

RESEARCH ARTICLE

Survival Rate of Extrahepatic Cholangiocarcinoma Patients after Surgical Treatment in Thailand

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Abstract

Background: Intra- and extrahepatic cholangiocarcinoma (CCA) is the most common cancer in Thailand, especially in the northeast region. Most extrahepatic CCA patients consult a doctor at a late stage. Surgery is still the best treatment. **Objectives:** The aim of this study was to evaluate survival rates and factors affecting survival in extrahepatic CCA patients following surgery at Srinagarind Hospital, Khon Kaen University, Thailand. **Materials and Methods:** A retrospective cohort study was conducted with 58 patients who were diagnosed and treated by surgical resection by the same surgeon at Srinagarind Hospital between 2005 and 2009. The patients were followed up until death or the end of the study (31 December, 2011). Survival rates were calculated by the Kaplan-Meier method, and the Cox proportional hazard model was used to identify independent prognostic factors. **Results:** The total follow-up time was 1,215 person-months, and the mortality rate was 50 per 100 person-years. The cumulative 1-, 3-, and 5-year survival rates were 62.1%, 21.7% and 10.8%, respectively. The median survival time after resection was 15 months. After adjusting for age, gender, lymph node metastasis and histological type, resection margin remained as a statistically significant prognostic factor for survival following surgery. A positive resection margin was associated with a 2.3-fold higher mortality rate than a negative margin. **Conclusions:** Resection margins are important prognostic factors affecting survival of extrahepatic CCA patients after surgery. A negative resection margin can reduce the mortality rate by 56%.

Keywords: Extrahepatic cholangiocarcinoma - surgical treatment - survival rate - Thailand

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Introduction

Cholangiocarcinoma (CCA), both intra- and extrahepatic bile duct CCA, is the most common cancer in Thailand, especially in the northeast region. Khon Kaen is one of the provinces in the northeast region of Thailand, which has a very high incidence of CCA with age-standardized annual incidence rates of 36.3 and 87.7 per 100,000 population in females and males, respectively (Khuhaprema et al., 2010).

Data from the hospital-based cancer registry of Srinagarind Hospital, a teaching hospital in Khon Kaen Province, show that many CCA patients come to seek treatment every year. For example, in 2009 there were 1,298 CCA patients (944 males, 354 females), who presented at the Srinagarind Hospital (Cancer Unit, Srinagarind Hospital, 2010). The incidence of this disease in Western countries is relatively low with diagnoses ranging 0.5-2 per 100,000 population (Anderson et al., 1992). The high incidence in Northeastern Thailand is probably due to environmental factors, especially the high local rates of infection by *Opisthorchis viverrini*, which is a strong risk factor for the subsequent development of

CCA (Poomphakwaen et al., 2009; Sripa et al., 2012).

CCA is a disease of the intrahepatic and extrahepatic bile duct, but does not include the papilla of Vater. Most CCA patients consult the doctor at a late stage of the cancer, and surgery is currently the best method of treatment. Due to the late stage of the CCA, the extent of metastases and an insufficient number of surgeons, surgery has been offered to only one-third of the patients (Uttaravichien et al., 1999; Ohtsuka et al., 2003).

Studies about survival rates or factors affecting the survival of CCA patients after resection, especially those with extrahepatic CCA, are rare, and the results vary from one country to another (Bhudhisawasdi, 1997; Khuntikeo, 2008; American Cancer Society, 2009; Unno et al., 2010). The aim of this study was therefore to evaluate the survival rates and factors affecting survival in extrahepatic CCA patients following surgical treatment at Srinagarind Hospital, Khon Kaen University, Thailand.

Materials and Methods

A retrospective cohort study was conducted with 58 patients, who were diagnosed (histologically confirmed)

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Table 1. Characteristics of Extrahepatic Cholangiocarcinoma Patients after Surgical Treatment (N=58)

Variables	No.	%
Gender:		
Male	40	69
Female	18	31
Age (years):		
<40	2	3.5
40-49	9	15.5
50-59	30	51.7
≥60	17	29.3
Mean (SD)	56 (8.41)	
Median (min:max)	55 (38:76)	
Education:		
Primary school	36	62.1
Secondary school	13	22.4
College/University	9	15.5
Occupation:		
Farmer	37	63.8
Government/Company	11	19
Commercial/Business	2	3.5
Labourer	2	3.5
Unemployed	6	10.2

Table 2. Stage Distribution, Lymph Node Metastasis, Resection Margin, Histological Type, Surgery Type and Final Status of Extrahepatic Cholangiocarcinoma Patients after Surgical Treatment (N=58)

Variables	No.	%
Stage of disease		
Stage I	3	5.2
Stage II	13	22.4
Stage IIIA	3	5.2
Stage IIIB	30	51.7
Unknown stage	9	15.5
Lymph node status		
N0 (No regional lymph node metastasis)	19	32.8
N1 (Regional lymph node metastasis)	30	51.7
Nx (Regional lymph nodes cannot be assessed)	9	15.5
Resection margin		
R0 (Resection margin negative)	27	46.6
R1 (Resection margin positive)	31	53.4
Histological type		
Noninvasive papillary carcinoma	5	8.6
Invasive papillary carcinoma	24	41.4
Tubular adenocarcinoma	25	43.1
Type cannot be assessed	4	6.9
Histological grading		
Well differentiated	22	37.9
Moderately differentiated	1	1.7
Poorly differentiated	3	5.2
Grade cannot be assessed	32	55.2
Surgery type		
Curative resection	27	46.6
Palliative surgery	31	53.4
Status at the end of study		
Alive	8	13.8
Dead	50	86.2

and treated by surgical excision by the same surgeon during the period 1 January, 2005, to 31 December, 2009, at Srinagarind Hospital, Khon Kaen, Thailand. The patients were followed up until death or the end of the study (31 December, 2011). The independent variables were age at diagnosis, gender, stage of disease, resection margin, histological type, histological grading and type of surgery

Table 3. Survival Rates of Extrahepatic Cholangiocarcinoma Patients after Surgical Treatment

Survival time	Median time (months) (95%CI)	Survival rates (%)	95%CI
3 Months	1.6 (0.1-2.5)	86.2	74.3-92.8
6 Months	2.5(1-3.7)	77.6	64.6-86.3
9 Months	2.8 (1.6-5.3)	72.4	58.9-82.1
1 Year	4.9 (2.4-6.9)	62.1	48.3-73.1
3 Years	12.6 (9.7-15.3)	21.7	12.0-33.2
5 Years	14.6 (11.3-19.5)	10.8	4.1-21.4

Table 4. Factors Effecting Survival Rates of Extrahepatic Cholangiocarcinoma Patients after Surgical Treatment (Multivariate Analysis)

Variables	No.	Median time (months) (95%CI)	Person-time (person-months)	IR/100	Crude HR	Adjusted HR	95%CI of Adj. HR	(p-value)
Age (years)								(p-value 0.539)
≥55	32	15 (11.3-25.3)	655	50	1	1		
<55	26	13 (6.7-27.8)	559	50	1.03	0.82	0.44-1.54	(p-value 0.48)
Gender								(p-value 0.084)
Female	18	19 (11.3-34.3)	440	36	1	1		
Male	40	14 (10.3-20.5)	774	58	1.56	1.31	0.62-2.76	
Lymph nodes status								(p-value 0.007)
N0	19	29 (12.6-43.5)	601	28	1	1		
N1	30	11 (5.7-16.6)	438	78	2.57	2.23	1.04-4.99	
Nx	9	15 (2.8-NA)	175	56	1.78	2.11	0.82-5.38	
Resection margin								(p-value 0.328)
R0	27	25 (14.3-38.8)	779	33	1	1		
R1	31	12 (6.7-15.2)	436	81	2.31	2.3	1.25-4.20	
Histological type								(p-value 0.328)
Noninvasive papillary carcinoma	5	NA	173	14	1	1		
Invasive papillary carcinoma	24	13 (6.7-20.5)	436	59	3.75	2.23	0.48-10.21	
Tubular adenocarcinoma	25	17 (11.3-27.8)	530	55	3.4	2.5	0.54-11.35	
Type cannot be assessed	4	3 (2.8-NA)	76	48	3.62	5.42	0.84-34.97	

*p-value from partial likelihood ratio test; HR=hazard ratio; NA=not applicable

performed. The dependent variable was the survival time of patients with extrahepatic cholangiocarcinoma. In order to calculate the survival time, the starting point was identified as the date of surgery, and the follow-up period ended when a patient died or on completion of the study. Censored data were used for those, who were still alive at the end of the study or lost to follow-up. The follow-up status of each patient was checked from medical records and by linkage with the death registry of the national statistics database.

Descriptive statistics was used for exploratory data analysis. Percentages were used to describe categorical data, and means with standard deviations or medians with ranges were used to describe continuous data. The observed survival rate was calculated by the Kaplan-Meier method. Median survival times with 95% confidence intervals (CIs) and the log-rank test were used for comparisons between groups. The Cox proportional hazard regression model was used to assess associations between the various independent variables (covariates) and survival, and the adjusted hazard ratios were tested for significance with the partial likelihood test. The level of significance was set as p<0.05. All analyses were performed using STATA

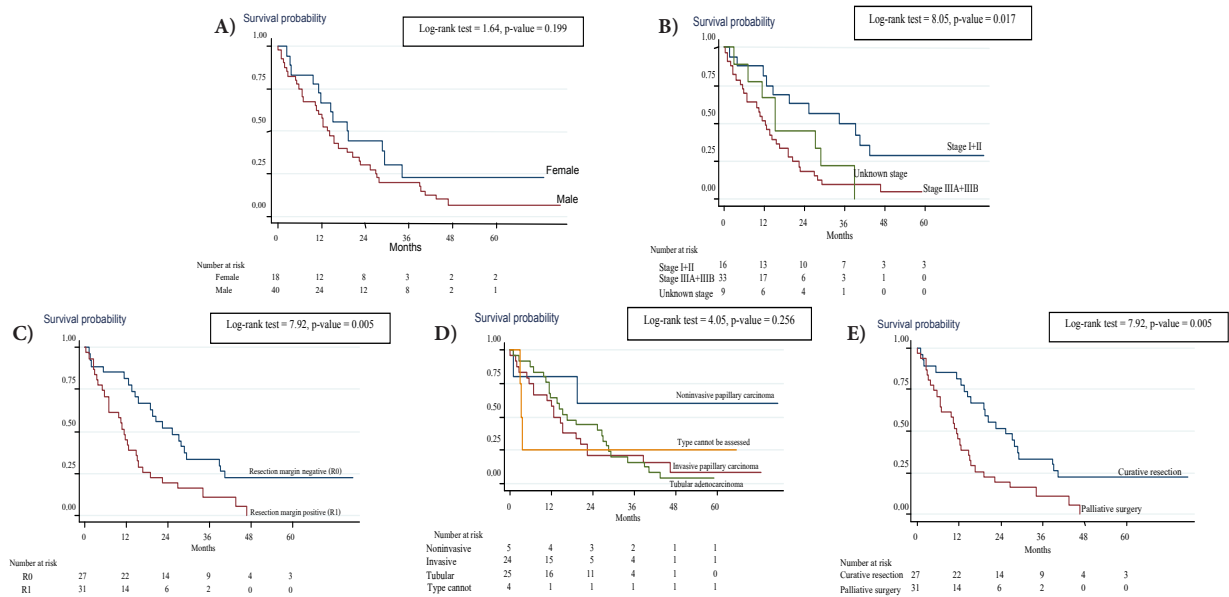


Figure 1. Survival Curve of Extrahepatic Cholangiocarcinoma Patients after Surgical Treatment. A) Gender, B) Stage, C) Resection margin, D) Histological type and E) Treatment

version 10.0 (StataCorp LP, 2007).

The research was approved by the Khon Kaen University Ethics Committee for Human Research (reference no. HE541333).

Results

The characteristics of the 58 patients with extrahepatic CCA, who were included in the study, are shown in Table 1. Most of patients were male (69%), and the mean age was 56 years. Table 2 summarises the clinical features of the patients, their type of surgery and the outcome. Most patients were at a late stage, and 53.1% had a positive resection margin. By the end of the study, 50 (86.2%) had died. With a total follow-up time of 1,215 person-months, the mortality rate was therefore 50 per 100 person-years.

Tables 3-4 and Figures 1-5 present the survival rates, survival times and factors affecting survival. The cumulative 1-, 3-, and 5-year survival rates were 62.1% (95%CI: 48.3-73.1), 21.7% (95%CI: 12.0-33.2) and 10.8% (95%CI: 4.1-21.4), respectively. The median survival time after resection was 15 months. After adjusting for age, sex, lymph node metastasis and histological type, resection margin remained as a statistically significant factor affecting survival. A positive resection margin (R1) was associated with a 2.30-fold higher mortality rate than a negative resection margin (R0) (95%CI: 1.25-4.20).

Discussion

The cumulative survival rates are consistent with the findings of previous studies (Neuhaus et al., 1999; Witzigmann et al., 2006; Li et al., 2011; Murakami et al., 2011). However, our findings are rather different from the from the lower survival rates found in some other studies (Bhudhisawasdi, 1997; Shi QF et al., 2007; Khuntikeo et al., 2008). The median survival in our study is similar to the median survival of 17 months found by Fuller et

al. (2009). Differences from the findings of other studies might due to patient characteristics, length of follow-up and treatment modalities.

Resection margin was found to be the significant factor affecting the survival of extrahepatic CCA patients after surgical resection. Our finding is in line with that of Kosuge et al. (1999), who found that patients with a positive resection margin (R1) had a 2.88 times higher mortality risk. The finding was also similar to those reported in other studies (Jarnagin et al., 2005; Witzigmann et al., 2006; Yubin et al., 2008; Unno et al., 2010; Murakami et al., 2011).

Cholangiocarcinoma is the most common cancer in the northeast area of Thailand, and extrahepatic bile duct cancer is part of this disease. This disease continues to be a major problem for public health in Thailand (Vatanasapt et al., 1993; Sriplung et al., 2005; 2006; Khuhaprema et al., 2010). The survival rates of patients who suffer from this disease are rather short compared to those of other diseases (Sriamporn et al., 1995). From the health professional point of view, along with primary prevention, we recommend that improvements in surgical procedures for the treatment of this disease are necessary in order to increase survival times and quality of life.

In conclusion, resection margins are an important prognostic factor affecting survival of extrahepatic CCA patients after surgical treatment. A negative resection margin can reduce the mortality rate following surgery by 56%. An improvement in surgical procedures is a priority.

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References

- American Cancer Society. Cancer facts and figures (2009). Atlanta: American Cancer Society.
- American Joint Committee on Cancer (2002). AJCC Cancer Staging Manual: In Extrahepatic bile ducts. 6th ed. New York: Springer.
- Anderson BB, Ukah F, Tette A, et al (1992). Primary tumors of the liver. *J National Med Assoc*, **84**, 129-35.
- Bhudhisawasdi V (1997). Place of surgery in opisthorchiasis associated cholangiocarcinoma. *Southeast Asian J Trop Med Public Hlth*, **28**, 85-90.
- Cancer Unit, Srinagarind Hospital (2010). Hospital-based tumor registry 2009: statistical report. Khon Kaen: Faculty of Medicine, Khon Kaen University.
- Fuller CD, Wang SJ, Choi M, et al (2009). Multimodality therapy for locoregional extrahepatic cholangiocarcinoma: a population based analysis. *PMC*, **115**, 5175-83.
- Jarnagin WR, Bowne W, Klimstra DS, et al (2005). Papillary phenotype confers improved survival after resection of hilar cholangiocarcinoma. *Ann Surg*, **241**, 703-14.
- Khuhaprema T, Srivatanakul P, Attasara P, et al editors (2010). Cancer in Thailand: Vol. V, 2001-2003. Bangkok: Bangkok Medical Publisher.
- Khuntikeo N, Phugkhem A, Bhudhisawasdi V, et al (2008). Major hepatic resection for hilar cholangiocarcinoma without preoperative biliary drainage. *Asian Pac J Cancer Prev*, **9**, 83-5.
- Kosuge T, Yamamoto J, Shimada K, et al (1999). Improved surgical results for hilar cholangiocarcinoma with procedures including major hepatic resection. *Ann Surg*, **230**, 663-71.
- Li H, Qin Y, Cui Y, et al (2011). Analysis of the surgical outcome and prognostic factors for hilar cholangiocarcinoma: A Chinese experience. *Dig Surg*, **28**, 226-31.
- Murakami Y, Uemura K, Sudo T, et al (2011). Prognostic factors after surgical resection for intrahepatic, hilar, and distal cholangiocarcinoma. *Ann Surg Oncol*, **18**, 651-8.
- Neuhaus P, Jonas S, Bechstein WO, et al (1999). Extended resection for hilar cholangiocarcinoma. *Ann Surg*, **230**, 808-19.
- Ohtsuka M, Ito H, Kimura F, et al (2003). Extended hepatic resection and outcomes in intrahepatic cholangiocarcinoma. *J Hepato-Biliary-Pancreatic Surg*, **10**, 259-64.
- Poomphakwaen K, Promthet S, Kamsa-ard S, et al (2009). Risk factors for cholangiocarcinoma in Khon Kaen, Thailand : a nested case-control study. *Asian Pac J Cancer Prev*, **10**, 251-8.
- Shi QF, Liang TB, Qin YS, et al (2007). Evaluation of surgical approach for extrahepatic cholangiocarcinoma. *Hepatobiliary Pancreat Dis Int*, **6**, 622-6.
- Sriamporn S, Black R, Sankaranarayanan R, et al (1995). Cancer survival in Khon Kaen Province, Thailand. *Int J Cancer*, **61**, 296-300.
- Sripa B, Brindley PJ, Mulvanna J, et al (2012). The tumorigenic liver fluke *Opisthorchis viverrini* – multiple pathways to cancer. *Trends Parasitol*, **28**, 395-407.
- Sriplung H, Sontipong S, Martin N, et al (2005). Cancer incidence in Thailand, 1995-1997. *Asian Pac J Cancer Prev*, **6**, 276-81.
- Sriplung H, Wiangnon S, Sontipong S, et al (2006). Cancer incidence trends in Thailand, 1989-2000. *Asian Pac J Cancer Prev*, **7**, 239-44.
- StataCorp LP (2007). Stata Release 10: User's guide. College Station TX: Stata Press.
- Unno M, Katayose Y, Rikiyama T, et al (2010). Major hepatectomy for perihilar cholangiocarcinoma. *J Hepatobiliary Pancreat Sci*, **17**, 463-9.
- Uttaravichien T, Bhudhisawasdi V, Pairojkul C, et al (1999). Intrahepatic cholangiocarcinoma in Thailand. *J Hepato-Biliary-Pancreatic Surg*, **6**, 128-35.
- Vatanasapt V, Martin N, Sriplung H, et al (1995). Cancer incidence in Thailand 1988-1991. *Cancer Epidemiol, Biomarkers and Prev*, **4**, 475-83.
- Witzigmann H, Berr F, Ringel U, et al (2006). Surgical and palliative management and outcome in 184 patients with hilar cholangiocarcinoma. *Ann Surg*, **244**, 230-9.
- Yubin L, Chihua F, Zhixiang J, et al (2008). Surgical management and prognostic factors of hilar cholangiocarcinoma: Experience with 115 cases in China. *Ann Surg Oncol*, **15**, 2113-9.