0.42	(0.28-0.62)	
Lymph node metastasis					< 0.001
N1, 2	6.17	1	1		
N0	2.19	0.38	0.4	(0.27-0.59)	
Histology type					0.018
Papillary carcinoma	2.38	1	1		
Others	4.11	1.61	1.58	(1.08-2.30)	

<sup>1</sup>Each hazard ratio was adjusted for age and other factors listed in the table. IRR: Incidence rate per 100 person-months.

Lymph node metastasis has been identified as a strong factor indicating a very poor prognosis<sup>[4,7,9,10,29]</sup>. This is also the case in our study since of the 32.7% patients who had lymph node metastasis only 2.5% had a 5-year survival.

Papillary carcinoma associated with intraductal tumor and less aggressive behavior resulted in a significantly longer median survival after resection of 55.7 mo compared to the nodular sclerosing type of 33.5 mo<sup>[28,31]</sup>. This study shows that papillary carcinoma is an independent prognostic factor with a 5-year survival rate of 27.7%, whereas other CCA types resulted in only a 10.2% survival rate.

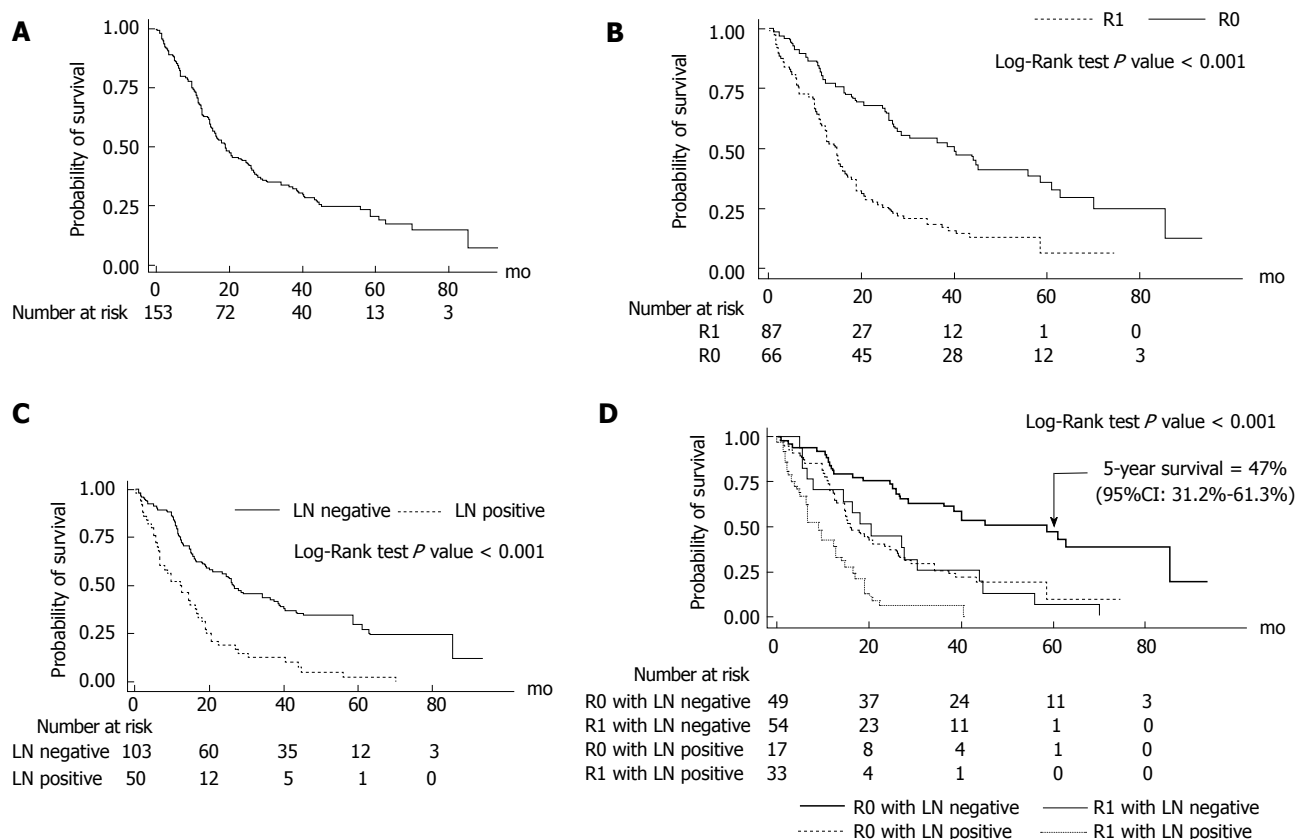
Recent studies showed that R0 resection was the factor indicating a good prognosis resulting in a 40.7%-52% 5-year survival compared to R1 resection with 5-year survival of 7.9%-32%<sup>[7,17,19,25]</sup>. More radical surgery had to be considered in order to achieve a more negative margin, such as combined vascular resection where studies have reported a 5-year survival of 47.6%-58% with mortality of 2%-8.8%<sup>[19,20]</sup>, and left or right trisectionectomy resulting in a 5-year survival of 36.8%-64.2% with an acceptable mortality of 0%-1.2%<sup>[16-18,32,33]</sup>.

Our study, which was based on current surgical techniques, showed a 5-year survival in the R0 group

**Table 7** Five-year survival after curative resection for perihilar cholangiocarcinoma in previous studies

Ref.	Place	Year	Resections	Morbidity	Mortality	R0	5-year survival rate
Present study	Thailand	2014	153	30%	2.00%	43.1%	20.6%
Nimura <i>et al</i> <sup>[21]</sup>	Japan	2000	100	49%	9.00%	61.0%	26.0%
Kondo <i>et al</i> <sup>[22]</sup>	Japan	2004	40	48%	0	95.0%	NA
Dinant <i>et al</i> <sup>[27]</sup>	Netherlands	2005	54	59%	11.00%	46.0%	38.00%
Jarnagin <i>et al</i> <sup>[26]</sup>	United States	2005	106	62.3%	7.50%	77.0%	NA
DeOliveira <i>et al</i> <sup>[29]</sup>	United States	2007	173	61%	5.00%	19.0%	10.00%
Ito <i>et al</i> <sup>[4]</sup>	United States	2008	38	32%	0	63.0%	33.00%
Paik <i>et al</i> <sup>[18]</sup>	Korea	2008	16	75%	0	81.2%	64.00%
Khuntikeo <i>et al</i> <sup>[23]</sup>	Thailand	2008	30	76.70%	6.70%	NA	0%
Hirano <i>et al</i> <sup>[24]</sup>	Japan	2010	146	44%	3.40%	87.0%	35.5%
Igami <i>et al</i> <sup>[25]</sup>	Japan	2010	298	43%	2.00%	74.0%	42.0%
Nagino <i>et al</i> <sup>[19]</sup>	Japan	2010	50	54%	2.00%	66.0%	30.3%
Cheng <i>et al</i> <sup>[10]</sup>	China	2012	176	26.3%	2.90%	78.4%	13.5%
Natsume <i>et al</i> <sup>[17]</sup>	Japan	2012	201	44.2%	1.00%	84.9%	35.2%
de Jong <i>et al</i> <sup>[6]</sup>	United States	2012	224	NA	6.70%	66.5%	20.2%
Nagino <i>et al</i> <sup>[7]</sup>	Japan	2013	574	57.30%	4.70%	76.5%	32.5%
Pattanathien <i>et al</i> <sup>[26]</sup>	Thailand	2013	58	NA	NA	46.6%	10.8%

NA: Not available.

**Figure 2** Kaplan-Meier survival curve. A: Kaplan-Meier survival curve of perihilar cholangiocarcinoma; B: Kaplan-Meier survival curve of perihilar cholangiocarcinoma according to residual tumor status; C: Kaplan-Meier survival curve of perihilar cholangiocarcinoma according to lymph node metastasis; D: Kaplan-Meier survival curve of perihilar cholangiocarcinoma according to residual tumor status and lymph node metastasis.

of 35.6%, which was much greater than in the R1 group with a survival of 6.4%. Right hepatectomy was the procedure that achieved the lowest rate of R0 resection, probably due to the preservation of segment 4 liver parenchyma which increased the chance of a histologically positive margin. Appropriately designed studies are needed to investigate this finding (Table 4).

R0 resection was carried out in 43.1% of all patients which compares favorably with previous studies where the R0 resection ranged from 19% to 95% (Table 6).

There is one randomized control trial showing the benefit of chemotherapy in advanced biliary tract cancer<sup>[34]</sup>, but there are no randomized trials to prove the benefit of chemotherapy in an adjuvant setting.

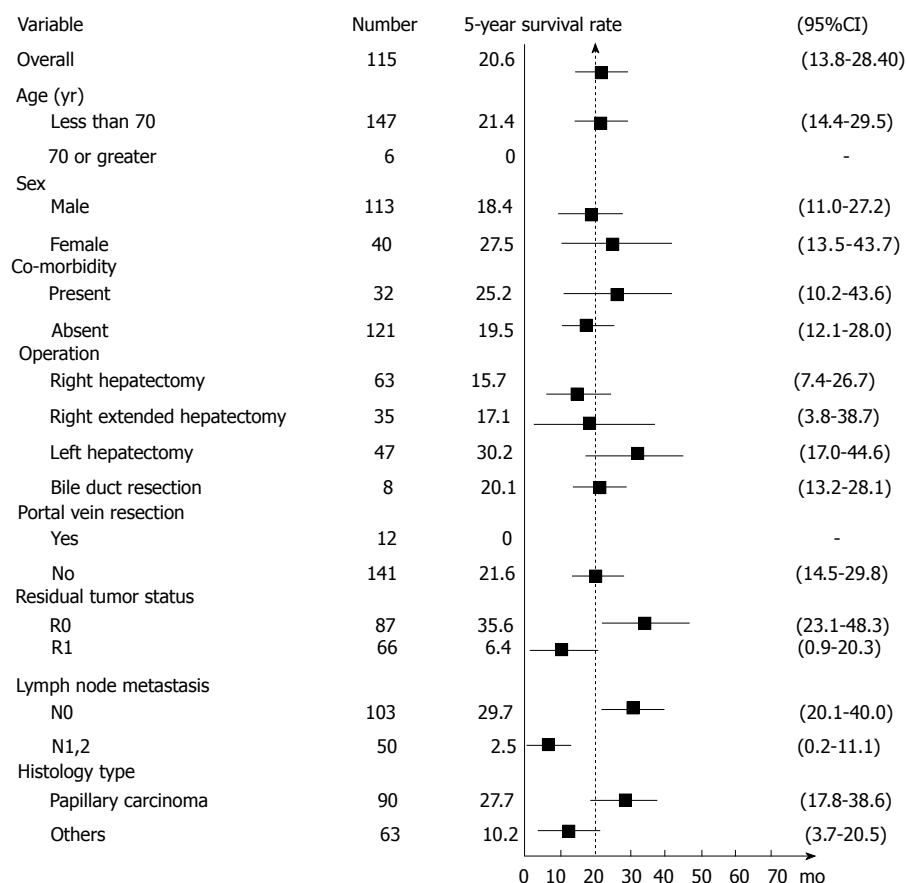


Figure 3 Five-year survival rate of clinico-pathological parameters.

This study was not designed to prove the benefit of chemotherapy but there is one retrospective study from our institute from the years 2009-2011 that may imply benefit of adjuvant chemotherapy. The study included 263 patients who underwent curative resection for all types of cholangiocarcinoma. Patients who received adjuvant chemotherapy had a significantly longer median survival time of 21.6 mo compared to those with no adjuvant chemotherapy of 13.4 mo. Benefit was also found in lymph node metastasis, R1 resection, higher carbohydrate antigen 19-9 and higher stage<sup>[35]</sup>.

Based on the information from this study, we can suggest measures to improve long-term survival outcome. Focus should center on: (1) screening tools and screening policy to detect early lymph node negative cases; and (2) radical surgical techniques and perioperative care to improve the R0 resection rate and to minimize post-operative morbidity and mortality.

In conclusion, curative resection in PCCA is possible with current surgical procedures resulting in a two-fold greater survival outcome compared to previous studies from Thailand. Independent factors that were associated with good survival outcome were R0 resection, no lymph node metastasis, and papillary histology.

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## COMMENTS

### Background

The highest incidence worldwide of perihilar cholangiocarcinoma (PCCA) occurs in the northeast of Thailand. Major hepatectomy with bile duct resection is the standard curative procedure; however, to date the 5-year survival rate in Thailand of 0%-10.8%, has been unsatisfactorily low.

### Research frontiers

Curative resection in PCCA is safe with improved surgical procedures resulting in a two-fold greater survival outcome compared to previous studies from Thailand. Independent factors that were associated with good survival outcome were R0 resection, no lymph node metastasis, and papillary histology.

### Innovation and breakthroughs

Advances in surgical technique combined with early stage diagnosis can lead to a substantially improved prognosis and 5-year survival in PCCA patients.

### Applications

To improve long-term survival outcome focus should center on (1) radical surgical techniques and perioperative care to improve the R0 resection rate and to minimize post-operative morbidity and mortality; and (2) screening tools and screening policy to detect early lymph node negative cases.

### Terminology

Perihilar cholangiocarcinoma is defined as “tumors that are located in the extrahepatic biliary tree proximal to the origin of the cystic duct”.

### Peer-review

The present study has been performed in the place that the highest incidence of cholangiocarcinoma is reported. The study was well designed and conducted with great invention.



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