

## RESEARCH ARTICLE

# Survival of Cholangiocarcinoma Patients in Northeastern Thailand after Supportive Treatment

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### Abstract

**Background:** Cholangiocarcinoma (CCA) is a very common cancer in Northeastern Thailand. Most CCA patients see a physician at a late stage when curative surgery is not possible. After diagnosis, they generally are treated by partial surgery/percutaneous drainage, chemotherapy and supportive treatment. **Objective:** This study aimed to assess the survival rates of CCA patients after supportive treatment. **Methods:** A retrospective cohort design was applied in this study. Data for 746 CCA patients were extracted from the hospital-based cancer registry of Srinagarind Hospital, Khon Kaen University. The patients were diagnosed (at least by ultrasonography) between 1 January, 2009 and 31 December, 2009 and then followed up for current status until 30 June, 2011. The cumulative survival rate was calculated by the Kaplan-Meier method, and independent prognostic factors were investigated using Cox regression. **Results:** The total follow-up time was 5,878 person-months, and the total number of deaths was 637. The mortality rate was therefore 10.8 per 100 person-year (95% CI : 10.1-11.7). The cumulative 3, 6, 9, 12 and 24 month survival rates were 59%, 39%, 31%, 24% and 14%, respectively. The median survival time after supportive treatment was 4 months. After adjusting for gender, age, stage, distant metastasis, histological grading and treatment, stage was a significant predictor of survival of CCA patients. Those in stage III and stage IV had a 6.78 fold higher mortality than the stage I and stage II cases (95% CI : 1.6-28.7). **Conclusion:** It is very important to encourage patients to see health personnel at an early stage.

**Keywords:** Cholangiocarcinoma - supportive treatment - survival time - North-East Thailand

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### Introduction

Primary liver cancer was the leading cancer in Thailand in men and the third in women in the period 1998-2000 (Khuhaprema et al., 2007). Primary liver cancer comprises two major types of cancer-hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA) (Sripa and Pairojkul, 2008). CCA is the second most common type of primary liver cancer, the latter accounting for 5% of all primary cancer in most areas of the world (Craig et al., 1989). However, in Thailand, especially in Khon Kaen province situated in the Northeastern region there is a very high prevalence 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) and is the most common cause of death from cancer (Vatanasapt et al., 1990).

Most CCA patients see a physician in the late stage of disease, because the tumours are clinically silent in early stages, and clinically this results in poor prognosis (Mihalache et al., 2010) with curative surgery generally not being possible. After diagnosis, CCA patients in the late stage are treated by partial surgery/percutaneous

drainage, chemotherapy and supportive treatment.

A previous study of survival in CCA patients focused on specific groups, such as those receiving surgical excision and had diagnosis in early state (Pattanathien et al., 2013; Sriputtha et al., 2013) but studies of results of supportive treatment have been limited. Most CCA patients see the physician only one time and are lost to follow up. The aim of this study was to evaluate the survival of CCA patients diagnosed in a late stage and receiving supportive treatment in Northeastern Thailand. The anticipate findings should be useful for encouraging improvement of methods for early diagnosis of CCA.

### Materials and Methods

A retrospective cohort study was conducted with 746 patients who were diagnosed (at least ultrasonography) and treated by supportive treatment during the period 1 January 2009 to 31 December, 2009 at Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Northeastern Thailand. The patients were followed up until death or the end of the study (30 June, 2011). The independent variables were age at diagnosis, gender, stage

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of disease, distant metastasis, histological grading and treatment. The dependent variable was the survival time of patients with cholangiocarcinoma. In order to calculate the survival time, the staging point was identified as the date of diagnosis and the follow-up period ended when patients died. Censor, patients who were still alive at the end of the study or lost to 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 version 10.0 (StataCorp LP, 2007)

The research was approved by the Khon Kaen University Ethics Committee for Human Research (reference no. HE551380)

## Results

Regarding the characteristics of the 746 CCA patients included in the study, most were male (68.4%), and the mean age was 60.7 years. Summarized are details for features such as stage of disease, distant metastasis, histological grading and treatment. Most patients were at a late stage (stage IV 52.2%, unknown 44.1%), with distant metastasis M1 in 50.8% (unknown 42.5%) those receiving only supportive treatment were 67.0%, with partial surgery/percutaneous drainage in 16.6% and chemotherapy in 6.4%. By the end of the study, 637 (85.4%) had died. With a total follow-up time of 5,878 person-months, the mortality rate was therefore 10.8 per 100 person-years.

Tables 1 and 2 and Figure 1 present the survival rates, survival times and factors affecting survival after supportive treatment. The cumulative 3, 6, 9, 12 and 24 months survival rates were 59.1% (95% CI: 55.5-62.6), 38.6% (95% CI: 35.1-42.1), 30.7% (95% CI: 27.4-34.1), 23.9% (95% CI: 20.9-26.9) and 14.4% (95% CI: 11.9-17.1), respectively. The median survival time after supportive treatment was 4 months. After adjustment for the variables gender, age, stage of disease, distant metastasis, histological grading and treatment of the

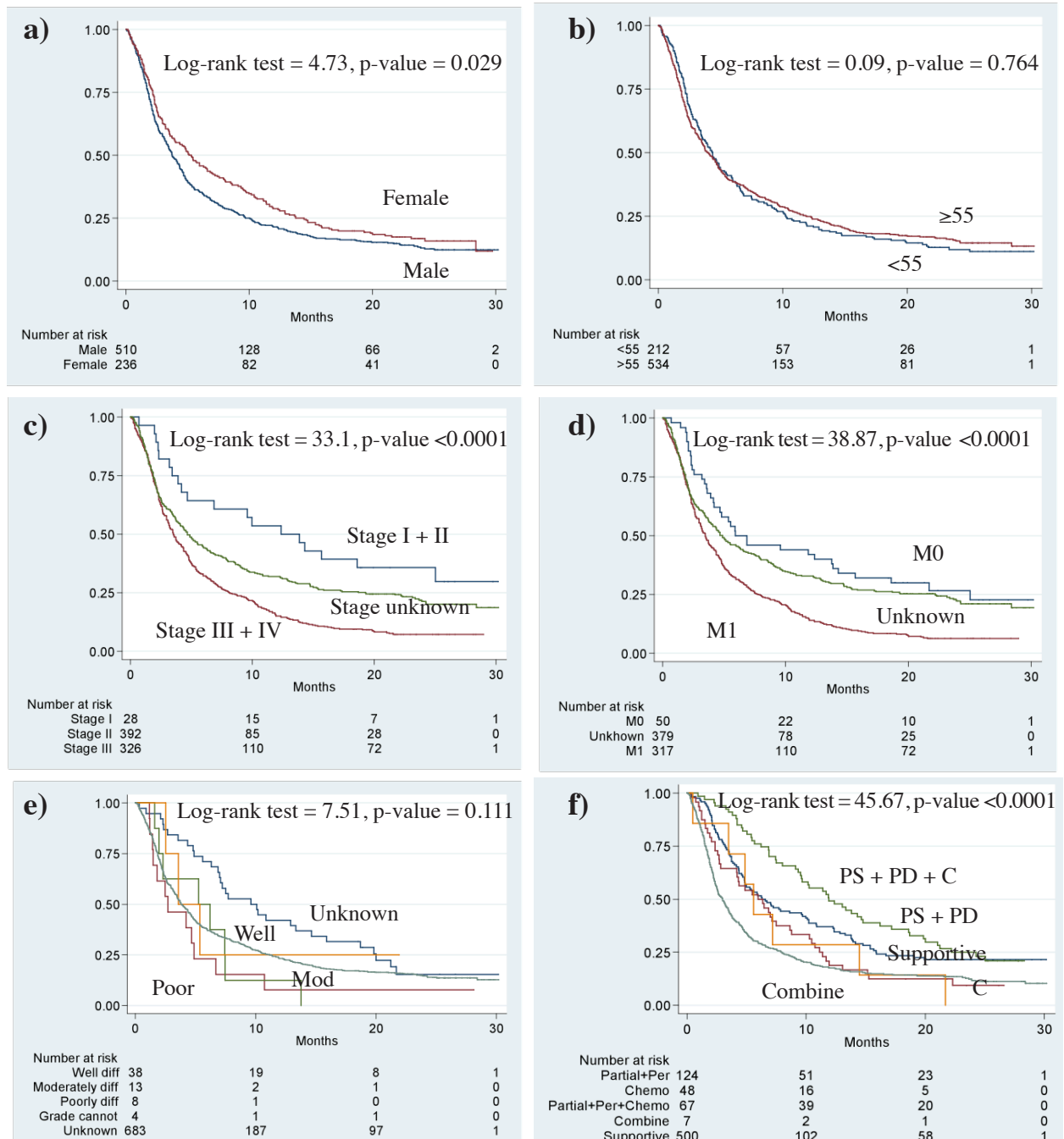
**Table 1. Survival Rates of CCA Patients after Supportive Treatment**

Survival time	Median survival time (95%CI)
3 Months	59.1 (55.5-62.6)
6 Months	38.6 (35.1-42.1)
9 Months	30.7 (27.4-43.1)
1 Year	23.9 (20.9-26.9)
2 Years	14.4 (11.9-17.1)

**Table 2. Factors Effecting Survival Rates of Cholangiocarcinoma Patients after Supportive Treatment**

Variables	MST (95%CI)	Person-months	IR/100	HR Crude	HR adj.	95% CI (HR adj.)	P-value
Gender							0.019
Female	5.1 (3.9-6.6)	2,101	9	1	1		
Male	3.8 (3.3-4.3)	3,777	12	1.2	0.82	0.69-0.96	
Age(year)							0.497
<55	4.3 (3.5-5.0)	1,640	11	1	1		
≥55	3.9 (3.5-4.7)	4,238	10	0.97	0.94	0.79-1.11	
Stage of disease							0.009
Stage I+II	12.3 (4.2-25)	372	5	1	1		
Stage III+IV	3.5 (3.1-4.1)	2,426	15	2.34	6.78	1.60-28.70	
Unknown stage	4.6 (3.7-5.9)	3,079	8	1.56	9.77	2.18-43.67	
Distant metastasis							0.235
M0	5.9 (4.1-13.8)	559	7	1	1		
M1	3.4 (3.0-4.0)	2,270	16	1.96	1.28	0.84-1.95	
Unknown	4.8 (3.8-6.3)	3,049	8	1.23	0.47	0.26-0.83	
Histological grading							0.147
Well differentiated	9.6 (6.8-14.6)	447	7	1	1		
Moderately differentiated	2.7 (1.4-4.8)	72	16	2.13	1.66	0.83-3.30	
Poorly differentiated	5.3 (1.6-7.4)	46	17	1.87	2.13	0.96-4.71	
Grade cannot be assessed	3.6 (2.5-NA)	33	9	1.19	1.45	0.40-5.21	
No histology	3.8 (3.4-4.3)	5,280	11	1.53	1.32	0.89-1.94	
Treatment							0.444
Partial surgery/PD	6.3 (4.8-9.9)	1,282	8	1	1		
Chemotherapy	5.9 (2.8-8.6)	381	11	1.35	1.15	0.79-1.66	
Partial surgery/PD+Chemo	11.9 (9.3-16.2)	926	6	0.78	0.81	0.58-1.14	
All above	5.5 (0.4-14.4)	58	12	1.42	1.09	0.49-2.39	
Supportive treatment	2.9 (2.5-3.4)	3,231	13	1.7	1.87	1.48-2.36	

MST, Median survival time; PD, Percutaneous drainage



**Figure 1. Survival Probability Rates of CCA Patients after Supportive Treatment.** By a) Gender; b) Age; c) Stage; d) Distant metastasis; e) Histological grading; and f) Type of treatment.

disease, stage of disease remained as a statistically significant factor affecting survival. CCA patients who were in stage III and stage IV had a 6.78 fold higher mortality than who were in stage I and stage II (95% CI: 1.6-28.7).

## Discussion

The present analysis of the various factors that affected the survival of CCA patients after adjusted variables: gender, age, stage of disease, distant metastasis, histological grading and treatment, found that stage of disease was the factors that affect the survival of CCA patients who had supportive treatment. CCA patients in stage III and stage IV were 6.78 fold at risk of death of

CCA patients in stage I and stage II, which is consistent with the study of Vern-Gross et al. (2010) who found that CCA patients with no distant metastasis, survival rates were higher than CCA patients with metastases, and Madariaga et al. (1998) found that in CCA patients with multiple tumour nodules, the risk of death was 3.5 fold than CCA patients with a single tumour mass. This means that the stage of disease of CCA patients were in late stage had a higher risk of death than in early stage. However, although CCA patients in the late stage of the disease, supportive treatment can help CCA patients relieve symptoms and improve the patient's quality of life, lead to end-stage patients with minimal suffering.

In term of survivals of CCA patients who had supportive treatment, the survival rate at 3, 6, 9, 12

and 24 months were 59.1 %, 38.6, 30.7, 23.9 and 4.14, respectively, and the median duration of survival posture to 4 months (95% CI: 3.6-6.4), which differs from the study of Park et al. (2011) who found that the median duration of survival is 21 months and survival rate in first years were 69.0 and found that CCA patients with the spread of cancer to other organs, the prognosis is not good. Kawarada et al. (2002) found that the survival rate of the first years were 54.1 for CCA patients who treated by surgery and did not had spread of cancer to lymph nodes, CCA patients in the early stages of the disease, the survival rate is greater than in this present study. Knupel et al. (2011) found that giving chemotherapy, median survival time was 9.2 months, which is not much different from this study, found that the chemotherapy, median survival was 5.9 months and found that chemotherapy combined with other treatment methods, increased the survival of CCA patients. The median survival time of CCA patients after supportive treatment found in this study is 4 months which is lower than those CCA patients after surgical treatment; 15 and 12.4 months respectively (Pattanathien et al., 2013; Sriputtha et al., 2013).

However, the results of this study may be different with other studies; variables affecting treatment and survival outcomes, such as the numbers of samples, the duration of the study and data collection, medical knowledge, medical treatment and technology, some studies used a period of follow up to 20 years, but some studies use a one year follow-up and treatment has varied by country, physician and patient post diagnosis status.

In conclusion, stage of disease was an important prognosis factor affecting survival of CCA patients who had diagnosis in late stage. The encourage patients to see health personnel at early stage is very important.

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## References

- Craig JR, Peter RL, Edmondson HA (1989). Tumors of the liver and intrahepatic bile ducts. Washington DC: Armed forces Institute of Pathology, 197-211.
- Kawarada Y, Yamagiwa K, DasBC (2002). Analysis of the relationships between clinicopathologic factors and survival time in intrahepatic cholangiocarcinoma. *Am J Surg*, **183**, 679-85.
- Khuhaprema T, Srivatanakul P, Sriplung H, et al (2007). Cancer in Thailand: Vol. IV, 1998-2000. Bangkok: Bangkok Medical Publisher.
- Khuhaprema T, Srivatanakul P, Attasara P et al (2010). Cancer in Thailand Vol. V, 2001-2003. Bangkok: National Cancer Institute.
- Knupel M, Kubicka S, Vogel A, et al (2011). Combination of conservative and interventional therapy strategies for intra- and extrahepatic cholangiocellular carcinoma: a retrospective survival analysis. *Gastroenterol Res Practice*, **19**, 1-8.
- Madariaga JR, Iwatsuki S, Todo S, et al (1998). Liver resection for hilar and peripheral cholangiocarcinomas: A study of 62 cases. *Ann Surg*, **227**, 70-9.
- Mihalache F, Tantau M, Diaconu B, et al (2010). Survival and quality of life of cholangiocarcinoma patients: a prospective study over a 4 year period. *J Gastrointest Liver Dis*, **19**, 285-90.
- Park H, Choi KH, Choi S, et al (2011). Clinicopathological characteristics in combined hepatocellular cholangiocarcinoma: a single center study in Korea. *Yonsei Med J*, **52**, 753-760.
- Pattanathien P, Khuntikeo N, Promthet S, et al (2013). Survival rate of extrahepatic cholangiocarcinoma patients after surgical treatment in Thailand. *Asian Pacific J Cancer Prev*, **13**, 231-34.
- Sripa B, Pairojkul C (2008). Cholangiocarcinoma: lessons from Thailand. *Curr Opin Gastroenterol*, **24**, 349-56.
- Sriputtha S, Khuntikeo N, Promthet S, et al (2013). Survival rate of intrahepatic cholangiocarcinoma patients after surgical treatment in Thailand. *Asian Pacific J Cancer Prev*, **14**, 1107-10.
- StataCorp LP (2007). Stata Release 10: User's Guide. College Station TX: Stata Press.
- Vatanasapt V, Tangvoraphonkchai V, Titapant V, et al (1990). A high incidence of liver cancer in Khon Kaen province, Thailand. *Southeast Asian J Trop Med Public Health*, **21**, 489-94.
- Vern-Gross TZ, Shivnani AT, Chen K, et al (2010). Survival outcomes in resected extrahepatic cholangiocarcinoma: effect of adjuvant radiotherapy in a surveillance, epidemiology and end result analysis. *Int J Radiation Oncology Biol Phys*, **5**, 1-10.