RESEARCH ARTICLE

Factors Affecting Survival Time of Cholangiocarcinoma Patients: A Prospective Study in Northeast Thailand

Somkiattiyos Woradet[1], Supannee Promthet[1]*, Nopparat Songserm[2], Donald Maxwell Parkin[3]

Abstract

Cholangiocarcinoma (CCA) is a major health problem and cause of death among people in Northeastern Thailand. In this prospective study 171 patients newly diagnosed with CCA by physicians in 5 tertiary hospitals in four provinces of northeastern of Thailand between February and July 2011 were followed up to January 2012. The outcome was survival time from diagnosis to death. A total of 758.4 person-months of follow-up were available. The mortality rate was 16.9 per 100 person-months (95%CI: 14.1-20.1). The median survival time among CCA patients was 4.3 months (95%CI: 3.3-5.1). Cox's proportional hazard model was used to study the independent effects of factors affecting survival time among patients. Statistically significant factors included advanced stage at diagnosis (HR: 2.5, 95%CI: 1.7-3.8), presentation with jaundice (HR: 1.7, 95%CI: 1.1-2.4) or ascites (HR: 2.8, 95%CI: 1.8-4.4), and positive serum carcinoembryonic antigen (HR: 2.3, 95%CI: 1.2-4.3). Patients who had received standard treatment had a better prognosis that those who did not (HR: 0.5, 95%CI: 0.3-0.7).

Keywords: Cholangiocarcinoma - survival - clinical factor - conventional treatment - alternative medicine

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Introduction

Liver cancer was the fifth most common cancer in men, the seventh in women and the third most common cause of death in both sexes from cancer worldwide in 2008, and almost 85% of the cases occur in developing countries (Ferlay et al., 2010). Cholangiocarcinoma (CCA) is the second most common type of liver cancer and accounted for an estimated 15% of primary liver cancer worldwide (Parkin et al., 1993). However, CCA is very common in north-east Thailand, where it accounts for between 58% and 89% of primary liver cancers of men (Parkin et al., 1993; Vatanasapt et al., 1995; Sriplung et al., 2005; Kamsa-ard et al., 2011), and is the most common cause of death from cancer (Vatanasapt et al., 1990). Most cases are clinically silent in the early stages of disease, and are detected at an advanced stage (Blechacz et al., 2008; Mihalache et al., 2010), with a correspondingly poor prognosis. The median survival is about 4-5 months (Mihalache et al., 2010; Yusoff et al., 2012) and one-year survival between 22% and 28% (Sriamporn et al., 1995; Mihalache et al., 2010). Survival time of patients with CCA can be improved by early detection followed by curative resection (Blechacz et al., 2008; Mihalache et al., 2010; Li et al., 2011). Unfortunately, only few CCA patients are eligible for curative surgery (Mihalache et al., 2010; Yusoff et al., 2012).

Previous studies of survival in CCA patients have focused on specific subgroups- such as those at advanced stage (Park et al., 2009), receiving surgical resection (Murakami et al., 2011; Pattanathien et al., 2013; Sriputtha et al., 2013) or adjuvant therapy (Knüppel et al., 2012), or specific tumour locations (Cheng et al., 2007; Hasegawa et al., 2007; Nakagohri et al., 2008; Guglielmi et al., 2009; Bunsiripaiboon et al., 2010; Cho et al., 2010; Nuzzo et al., 2010; Li et al., 2011). In addition, most studies were retrospective, only one prospective study (Mihalache et al., 2010) has been reported, and there are none from Asian countries. To our knowledge, there has been no previous prospective study among unselected patients of the factors affecting survival of CCA patients in Thailand.

Materials and Methods

Study design

The subjects enrolled into the study were newly diagnosed as CCA by at least one of the following six diagnostic procedures: ultrasonography (U/S), computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP),

*[1]Department of Epidemiology, Faculty of Public Health, Khon Kaen University, [2]Department of Community Health, Faculty of Public Health, Ubon Ratchathani Rajabhat University, Thailand, [3]Clinical Trial Service Unit & Epidemiological Studies Unit, University of Oxford, United Kingdom *For correspondence: supannee@kku.ac.th*

endoscopic retrograde cholangiopancreatography (ERCP), and histology. The subjects were recruited between February and July 2011 from the 5 tertiary hospitals serving four provinces of the northeast of Thailand (Srinagarind Hospital, Khon Kaen Regional Hospital, Maha-Sarakham Provincial Hospital, Kalasin Provincial Hospital, and Roi-Et Provincial Hospital). A total of 237 patients with CCA were observed and followed-up in both hospital and community after diagnosis until January, 2012. The diagnosis date was the date that patients first presented themselves at those tertiary hospitals and were diagnosed by a physician as CCA.

Ethical approval

This present study was approved by the Khon Kaen University Ethics Committee for Human Research (Reference No. HE532325).

Independent variables

The variables of interest in this study were demographic factors (sex, age at recruitment, marital status, education level, occupation, and household income per month), clinical manifestations (method of diagnosis, stage at diagnosis, tumour location, jaundice, and ascites), presence or absence of tumour markers [CA 19-9, carcinoembryonic antigen (CEA)], and type of treatment (conventional treatment type, and use of alternative medicine). Demographic and clinical data were collected by interview and record review at the time of enrollment into the study. Information on treatment was obtained by record reviews at one month and two months after enrollment among surviving patients.

The independent variables were routinely gathered and observed by specially trained research assistants in each hospital. Monitoring and quality control procedures were established at the beginning of the study to ensure that there was maximum reliability and validity.

Outcome variable

The outcome was the time from CCA diagnosis until death or the end of study at 31st January, 2012. Death status (cause of death and date of death) was confirmed by linkage with the death certificates from the Civil Registration system. Survival was confirmed by a telephone call to the patients or public health officers in community health centers. Censored data were defined as alive at close of study, or death unrelated to CCA during the study period.

Statistical methods

Initially, the baseline demographic data and clinical information were presented as descriptive statistics. The Kaplan-Meier method was used to estimate the primary outcome of time from CCA diagnosis to death. The association between survival and the independent variables was performed using Cox's proportional hazard model, constructed using baseline demographic and clinical factors as prognostic factors for the time from CCA diagnosis to death. The variables were constructed using crude analysis to demonstrate the factors relating to the death of patients with CCA.

The factors with a p-value less than or equal to 0.10 by the Wald test in crude analysis were considered and entered into the initial model. Using a backward elimination method, the factors with the largest p-values (greater than 0.05) on the Wald test were successively excluded. The p-value of the partial likelihood ratio test was tested by model fitting; the final model included 8 factors: sex, age at recruitment, stage at diagnosis, jaundice, ascites, CEA, conventional treatment, and use of alternative medicine. In addition, the log-likelihood ratio was used to test the best fitting model, and the adjusted coefficient values were used to calculate the effect of demographic and clinical factors on survival time of CCA patients. The results of this study are presented as hazard ratios (HR) and 95% confidence intervals (95%CI). Statistical analysis was performed with STATA version 12.1.

Results

During the recruitment period, 237 patients were interviewed, but 66 (27.8%) cases did not meet the criteria for a confirmed diagnosis and were excluded, leaving only 171 CCA patients for follow up and analysis. A total of 758.4 person-months of follow-up were available. 128 patients died during the interval - a mortality rate of 16.9 per 100 person-months (95%CI: 14.1-20.1). The six-month survival was 35.7%. Median survival rate was 4.3 months (95%CI: 3.3-5.1) as shown in Figure 1.

About two-thirds (64.9%) of the subjects were male, one half were aged 60-69 years old (43.3%), and the average age was 63.6 (SD: 9) years (age range 37-86 years). Most subjects were married, of low educational level [primary school or less (91.2%)] and about four-fifths of them were farmers or agricultural labourers (79.5%). Two-thirds of patients (64.3%) had a household income less than or equal 5,000 Baht per month (US$165 in 2011) and average household income was 6,936 (SD: 8,074) Baht per month ($230) as shown in Table 1.

28.7% of CCA cases had been diagnosed by CT or MRI or MRCP and tumour markers, 53.8% were at an advanced stage and presented with jaundice (53.2%) or ascites (17.5%). In addition, about two fifths were positive for CA 19-9 (44.4%) or CEA (38.6%) as shown in Table 2.

Fifty eight (33.9%) of the patients received standard treatment, among this group 28 (48.3%) received biliary drainage only, 11 (19.0%) surgery only, and 9 (15.5%)

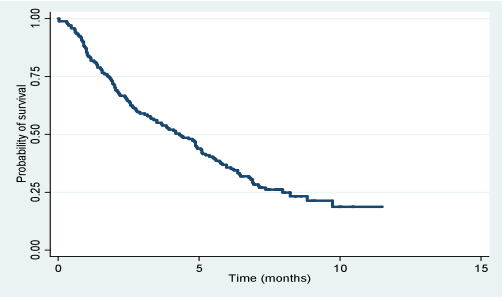

Figure 1. Kaplan-Meier Survival Estimate of Time from Diagnosis to Time of Death in the Cholangiocarcinoma Patients

Table 1. Crude Analysis of Demographic Factors Affecting Survival Time from Diagnosis to Death among Cholangiocarcinoma Patients

Factors	CCA patients N=171 (%)	Median survival (months)	Crude HR	95%CI	p value[a]
Sex					0.71
Male	111 (64.9)	4.2	1		
Female	60 (35.1)	4.9	0.9	0.7-1.3	
Age at recruitment (years)					0.16
<60	54 (31.6)	4.4	1		
60-69	74 (43.3)	4.8	0.8	0.6-1.3	
70+	43 (25.1)	3.4	1.3	0.8-2.0	
[Mean±SD 63.6±9.0; Median (min: max) 64 (37:86)]					
Marital status					0.93
Single or separated	33 (19.3)	5.1	1		
Married	138 (80.7)	4.2	0.98	0.6-1.5	
Education level					0.99
Primary or less	156 (91.2)	4.2	1		
Secondary or higher	15 (8.8)	4.8	1	0.5-1.9	
Occupation					0.50
Unemployed	24 (14.1)	3.3	1		
Agriculturist or labourer	136 (79.5)	4.4	0.8	0.5-1.2	
Officer or retailer	11 (6.4)	6.2	0.7	0.3-1.5	
Household income per month (Baht)					0.66
≤5,000	110 (64.3)	3.4	1		
5,001-10,000	41 (24.0)	4.8	0.9	0.6-1.4	
> 10,000	20 (11.7)	4.9	0.8	0.4-1.4	
[Mean±SD 6,936±8,074; Median (min: max) 5,000 (500: 50,000)]					

[a]p-value of Wald-test from crude analysis

Table 2. Crude Analysis of Clinical Factors Affecting Survival Time from Diagnosis to Death among Cholangiocarcinoma Patients

Factors	CCA patients N=171 (%)	Med. survival (months)	Crude HR	95%CI	p value[a]
Diagnostic type					0.320
Ultrasound only	32 (18.7)	2.2	1		
Ultrasound and tumour marker	31 (18.1)	2.7	1.1	0.6-1.9	
CT[b] or MRI[c] or ERCP[d]	37 (21.6)	4.9	0.6	0.4-1.1	
CT[b] or MRI[c] or ERCPd[d] and tumour marker	49 (28.7)	4.4	0.8	0.5-1.3	
Histology	22 (12.9)	5.4	0.7	0.4-1.3	
Stage at diagnosis					0.002
Early	33 (19.3)	5.2	1		
Advance	92 (53.8)	3.3	1.8	1.1-2.9	
Unclassified	46 (26.9)	5.8	0.9	0.5-1.6	
Tumour location					0.210
Intrahepatic CCA	96 (56.1)	3.9	1		
Extrahepatic CCA or Both	56 (32.8)	4.2	1.1	0.7-1.6	
Unclassified	19 (11.1)	6.4	0.6	0.3-1.2	
Jaundice					0.030
Absent	80 (46.8)	5.1	1		
Present	91 (53.2)	3.4	1.5	1.0-2.1	
Ascites					<0.001
Absent	141 (82.5)	4.9	1		
Present	30 (17.5)	1.6	2.4	1.6-3.7	
CA 19-9 (U/ml)					0.110
Negative (≤39)	31 (18.2)	6.1	1		
Positive (>39)	76 (44.4)	4.1	1.5	0.9-2.5	
Non-examination	64 (37.4)	3.8	1.7	1.0-2.9	
CEA[e] (mg/ml)					0.002
Negative (≤3.4)	26 (15.2)	8.8	1		
Positive (>3.4)	66 (38.6)	3.5	2.5	1.4-4.7	
Non-examination	79 (46.2)	3.9	2.5	1.4-4.6	

[a]p-value of Wald-test from crude analysis, [b]computed tomography, [c]magnetic resonance imaging, [d]endoscopic retrograde cholangiopancreatography, [e]carcinoembryonic antigen

Table 3. Crude and Adjusted Analysis of Factors Affecting Survival Time from Diagnosis to Death among Cholangiocarcinoma Patients

Factors	N	Crude HR	Adjusted HR[a]	95%CI	p value[a]
Sex					0.540
Male	111	1	1		
Female	60	0.9	1.1	0.8-1.6	
Age at recruitment (years)					0.060
<60	54	1	1		
60-69	74	0.8	0.8	0.5-1.2	
70+	43	1.3	1.3	0.8-2.1	
Stage					<0.001
Early and unclassified	79	1	1		
Advanced	92	1.9	2.5	1.7-3.8	
Jaundice					0.010
Absent	80	1	1		
Present	91	1.5	1.7	1.1-2.4	
Ascites					<0.001
Absent and unknown	141	1	1		
Present	30	2.4	2.8	1.8-4.4	
CEA[c] (mg/ml)					0.010
Negative (≤3.4)	26	1	1		
Positive (>3.4)	66	2.5	2.3	1.2-4.3	
Non-examination	79	2.5	2.5	1.3-4.7	
Conventional treatment					<0.001
No treatment/ Palliative care	113	1	1		
Standard treatment	58	0.7	0.5	0.3-0.7	
Alternative medicine					<0.001
No using alternative medicine	61	1	1		
Using alternative medicine	77	0.99	0.8	0.5-1.3	
Unknown	33	4.3	3.5	2.1-5.8	

[a]adjusted hazard ratio for all variable, [b]p-value from partial likelihood ratio test, [c]carcinoembryonic antigen

surgery and chemotherapy. 77 subjects (45%) had used alternative therapies, for the great majority (90.9%) this was healing treatment only (90.9%) with a few using healing and/or psychology treatment (9.1%).

On crude analysis, none of the demographic factors was significantly associated with survival time, as shown in Table 1. Several clinical factors showed a statistically significant association with survival time. Patients diagnosed at an advanced stage were twice likely to die (HR: 1.8, 95%CI: 1.1-2.9), and survival was also associated with presentation with jaundice or ascites, and a positive CEA, as shown in Table 2. The HR for those patients who received standard treatment was 0.7 (95%CI: 0.5-1.0)

The results of the multivariable analysis, using Cox's proportional hazard model, and including 8 factors (sex, age, stage, jaundice, ascites, CEA, conventional treatment, and alternative medicine) are shown in Table 3. The results show that receipt of conventional treatment is associated with a statistically significant reduced risk of death among patients compared to those who had no treatment or had palliative care (HR: 0.5, 95%CI: 0.3-0.7). Patients at an advanced stage at diagnosis were more likely to die (HR: 2.5, 95%CI: 1.7-3.8), as were those presenting with jaundice (HR: 1.7, 95%CI: 1.1-2.4) or ascites (HR: 2.8, 95%CI: 1.8-4.4). Subjects positive for CEA had a HR of 2.3 (95%CI: 1.2-4.3) and patients who were not examined for CEA had an increased risk of death also (HR: 2.5, 95%CI: 1.3-4.7). Finally, patients for whom there was no information on use of alternative medicine were much more likely to die (HR: 3.5, 95%CI: 2.1-5.8), than patients who had not used alternative medicine.

Discussion

CCA is a leading cause of death from cancer among people in Northeast Thailand. CCA patients have a poor prognosis – in our study, median survival time was only 4.3 months. An adjusted analysis using Cox's proportional hazard model revealed several factors with an independent effect on survival among CCA patients (advanced stage at diagnosis, presentation with jaundice or ascites, and positive CEA [or non-examination of CEA)]. Independently of these, patients who received standard treatment were more likely to have longer life.

The advantage of the present study is the relatively large sample size, the unselected nature of the patients studied, prospective design, and the rigorous statistical methodology used to quantify the magnitude of the effects on mortality of the subjects. One limitation is that only a minority of patients (12.9 %) had been diagnosed by histology, so it is possible that some other histologies were included. However, CCA is a very common cancer in Northeast Thailand, and clinicians are confident in basing their diagnosis on other modalities – the subjects included had positive findings by at least one of the following six diagnostic procedures: U/S, CT, MRI, MRCP, ERCP, and histology.

In the present study the six-month survival was 35.7 %, while in an earlier population-based study of liver cancer in Khon Kaen the 1-year survival was 28.5% (Sriamporn et al., 1995). Median survival time CCA diagnosis to death was 4.3 months similar to that in a prospective study in 133 CCA patients in Romania (5 months: Mihalache et al., 2010) and in a retrospective study in 69 CCA patients in Malaysia (Yusoff et al., 2012).

With respect to the clinical factors, patients who were at advanced stage at diagnosis, or presented with jaundice ascites were more likely to die. All these reflect late presentation, although jaundice and ascites proved to predict prognosis independently of clinical stage at diagnosis.

In this observational study, CCA patients who received standard treatment had a longer survival. Although this was independent of stage (as recorded) and clinical variables such as jaundice and ascites, one cannot exclude other factors influencing the choice of treatment in determining outcome. We have no information on how many patients were offered, but refused (or did not comply with) conventional treatment- these are factors that are associated with a poor prognosis among cancer patients (Verkooijen et al., 2005; Hamidi et al., 2010). Regarding alternative medicine, patients classified as "unknown" for use of alternative medicine were more likely to die compared to those patients who had not used alternative medicine. This was because three quarters of the patients in the "unknown" group had died in the first month of follow-up, before the first interview. Prognosis was only marginally better (and non-significant) among patients who used alternative medicine that in those who had not, a finding similar to a previous prospective study of 481 cancer patients (Yun et al., 2012), showing that cancer patients who used complementary and alternative medicine did not have better survival than nonusers.

In conclusion, factors such stage of disease, presentation with jaundice or ascites, receipt of standard treatment, and using alternative medicine were statistical significantly associated with survival time of CCA patients.

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