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Two-year Survival Outcomes among Patients with Cholangiocarcinoma Diagnosed during 2010 in Roi-et Province, Thailand

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Abstract

Cholangiocarcinoma (CCA) is a common cancer in Thailand. This study aimed to describe epidemiological characteristics and survival outcomes of patients diagnosed with CCA at Roi-et Cancer Center during January and December 2010. Cox proportional hazard regression analysis was used to analyze data from 119 patients diagnosed with imaging techniques. The median survival time was found to be 4.4 months and the 2-year survival rate was 14.5%. From multivariate analysis by Cox proportional hazard regression, carcinoembryonic antigen (CEA) level >5 µg/l and alkaline phosphatase (ALP) >150 IU/l were found to be indicators of decreased survival time while having surgery led to longer survival time. To improve survival outcome, early detection through screening program and early diagnosis must be organized. Prognostic values of CEA and ALP should be considered.

Keywords: survival, cholangiocarcinoma, prognosis, Thailand

Introduction

In 2008, 7.8 million people died from cancer worldwide, resulting in 13% of all causes of death.[1,2] About 70% of all cancer deaths during 2008 occurred in low and middle-income countries. Cholangiocarcinoma (CCA) accounts for about 10-25% of primary liver cancers in many parts of the world, with age-standardized incidence rates (ASR) between 0.3 to 1.5 per 100,000 population in the western countries.[3-5] Most CCA patients had unresectable diseases at presentation and died within 12 months. Overall survival rate, including resected patients, was poor with less than 5% of patients survived up to five years, which has not changed significantly over the past 30 years.[6] However, many other factors might affect a patient's prognosis such as location of cancer, whether it is removable by surgery (resectable) and general health condition.[7]

In 2010, hepatobiliary cancer was one of the top five cancers in Thailand.[8] The CCA incidence in Thailand was exceedingly high, with ASR of 33.4 per 100,000 population in men and 12.3 in women.[9] Over 75% of hepatobiliary cancer in the northeastern region were found to have CCA while in other regions, proportion of CCA ranged about 25-40%.[10]

Roi-et, a province in the northeastern region of Thailand, was selected to be the study site since a high prevalence of CCA was found in the province[10] and Roi-et Hospital was upgraded to be the Regional Cancer Center of the northeastern region in May 2012. Survival time for each stage of CCA reflects severity of the disease as well as accessibility to early screening and quality of treatment received. Hence, this study focused on the survival outcome of CCA patients and factors affecting survival time of the patients.

Methods

A retrospective cohort study was designed to describe the characteristics of CCA patients, and demonstrate the survival analysis among CCA patients having different findings and receiving treatment procedures. The studied population included all patients who were diagnosed with CCA according to international classification of diseases (ICD-10) code of C269 in Roi-et Hospital during January-December 2010. All the medical charts were retrieved by nurses and statistician in the hospital. Those charts were copied with concealing name, hospital number and address. The records with evidence of computerized tomography (CT) scan, magnetic resonance imaging

(MRI) and any cholangiography were collected to confirm the diagnosis. The study process received the certificate of approval by the Committee for Research Ethics (Social Sciences) in Mahidol University, Thailand.

Data of all confirmed CCA patients were recruited from several sources, and reviewed by trained health officers, nurses and physicians. Profile and demographic data of CCA patients were accessed from Hos-XP, an application program for hospital service data. Date of CT scan examination was accounted as the diagnosis date. In addition, patients' symptoms and laboratory results were reviewed from medical records in outpatient department (OPD) and inpatient department (IPD). Records with blood tests done within 30 days before or after the date of CT scan or MRI were included in the analysis. Blood tests included testing for carcinoembryonic antigen (CEA), cancer antigen (CA) 19-9, alkaline phosphatase (ALP) and total bilirubin (TB).

All the interventions given to patients were reviewed from Hos-XP program, OPD and IPD charts, and included in the study, regardless of whether alternative treatments were received in other hospitals such as Udon Thani Cancer Center, Khon Kan Provincial Hospital and Srinagarind Hospital. Survival status of patients was obtained from database in the annual population survey of Roi-et Hospital and records in National Health Security Office. To identify the dead patients, birth date, gender and sub-district were matched. Since the information of deaths was retrieved for the period from 1 Jan 2010 to 31 Dec 2012, patients diagnosed as CCA during 1 Jan 2010 to 31 Dec 2010 were included in the study to calculate 2-year survival rate among these patients.

Afterwards, the data were checked for completion, coded and entered into a computerized database. The 25^{th}, 50^{th} and 75^{th} percentile of survival time and cumulative survival at 24^{th} month of patient with any types of CCA were calculated by Kaplan-Meier method.

Univariate analysis was conducted using log-rank test to compare the survival curve by variables in each group. Certain variables were selected purposively for multivariate model. Cox proportional hazard regression, explaining hazard ratio between patients who exposed to the given factors and those who had not exposed, was fitted. Significant level was considered at p-value less than 0.05. The given assumption was that no patient had lost to follow-up during two years. As for Cox proportional hazard regression, ratio of hazards for persons with different patterns of covariates was constant over time. The model assumption was checked by graphical approach, including hazard functions and log-minus-log plots of the baseline survival.

Results

There were total 427 patients diagnosed with CCA in the year 2010. Among them, only 271 (63.5%) records had imaging results showing suspected or confirmed CCA in either OPD or IPD chart, which included 269 CT scan, one MRI and one magnetic resonance cholangiopancreatography (MRCP). However, only 269 records were included in the study as death date was not available in two records (Figure 1).

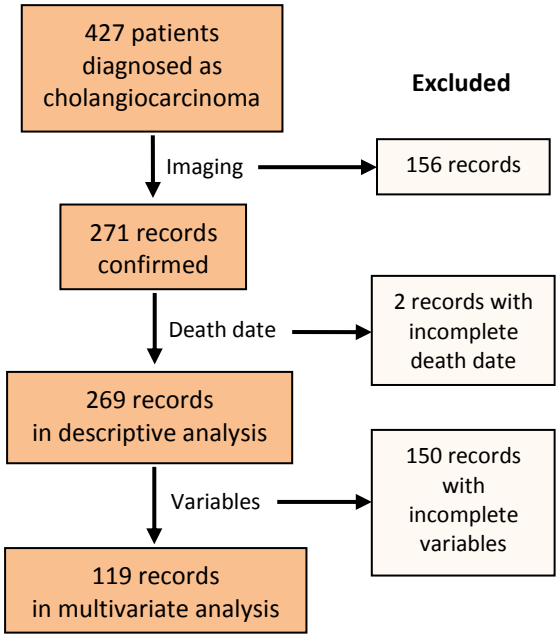

Figure 1. Recruitment of cholangiocarcinoma patient records in Roi-et Hospital for descriptive and multivariate analyses, 2010

Roi-et Hospital had started hepatic resection by one surgeon since the beginning of 2010 and thus, some patients were referred to other tertiary care hospitals. During 2-year follow up, there were 174 patients receiving any kinds of treatment only in Roi-et Hospital (not referred), seven with hepatic resection, six with cholecystectomy, six with exploratory laparoscopy, one with core needle liver biopsy and 57 with palliative surgery (Endoscopic retrograde cholangiopancreatography, bypass, stent and percutaneous transhepatic biliary drainage). Only one patient was receiving chemotherapy as an adjuvant therapy.

Among all 269 CCA patients with imaging, the median age at diagnosis was 62 years (range 40-90 years). The case distribution by demographic data, clinical presentation and treatment procedure are shown in table 1.

Table 1. Demographic characteristics, clinical presentation, treatment and outcomes of patients with cholangiocarcinoma diagnosed at Roi-et Hospital in Roi-et Province, Thailand, 2010 (n=269)

Factor	Number of case (%)	Number of death (% CFR)	Median survival time (Month)	P-value (Log-rank test)
Gender				
Male	179 (66.5)	155 (86.6)	4.3	0.52
Female	90 (33.5)	75 (83.3)	4.6	
Age (year)				
≤60	92 (34.2)	76 (82.6)	5.3	0.12
>60	177 (65.8)	154 (87.0)	3.8	
Occupation				
No	79 (29.4)	68 (86.1)	3.6	0.47
Government officer	13 (4.8)	8 (61.5)	4.4	
Farmer	155 (57.6)	137 (88.4)	4.4	
Monk	6 (2.2)	5 (83.3)	12.5	
General employee	16 (5.9)	12 (75.0)	4.1	
Health insurance				
No	3 (1.1)	3 (100.0)	1.1	0.25
Civil servants' medical benefit scheme	21 (7.8)	16 (76.2)	4.4	
Universal coverage	221 (82.2)	190 (86.0)	4.6	
Social security service	4 (1.5)	4 (100.0)	2.6	
Others	20 (7.4)	17 (85.0)	3.2	
Abdominal pain				
No	50 (18.6)	43 (86.0)	4.6	0.25
Yes	219 (81.4)	187 (85.4)	3.6	
Tumor markers				
Cancer antigen (CA) 19-9 (U/ml)				
≤200	74 (27.5)	54 (73.0)	6.4	0.058
>200	61 (22.7)	56 (91.8)	4.8	
No result	134 (49.8)	120 (89.6)	3.8	
Carcinoembryonic antigen (CEA) (µg/l)				
<5	56 (20.8)	38 (67.9)	9.9	<0.001
≥5	78 (29.0)	70 (89.7)	3.8	
No result	135 (50.2)	122 (90.4)	3.8	
Total bilirubin levels (mg/dL)				
<5	121 (45.0)	93 (76.9)	6.6	<0.001
≥5-10	23 (8.6)	21 (91.3)	3.2	
≥10	54 (20.1)	50 (92.6)	3.0	
No result	71 (26.4)	66 (93.0)	3.4	
Alkaline phosphatase level (IU/L)				
<150	50 (18.6)	31 (62.0)	13.2	<0.001
≥150-400	84 (31.2)	76 (90.5)	4.3	
≥400	64 (23.8)	59 (92.2)	2.8	
No result	71 (26.4)	64 (90.1)	3.6	
Surgery including hepatic resection, cholecystectomy, liver biopsy, and exploratory surgery				
No	239 (88.8)	207 (86.6)	4.1	<0.005
Yes	30 (11.2)	23 (76.7)	11.9	

Following the matched database of National Health Security Office and death certificate registry during 1 Jan 2010 and 31 Dec 2012, 230 CCA patients had already died without any injuries. The survival rate among 269 CCA patients during 2-year follow-up was 14.5%, in other word, the fatality rate was 85.5%. The Kaplan-Meier survival estimation showed that the median overall survival time was 4.4 months and 25% of the cases died within the first 1.9 months since the date of diagnosis (Figure 2) and no one died within one month after having therapeutic surgery (hepatic resection, cholecystectomy, liver biopsy and exploratory surgery), despite with or without palliative surgery.

Factors of CEA, CA 19-9, TB, ALP and having surgery were significantly associated with the disease prognosis (Table 1). These factors and age more than 60 years were employed in Cox proportional hazard regression model.

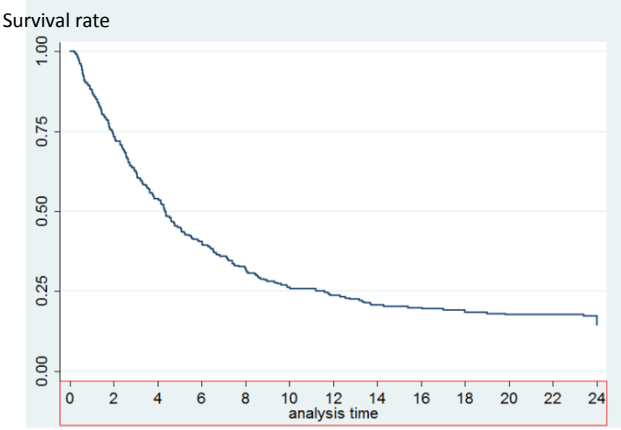

Figure 2. Kaplan-Meier survival curve of cholangiocarcinoma patients during 24 months after imaging diagnosis in Roi-et Hospital, Roi-et Province, Thailand, 2010 (n=269)

All the selected variables were re-categorized into two categories and tested for proportional hazard assumption. Eventually, all the variables met the assumption. When these variables were calculated for the hazard ratio, only three factors (CEA >5 µg/l, ALP >150 IU/l and having surgery) were significantly associated with the death outcome in 2-year follow up, with the hazard ratios of 1.7, 2.0 and 0.5 respectively (Table 2).

Table 2. Two-year follow-up hazard ratios of patients diagnosed as cholangiocarcinoma by multiple Cox proportional hazards regression in Roi-et Hospital, Roi-et Province, Thailand, 1 Jan to 31 Dec 2010 (n=119)

Clinical characteristic	Hazard ratio	95% CI
Carcinoembryonic antigen CEA ≥5 µg/l	1.7	1.10 - 2.72
Age >60 years old	1.1	0.58 - 1.53
Total bilirubin TB ≥5 mg/dl	1.3	0.78 - 2.07
Alkaline phosphatase ALP ≥150 IU/L	2.0	1.14 - 3.42
Cancer antigen CA 19-9 >200 U/ml	1.0	0.61 - 1.62
Undergoing surgery	0.5	0.27 - 0.87

Remark: log-likelihood ratio = (-375.79), p-value = 0.0001

Discussion

Two-third of all CCA cases had an evidence of CT scan or any imaging following the inclusion criteria. In other words, one-third (37%) were diagnosed without any imaging support, reflecting that accessibility to CT scan should be assessed and using ultrasonography as a diagnostics tool should be further evaluated.

The 2-year overall survival rate was 15% which was same as the result of a study in Malaysia during 1997-2007[15] and higher than the study in Cluj-Napoca during 2005-2009 (3%)[16]. However, most CCA patients (83%) from the study in Malaysia were extrahepatic CCA whereas over 99% of CCA patients in Thailand were intrahepatic type[17]. The median survival time was 4.4 months which was very close to the median survival time from the 10-year study in Malaysia[15]. Unfortunately, the survival curve could not be displayed for each type of CCA as most CCA patients were diagnosed by CT scan without specifying type of CCA. The number of deaths after surgery within 30 days was likely due to complications from surgery[18]. Nevertheless, no CCA patient in this study died within 30 days after having surgery.

In analysis by log-rank test, although demographic factors such as gender, age, occupation and health insurance did not associate with the survival outcome, TB, ALP, tumor marker and having surgery revealed a statistically affect to the survival outcome. Actually, another factor which might affect the death outcome of CCA was nutritional status that could be measured by body mass index (BMI). Despite that, information on height and weight on the date of diagnosis could not be retrieved, and BMI could not be calculated. Hence, a prospective study with a proper data collecting system should be considered.

CCA patients with different types of health insurance and occupation had the same mortality within two years, which reflected the equity to access to care in the government hospitals. This study showed that using results of CA 19-9 and serum bilirubin could not forecast the prognosis of CCA within two years, which was not consistent to a meta-analysis study in China[19].

According to the regression, six factors were included in the model, including age, CEA, CA 19-9, ALP, having surgery and TB. The sample size was decreased to 119 cases due to incomplete data. The only three factors which significantly associated with the survival outcome were CEA, ALP and receiving surgery. This could be possibly concluded that the CCA patients with CEA level more than five microgram per liter posed the hazard of 1.7 times higher than those with lower level. This could be possibly explained by positive correlation between tumor stage and CEA[20]. Hence, level of CEA could indicate treatment planning since higher cancer staging could possibly associate with higher level of CEA. However, some studies showed that both CEA and CA 19-9 could be elevated in CCA[21-23] and simply

the level of CEA might not sensitive or specific for CCA[24]. One study showed 100% sensitivity and 100% specificity of using CEA (>5.2 ng/ml) and CA 19-9 (>180 U/ml)[24] while other investigators did not obtain such outstanding results[25,26].

Abdominal pain as well as levels of TB and ALP could also be used to identify type and severity of the disease. The most common physical indications are abnormal liver function tests, jaundice, abdominal pain, generalized itching, and changes in stool or urine color.[27,28] To some extent, the symptoms depend upon location of the tumor. Patients with CCA in the extrahepatic bile ducts are more likely to have jaundice while those with tumors of intrahepatic bile duct more often have pain without jaundice.[28] Nevertheless, this study showed the significance only for ALP and thus, type of CCA and location of tumor should be further explored to explain the disease stage related to symptoms and laboratory findings.

Prognosis of CCA was generally poor with a 5-year survival of less than 5%.[29,30] As most patients initially presented with advanced stage, they were not well treated by surgical resection and 75% of them died within one year after diagnosis. Focusing on treatment intervention, the patients received surgical treatment had longer survival time, yet it was hard to conclude that the surgery could prolong the life of CCA patient since physicians normally provide merely supportive care to patients in advanced stages and do not perform surgery[31].

Conclusion

The median survival time among 269 CCA patients diagnosed by CT imaging in Roi-et Hospital during 2-year follow-up was 4.4 months. The fatality rate in two years following diagnosis was 85.5% which implied that diagnosis was too late. Thus, early screening and diagnosis should be emphasized. Accessibility to disease screening and more sensitive techniques to detect the precancerous stage should be innovated as well. In addition, sensitivity and specificity of the current screening tool should be further evaluated. As the factors of CEA (>5 µg/l), ALP (>150 IU/l) and having surgery showed statistically significant affect to 2-year survival time, levels of CEA and ALP could be important information for physicians.

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Suggested Citation

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