

**THE 1-YEAR OVERALL SURVIVAL OUTCOME AMONG 221
IMAGING-DIAGNOSED CHOLANGIOCARCINOMA PATIENTS
IN ROI-ET PROVINCE, THAILAND, 2012**



AUTTAKIAT KARNJANAPIBOONWONG

**A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF
MASTER OF PRIMARY HEALTH CARE MANAGEMENT
FACULTY OF GRADUATE STUDIES
MAHIDOL UNIVERSITY**

2013

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Auttakiat Karnjanapiboonwong

.....
Mr. Auttakiat Karnjanapiboonwong
M.D.
Candidate

Det. Kedcham

.....
Lect. Det Kedcham,
Ph.D.
Major advisor

Supattra Srivanichakorn

.....
Lect. Supattra Srivanichakorn,
M.D., M.P.H. (Health Development),
Medicine (Epidemiology)
Co-advisor

B. Mahaisavariya

.....
Prof. Banchong Mahaisavariya,
M.D., Dip. Thai Board of Orthopedics
Dean
Faculty of Graduate Studies
Mahidol University

Supattra Srivanichakorn

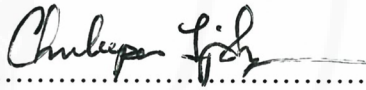
.....
Lect. Supattra Srivanichakorn,
M.D., M.P.H. (Health Development),
Dip. Thai Board of Preventative Medicine
(Epidemiology)
Program Director
Master of Primary Health Care Management
ASEAN Institute for Health Development
Mahidol University

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for the degree of Master of Primary Health Care Management
on
May 17, 2013


.....

Mr. Auttakiat Karnjanapiboonwong
M.D.
Candidate


.....

Ms. Chuleeporn Jiraphongsa,
M.D., Ph.D. (Epidemiology)
Chair


.....

Lect. Det Kedcham,
Ph.D.
Member


.....

Lect. Supattra Srivanichakorn,
M.D., M.P.H. (Health Development),
Dip. Thai Board of Preventive Medicine
(Epidemiology)
Member


.....

Prof. Banchong Mahaisavariya,
M.D., Dip. Thai Board of Orthopedics
Dean
Faculty of Graduate Studies
Mahidol University


.....

Lect. Supattra Srivanichakorn,
M.D., M.P.H. (Health Development),
Dip. Thai Board of Preventive Medicine
(Epidemiology)
Acting Director
ASEAN Institute for Health Development
Mahidol University

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AUTTAKIAT KARNJANAPIBOONWONG 5537777 ADPM/M

M.P.H.M.

THESIS ADVISORY COMMITTEE: DET KEDCHAM, Ph.D.,
SUPATTRA SRIVANICHAKORN, M.D., MPH, Cert. Board (EPIDEMIOLOGY),
Cert. Board (FAMILY MEDICINE)

ABSTRACT

Thailand has been burdened with the problem of cholangiocarcinoma for many years, but the factors which may influence the prognosis of the disease during treatment have not been studied seriously. This study aimed to describe the epidemiological characteristics and survival outcomes among the 221 imaging-diagnosed cholangiocarcinoma patients in the Roi-et cancer center from January to October 2010 from the Hos-XP program. Cox-proportional hazard regression was applied among 62 patients, who supplied all requested data, to study the hazard ratio among particular factors.

The one-year median survival time was 10 months, and the one-year survival rate was 45%. There was no association between survival time and age >60 years, sex, occupation, type of health insurance, bilirubin level > 5 mg/dl, CA 19-9 level, and receiving surgery or a palliative operation. Only the factor of CEA level > 5 µg/l had a statistically significant effect on one-year survival time. CEA level can be used to make a decision for treatment. However, a five-year follow-up with well-designed data collection should be considered.

KEY WORDS: 1-YEAR SURVIVAL / CHOLANGIOCARCINOMA /
HAZARD RATIO / PROGNOSIS / THAILAND

79 pages

การศึกษาการรอดชีวิตในระยะ 1 ปี ของผู้ป่วยมะเร็งท่อน้ำดีที่ได้รับการวินิจฉัยทางรังสีวิทยาจำนวน 221 คน ในโรงพยาบาลร้อยเอ็ด ปี 2556

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อรรถเกียรติ กาญจนพิบูลวงศ์ 5537777 ADPM/M

สม.ม.

คณะกรรมการที่ปรึกษาวิทยานิพนธ์: เดช เกตุกล้า, Ph.D., สุพัตรา ศรีวณิชชากร, MPH, Cert. Board (EPIDEMIOLOGY), Cert. Board (FAMILY MEDICINE)

บทคัดย่อ

วัตถุประสงค์ของการศึกษานี้คือเพื่อบรรยายลักษณะทางระบาดวิทยา การรอดชีวิต ในช่วง 1 ปี และปัจจัยที่มีอิทธิพลต่ออัตราการรอดชีวิตในช่วง 1 ปีของผู้ป่วยที่ได้รับการวินิจฉัยว่าเป็นมะเร็งท่อน้ำดีจำนวน 221 คน จากการฉายภาพทางรังสีวิทยาระหว่างเดือน มกราคม ถึง ตุลาคม 2553 โดยการทบทวนบันทึกข้อมูลภายในโรงพยาบาลผ่านโปรแกรม Hos-XP และ เวนระเบียนผู้ป่วยนอก และผู้ป่วยใน และวิเคราะห์หาปัจจัยที่มีอิทธิพลต่ออัตราการรอดชีวิตโดยใช้สมการ Cox-proportional hazard regression กับข้อมูลผู้ป่วยที่ปัจจัยที่ศึกษาครบถ้วนจำนวน 62 คน

ค่ามัธยฐานของระยะเวลาการรอดชีวิตในช่วง 1 ปี เท่ากับ 10 เดือน อัตราการรอดชีวิตเป็น 45% และไม่พบความสัมพันธ์ระหว่างระยะเวลาการรอดชีวิต กับ อายุ เพศ อาชีพ สิทธิการรักษา ระดับไบลูรีบิน CA 19-9 และการได้รับการผ่าตัดมีเพียงระดับของ CEA ที่ระดับ 5 ไมโครกรัม/ลิตร เท่านั้นที่มีอิทธิพลต่ออัตราการรอดชีวิตในช่วง 1 ปี อย่างมีนัยสำคัญทางสถิติ ดังนั้น ผลการตรวจหาระดับ CEA สามารถใช้ประกอบการตัดสินใจในการพิจารณาให้การรักษาผู้ป่วยโรคมะเร็งท่อน้ำดีได้อย่างไรก็ตามการติดตามศึกษาอัตราการรอดชีวิตระยะยาว 5 ปี ร่วมกับการออกแบบการเก็บข้อมูลที่เหมาะสมควรได้รับการพัฒนา

CONTENTS

	Page
ACKNOWLEDGMENTS	iii
ABSTRACT (ENGLISH)	iv
ABSTRACT (THAI)	v
LIST OF TABLES	ix
LIST OF FIGURES	x
CHAPTER I INTRODUCTION	1
1.1 Rationale and justification	1
1.2 Research question	4
1.3 Research objectives	4
1.3.1 General objectives	4
1.3.2 Specific objectives	5
1.4 Conceptual framework	6
1.5 Operational definition	7
1.6 Limitation of the study	11
CHAPTER II LITERATURE REVIEW	12
2.1 Anatomy of biliary tree	12
2.2 Cholangiocarcinoma and type of cholangiocarcinoma	13
2.3 Signs and symptoms	13
2.4 Cause of CCA	14
2.5 Diagnosis method	15
2.6 Intrahepatic cholangiocarcinoma (ICC)	17
2.7 Extrahepatic cholangiocarcinoma (ECC)	19
2.8 Staging	20
2.9 Treatment	21
2.9.1 The surgical treatment for ICC	22
2.9.2 The surgical treatment for ECC	23
2.9.3 Palliative therapy	23

CONTENTS (cont.)

	Page
2.10 Survival analysis of CCA	26
2.11 Survival of ICC 28	28
2.12 Survival of ECC 29	29
2.13 The factor influencing the prognosis of CCA in Thailand	31
2.14 Global CCA situation	31
2.15 CCA situation in Thailand	32
2.16 CCA control strategy in Thailand	32
2.17 Roi-ed hospital	33
CHAPTER III RESEARCH METHODOLOGY	35
3.1 Study design	35
3.2 Place of study	35
3.3 Studied population	35
3.3.1 Sample size	35
3.3.2 Inclusion criteria	36
3.3.3 Exclusion criteria	36
3.4 Ethical consideration	36
3.5 Research instrument	37
3.6 Validity and reliability test of instrument	37
3.7 Data collection procedure	37
3.8 Data processing and analysis	40
3.8.1 Descriptive analysis	40
3.8.2 Bivariate analysis	40
3.8.3 Multivariate analysis	40
3.8.3.1 Model selection procedure	40
3.8.4 Goodness of fit of final model	41

CONTENTS (cont.)

	Page
CHAPTER IV RESULTS	42
4.1 Descriptive study	42
4.1.1 Characteristic of CCA patient	42
4.1.2 Survival time	48
4.2 Analytic study to identify risk factors	49
4.2.1 Bivariate analysis by log-rank test	49
4.2.1.1 Among 221 CCA patients	49
4.2.1.2 Among 62 CCA patients	52
4.2.2 Multivariate analysis by cox-proportional hazard regression	55
4.2.2.1 Model assumption testing	55
4.2.2.2 Backward elimination stepwise	62
4.2.2.3 Goodness-of-fit test	62
CHAPTER V DISCUSSIONS	64
5.1 Descriptive study with median survival time	64
5.2 Analytic study to identify factor influencing the survival outcome	65
5.2.1 Bivariate analysis using log-rank test	65
5.2.2 Multivariate analysis (Cox-proportional hazard regression)	67
5.3 Limitations	67
CHAPTER VI CONCLUSION AND RECOMMENDATION	69
REFERENCES	70
BIOGRAPHY	79

LIST OF TABLES

Table	Page
1.1 Independent variables which will be collected and their definition	9
1.2 Dependent variables which will be collected and their definition	11
2.1 The treatment result after hepatic resection among intrahepatic cholangiocarcinoma patient	22
2.2 Clinical and surgical prognostic factors and pathological prognostic factors in extrahepatic CCA	30
4.1 The source of data which the data was retrieved from and the completeness of the data to be accepted into the model	44
4.2 Number, and percent proportion of CCA patients diagnosed in year 2010 in Roi-et hospital stratified by demographic, clinical presentation and treatment procedure and incidence rate of each factor	46
4.3 CCA patients diagnosed in year 2010 in Roi-et hospital stratified by demographic, clinical presentation and treatment procedure with median survival time and the significant level (p-value) from the log-rank test each fact	50
4.4 The number of CCA case of each factor among 62 CCA cases who were treated at Roi-et hospital having completed all variables	52
4.5 Schoenfeld's global test to test the proportional hazards assumption in the Cox proportional hazards model each factor among 62 CCA patients	61
4.6 Hazard ratio of having the factor of CEA level, age and total bilirubin (TB) level among patient diagnosed as CCA in Roi-et Hospital during 1 st January - 31 st October 2010 by multiple cox-proportional hazards regression	62
4.7 Goodness-of-fit test for the inclusion of design variables based on 2 quantiles of risk (Added variables version of the Groennesby and Borgan test) to test the goodness-of-fit of the cox-proportional hazard model containing variable of age, CEA level, and bilirubin level	63

LIST OF FIGURES

Figure	Page
2.1 Anatomy of biliary tree	12
2.2 Bismuth – Corlette classification	20
2.3 Map of Thailand and the location of Roi-et province and Roi-et map ...	33
3.1 Diagram showing recruitment of CCA cases and death status among 221 studied CCA patients, Roi-et hospital	39
4.1 Kaplan-Meier survival curve among 221 CCA patients who were followed up for 12 months after getting imaging diagnosis in Roi-et Hospital in year 2010 (N=221)	49
4.2 Log-minus-log plots of the baseline survival function of CCA patients with factor of underlying disease diabetes mellitus (DM). The difference between 2 graphs, DM and Non-DM looks constant over time (N=62) ..	56
4.3 Log-minus-log plots of the baseline survival function of CCA patients with factor of ALP level, <150 IU/L, 150 -400 IU/L and \geq 400 IU/L. The difference between 3 graphs looks constant over time (N=62).....	56
4.4 Log-minus-log plots of the baseline survival function of CCA patients with factor of age. The difference between 2 graphs, age \leq 60 years old and $>$ 60 years old looks constant over time (N=62)	57
4.5 Log-minus-log plots of the baseline survival function of CCA patients with factor of CEA level. The difference between 2 graphs, CEA < 5 micrograms/l and CEA \geq 5 micrograms/l looks constant over time. (N=62)	57
4.6 Log-minus-log plots of the baseline survival function of CCA patients with factor of intervention given to the CCA patient. The difference between 3 graphs, supportive care, palliative care and surgery looks constant over time. (N=62)	58

LIST OF FIGURES (cont.)

Figure		Page
4.7	Log-minus-log plots of the baseline survival function of CCA patients with factor of having abdominal pain. The difference between 2 graphs, having abdominal pain and no abdominal pain looks constant over time. (N=62)	58

CHAPTER I

INTRODUCTION

1.1 Rationale and justification

From WHO's annual compilation of health-related data in year 2012 (World Health Statistics 2012) demonstrate that 7.8 million people worldwide died from cancer in the year of 2008(1). The mortality from cancer is 13% of all cause of death in the world(2). About 70% of all cancer deaths in 2008 occurred in low- and middle-income countries. Lung, stomach, liver, colon and breast cancer cause the most cancer deaths each year. Cholangiocarcinoma (CCA) accounts for about 10–25% of the primary liver cancers in most parts of the world with age-standardized incidence rates (ASRs) between 0.3 and less than 1.5 per 100 000 in Western countries(3-5). An increasing trend of CCA incidence has been reported in many parts of these countries(6). Furthermore, CCA rates increased more than 120% in black and white American men recruited in the Surveillance, Epidemiology and End Results program during 1976–2000(7, 8). The incidence of CCA in Eastern Asia is also low, such as in Korea and Japan (ASRs less than 1.5) (8). The CCA incidence in Thailand is, however, exceedingly high with ASRs of 33.4 per 100 000 in men and 12.3 per 100 000 in women(9).

Thailand is the middle income countries that also face the problem of cancer. The data from Hospital-Based Cancer Registry of National Cancer Institute in Thailand in year 2010 shows that top five of cancer prevalence is colon cancer, hepato-biliary cancer, lung cancer, breast cancer and cervical cancer respectively(10). Among liver and bile duct cancer can be classified into 3 types of cancer by histological study namely hepatocellular carcinoma (HCC), cholangiocarcinoma (CCA) and others. The results from histological study in 7 cancer centers and 3 universities in year 2001 – 2003, more than 75% of hepato-biliary cancer in Northeast region was from Cholangiocarcinoma and around 20% was from hepatocellular

carcinoma. In other regions the percentage proportion of hepatocellular carcinoma was about 50-70%, cholangiocarcinoma was about 25 – 40%(11).

The CCA is the cancer originating in any parts of the bile duct and, based on their location, are divided into 2 main groups including intrahepatic bile duct and extrahepatic bile duct cancers. Treatment by surgery with complete cancer moving out (negative margin) is only one way to cure it; however it depends on stage of disease. In case of patient who cannot be excised the cancer totally, the supporting care, ablative therapy together with cryotherapy and radiofrequency may be considered but there were no the role of chemotherapy. So far, there is no definitive adjuvant regimen to expand the survival time(12). Meanwhile, the research from Japan demonstrates conversely that repeated surgery, combined with new effective regimens of chemotherapy could benefit the survival of Intrahepatic CCA patients(13). The CCA is notoriously difficult to diagnose and is usually fatal because of its late clinical presentation and the lack of effective non-surgical therapeutic modalities(14).

Most patients have unresectable disease at presentation and die within 12 months from the effects of cancer cachexia and a subsequent rapid decline in performance status. Overall survival rate, including resected patients, is poor, with less than 5% of patients surviving to 5 years, a rate which has not changed significantly over the past 30 years(15). Although cholangiocarcinoma is a relatively rare tumor around the world, interest in this disease is rising as incidence and mortality rates for intrahepatic tumors increase markedly worldwide(16). The statistics from the National Cancer Institute's SEER program in USA illustrate the percentage of 5 years survival rate among intrahepatic/extrahepatic CCA patient is 15%/30% for stage I, 6%/24% for stage II and III and 2%/2% for stage IV. However, many other factors may affect a person's outlook, such as the location of the cancer, whether or not it is resectable (removable by surgery), and a person's general health(17). One study from Thailand by Uttaravichien.T published in year 1999 considering the 1, 3 and 5 years survival rate according to stage of intrahepatic CCA shows that the 1, 3 and 5 years survival rate after surgery among stage III is 100%, 33%, 3 persons respectively. Stage IV-A patient's is 80%, 30% and 0% respectively. Stage IV-B's is 26%, 12% and 0% respectively(18).

There were several factors studied previously that might affect the prognosis of CCA beside of staging. The demographic data of patient, some study shows no significant differences in the survival time according to age and sex from the study of (Uttaravichien. T, 1999)(18), but the study in Republic of Korea show that the patient older than 60 years old have median survival time significantly less than the younger patients whereas there were no significant difference between gender (Cho, S.Y.,2010)(15). Actually, there were many processes to care the CCA patients. The socioeconomic factors also associated with the prognosis of the disease not only from the treatment accessibility but also the knowledge of self-care and the risk of getting liver fluke infestation from raw freshwater fish eating behavior. The health insurance in Thailand under “30 scheme” has been launched since 2002 which allowed patients with cancer access the health care much more than before. It might improve the prognosis of the disease among CCA patient, however since the survival study in Thailand in 1999(18); so far there have been no research about the survival outcome of CCA in Thailand. The liver fluke infestation problem was reported that most of liver fluke infestation patients were farmers living in the rural area who basically have lower educational level. The treatment technique applied the survival analysis; curative resection is still known to be the only effective therapeutic measure (19). Some clinicopathologic factors have been reported to be related to a dismal prognosis after resection, such as lymph node metastasis, a certain gross type, and positive resection margin(20-23). Some reports have suggested that lymph node metastasis is the most important prognostic factor for survival(20). However, there is no established consensus on the prognosis significance of lymph node dissection or even the extent of lymph node dissection (24). In addition, the health status of patient also affect directly to the disease prognosis, which can be measured by underlying disease they had, nutritional level by looking at Body Mass Index. Clinical and laboratory presentation also can be used to predict the prognosis such as jaundice and bilirubin level can represent the degree of invasion and the location of tumor, the level tumor marker CA 19-9 higher than 200 U/ml give the median survival time shorter than the patients who had the level ≤ 200 U/ml statistically significantly(15). Using chemotherapy and radiotherapy are not clear if chemotherapy used in this situation helps people live longer (25, 26). Meanwhile, the research from Japan demonstrates conversely that

repeated surgery, combined with new effective regimens of chemotherapy could benefit the survival of Intrahepatic CCA patients(13).

Thailand has encountered with the problem of CCA for many years by focusing on the risk prevention (27, 28), early diagnosis and treatment but the factors which may influence the prognosis of disease during treatment in Thailand were hardly studied. Survival time of each stage of CCA does not only represent the severity of the disease but also reflect the quality of treatment guideline whereas there were few survival studies in the past several years in Thailand despite Thailand is the endemic area of CCA(29, 30). Therefore, this research focuses on studying the survival outcome of CCA patients to describe the present disease prognosis and also identifies risk factors associating with the prognosis of CCA.

Roi-et province is the province in northeastern region of Thailand, were selected to be the studied site, due to Roi-et province also has the high prevalence of CCA and Roi-et hospital were upgraded to be the Regional Cancer Center in Northeastern region formally in May 2012.

1.2 Research questions

1. What is the survival rate and survival time among CCA patient in Roi-et hospital during January - October 2010?
2. How can the clinical finding, treatment process and tumor characteristics of cholangiocarcinoma predict the prognosis of CCA patient?

1.3 Research objectives

1.3.1 General objectives

- 1.3.1.1 To describe the epidemiological characteristic of CCA patient diagnosed in Roi-et cancer center in Roi-et hospital during January –October 2010.

1.3.1.2 To describe the survival outcome among studied CCA patient with the different factors.

1.3.1.3 To determine the factors that influence the survival time of studied CCA patient treated in Roi-et cancer center in Roi-et hospital

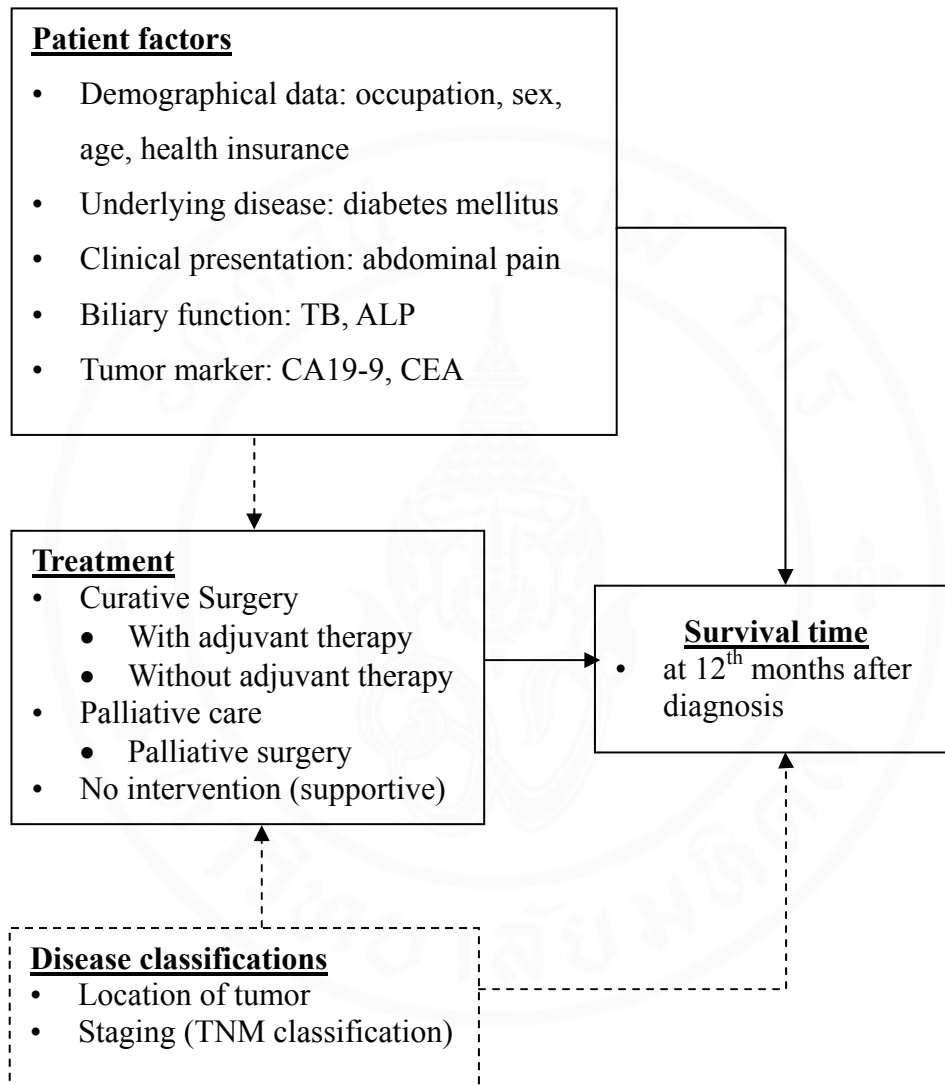
1.3.2 Specific objectives

1.3.2.1 To determine the survival rate at month 12th after receiving diagnosis CCA patient each classification of the disease treated at Roi-et cancer center in Roi-et hospital during January - December 2007

1.3.2.2 To identify the survival time of the CCA patient with the given variable including patient information, treatment technique and tumor classification among CCA patients.

1.3.2.3 To compare the CCA survival curve between the different factors that can influence the prognosis of the disease among patients in each classification of CCA cancer.

1.4 Conceptual framework



1.5 Operational definition

CCA: Cholangiocarcinoma is the cancer originating in any parts of the bile duct.

Survival rate: The proportion or probability of patient who free from particular event (censor) at the given period of time. It also can be called survival probability or survival function.

Event: The final outcome of interest, in this study use the “death” to be the event.

Censor: The event-free studied population during study period. In this study, losing follow up or being alive are accounted to be the censor.

Diabetes mellitus: The diabetes mellitus diagnosed by physician that patient have had before getting cholangiocarcinoma

Tumor marker: substance found in the blood, urine, or body tissues that can be elevated in cancer, among other tissue types. There are many different tumor markers, each indicative of a particular disease process, and they are used in oncology to help detect the presence of cancer. An elevated level of a tumor marker can indicate cancer; however, there can also be other causes of the elevation.

CA 19-9: Carbohydrate Antigen 19-9, also called cancer antigen 19-9, the tumor marker detected in patient with colon cancer, pancreatic cancer and also cholangiocarcinoma the tumor marker of cholangiocarcinoma.

CEA: Carcinoembryonic antigen, another kind of tumor markers which can be detected in cholangiocarcinoma.

TNM classification: A cancer staging system that describes the extent of cancer in a patient's body. Developed by American Joint Committee on Cancer: AJCC, 2002

T describes the size of the tumor and whether it has invaded nearby tissue,
N describes regional lymph nodes that are involved,
M describes distant metastasis (spread of cancer from one body part to another).

Curative surgery: The surgery which conduct by the purpose of curing the disease. Normally it will be used when imaging tests indicate a good chance that the surgeon will be able to remove all of the cancer. Doctors could use the term resectable to explain the malignant tumor they believe can be removed totally

Palliative surgery: The surgery performed to relieve symptoms or treat complications. It normally was performed when the cancer is too widespread to be completely removed. It is not expected to cure the disease, but it can sometimes increase quality of life.

Adjuvant therapy: The treatment that is given in addition to the primary treatment, usually given after surgery where all detectable disease has been removed. There are 2 main way typically used, adjuvant chemotherapy and adjuvant radiotherapy.

Biliary bypass: The palliative surgery to allow the bile to flow into the intestines to reduce the symptoms such as jaundice or itching.

Stent: The plastic or expandable metal tube which are inserted through the bile duct to prevent localized bile-flow constriction.

The definition of independent and dependent variable are described in the table1 and table 1.1.

Table 1.1 Independent variables which will be collected and their definition

Independent variable	Definition
<u>Patient factors</u>	
<ul style="list-style-type: none"> • Demographical data 	<ul style="list-style-type: none"> • Age: patient's age is calculated according to the year basis and classified into 2 groups; ≤ 60 years and > 60 years(15) • Sex: male and female • Occupation: government and non-government which include farmer, monk, general employee and no job • The right to get health service <ul style="list-style-type: none"> ○ Universal coverage ○ Non-Universal coverage <ul style="list-style-type: none"> ▪ Civil servant medical service ▪ Social security ▪ Private insurance
<ul style="list-style-type: none"> • Underlying disease 	<ul style="list-style-type: none"> • Diabetes
<ul style="list-style-type: none"> • Nutritional status 	<ul style="list-style-type: none"> • Body Mass Index (BMI): body weight (kg) divided by square of height (cm) <ul style="list-style-type: none"> ○ < 18 kg/m² ○ $18 - 23$ kg/m² ○ > 23 kg/m²
<ul style="list-style-type: none"> • Clinical presentation 	<ul style="list-style-type: none"> • Abdominal pain: The patients' record which shows that abdominal pain was sign and symptom was assigned to group of having abdominal pain. A record which shows no abdominal pain and a record which there were no evidence of abdominal sign were assigned to no abdominal pain group.

Table 1.1 Independent variables which will be collected and their definition (cont.)

Independent variable	Definition
<ul style="list-style-type: none"> • Laboratory test 	<ul style="list-style-type: none"> • Tumor marker; CA 19-9 (U/ml): divided into 2 groups < 200 and >200(15, 31) • Preoperative total bilirubin level will be ordered in to 3 levels. <ul style="list-style-type: none"> ○ <5 mg% ○ > 5 – < 10 mg% ○ > 10 mg%
<u>Treatment</u>	
<ul style="list-style-type: none"> • Surgery 	<ul style="list-style-type: none"> • Hepatic resection • Extended resection (standard surgery with vessel resection or pancreatectomy) • Lymph node resection
<ul style="list-style-type: none"> • Palliative care <ul style="list-style-type: none"> ○ Palliative surgery ○ Other palliative care 	<ul style="list-style-type: none"> • Biliary bypass • Stent • Chemotherapy • Chemotherapy, radio therapy
<ul style="list-style-type: none"> • No intervention 	<ul style="list-style-type: none"> • Supportive care

Table 1.2 Dependent variables which will be collected and their definition

<u>Survival outcome</u>	
Dependent variable	Definition
<ul style="list-style-type: none"> • Survival rate 	<p>The proportion or probability of patient who free from particular event at the given period of time. It also can be called survival probability or survival function. In this study the 12-, 36- and 60-months survival rate after giving the diagnosis and after treatment will be figured out (figure1).</p>
<ul style="list-style-type: none"> • Survival time 	<p>The time period during when the patient was diagnosed as CCA to the particular point of time. Normally, to calculate the period of survival time, the percentile among all data collected from each patient with the given factor will be considered. In this study, the survival time after giving the diagnosis and after treatment to death at 25th, 50th and 75th percentile will be calculated.</p>

1.6 Limitation of the study

1. Hospital-based data, retrospective data, cannot get the information of patients' self-care and other alternative treatments.

2. The study is based on the Roi-et province context, so the data would not represent the guideline used in other setting. The treatment procedures do not only depend on the national treatment guideline, but also depend on the patient findings doctors found and the decision of the doctors.

CHAPTER II

LITERATURE REVIEW

2.1 Anatomy of biliary tree

The bile duct is a thin tube, about 4 to 5 inches long, that reaches from the liver to the small intestine. The major function of the bile duct is to move a fluid called bile from the liver and gallbladder to the small intestine, where it helps digest the fats in foods. Different parts of the bile duct system have different names. In the liver it begins as many tiny tubes (ductules) where bile collects from the liver cells. The ductules come together to form small ducts, which then merge into larger ducts and eventually the left and right hepatic ducts. The ducts within the liver are called intrahepatic bile ducts. These ducts exit from the liver and join to form the common hepatic duct at the hilum. About one-third of the way along the length of the bile duct, the gallbladder (a small organ that stores bile) attaches by a small duct called the cystic duct. The combined duct is called the common bile duct. The common bile duct passes through part of the pancreas before it empties into the first part of the small intestine (the duodenum), next to where the pancreatic duct also enters the small intestine.

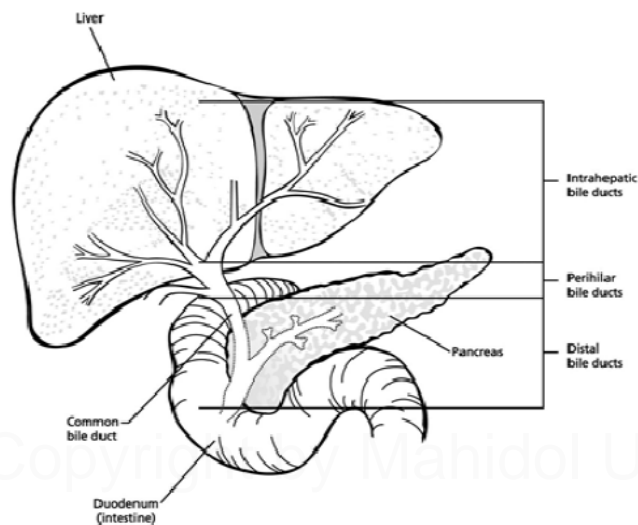


Figure 2.1 Anatomy of biliary tree

2.2 Cholangiocarcinoma and type of cholangiocarcinoma

Cholangiocarcinoma is the cancer originating from epithelium cell of bile duct and cystic duct but not included gall bladder and Papilla of Vater. The CCA is divided into 2 main groups including intrahepatic cholangiocarcinoma (ICC) and extrahepaticcholangiocarcinoma (ECC). The CCA patient with clinical jaundice 20% is intra-hepatic type, 60% is hepatic hilar (perihilar) and the rest 20% was found in the patient having both intra-heptic type and extra-hepatic type(25).

2.3 Signs and symptoms

The most common physical indications of cholangiocarcinoma are abnormal liver function tests, jaundice (yellowing of the eyes and skin occurring when bile ducts are blocked by tumor), abdominal pain (30%–50%), generalized itching (66%), weight loss (30%–50%), fever (up to 20%), and changes in stool or urine color(12, 32). To some extent, the symptoms depend upon the location of the tumor: patients with cholangiocarcinoma in the extrahepatic bile ducts (outside the liver) are more likely to have jaundice, while those with tumors of the bile ducts within the liver more often have pain without jaundice(12).

Blood tests of liver function in patients with cholangiocarcinoma often reveal a so-called "obstructive picture," with elevated bilirubin, alkaline phosphatase, and gamma glutamyltransferase levels, and relatively normal transaminase levels. Such laboratory findings suggest obstruction of the bile ducts, rather than inflammation or infection of the liver parenchyma, as the primary cause of the jaundice. The CA19-9 is elevated in most cases of cholangiocarcinoma, however high amounts of this substance often means that cancer is present, but the high levels can be caused by problems other than bile duct cancers. Also, not all bile duct cancers make this tumor marker, so low or normal levels do not mean there is no cancer(26).

2.4 Cause of CCA

The risk factors that make a person more likely to develop CCA are the certain diseases of the liver or bile ducts including the primary sclerosing cholangitis, bile duct stone, choledochal cysts, liver fluke infestation and cirrhosis(26). The older people are more likely than younger people to get CCA(33). Obesity can increase the risk of developing CCA because obesity increases the risk of bile duct stone. From the previous studies(34) showed that people with diabetes have a greater risk of CCA but not much. Other possible risk factors are smoking, alcoholic liver disease, pancreatitis, HIV infection i.e.(35).

The most common risk among Western world is primary sclerosing cholangitis (PSC), an inflammatory disease of the bile ducts which is itself closely associated with ulcerative colitis (UC)(33). Epidemiologic studies have suggested that the lifetime risk of developing cholangiocarcinoma for a person with PSC is on the order of 10%–15%(36), although 30% in CCA patient were found PSC from autopsy(37). The mechanism by which PSC increases the risk of cholangiocarcinoma is not well understood.

Congenital liver abnormalities, such as Caroli's syndrome or choledochal cysts, have been associated with 15% risk of developing cholangiocarcinoma in lifetime (38, 39). The existing of gallstones (cholelithiasis) is not clearly associated with cholangiocarcinoma. However, intrahepatic stones (called hepatolithiasis), which are rare in the Western region but common in several parts of Asia, have been strongly associated with cholangiocarcinoma(40).

Colonization with the liver flukes *Opisthorchis viverrini* (found in Thailand, Laos, and Malaysia) or *Clonorchis sinensis* (found in Japan, Korea, and Vietnam) has been associated with the occurring of cholangiocarcinoma(41, 42). Liver fluke infestation is the main cause of CCA problem in Thailand. Opisthorchiasis has been extensively studied in Thailand, where an estimated 6 million people are infected with the liver fluke (calculated from overall 9.4% prevalence within the population in 2001)(43). Most prevalence of Opisthorchiasis in the Northeastern and Northern region in Thailand due to the tradition of eating raw freshwater fish that metacercaria of *Opisthorchis Viverini* live in. Moreover, having the preserved fish which the

N-Nitrosocompound and Nitrosamines substance normally were added during food processing will be catalyst the CCA forming process of liver fluke infestation(44). Patients with chronic liver disease, whether in the form of viral hepatitis (e.g. hepatitis B or hepatitis C)(45), alcoholic liver disease, or liver cirrhosis increase risk of cholangiocarcinoma significantly (35). HIV infection was also identified in one study as a potential risk factor for cholangiocarcinoma, although it was unclear whether HIV itself or other correlated and confounding factors (e.g. hepatitis C infection) were responsible for the association(35).

2.5 Diagnosis method (17)

The diagnosis and staging of cholangiocarcinoma require a multimodality approach involving laboratory, radiologic, endoscopic, and pathologic analysis. The diagnostic modalities described in the following sections are useful to help achieve diagnostic accuracy.

Bilirubin level: The doctor may order lab tests to find out how much bilirubin is in the blood. Bilirubin is the chemical that causes jaundice. Problems in the bile duct, gallbladder, or liver may cause too much bilirubin to remain in the blood. A high bilirubin level tells the doctor that there may be problems with the bile duct, gallbladder, or liver.

Tumor markers: The substances made by cancer cells that can sometimes be found in the blood. People with bile duct cancer may have high blood levels of the carcinoembryonic antigen (CEA) and CA 19-9 tumor markers. High amounts of these substances often mean that cancer is present, but the high levels can be caused by problems other than bile duct cancers. For instance, the setting of other gastrointestinal or gynecologic malignancies or other bile duct pathology such as cholangitis and hepatolithiasis(46). Also, not all bile duct cancers make these tumor markers, so low or normal levels do not mean there is no cancer.

Ultrasound (US or ultrasonography): US is often the first imaging test done in people who have symptoms such as jaundice or pain in the right upper part of their abdomen. For this test, a small instrument called a transducer emits sound waves

and picks up their echoes as they bounce off internal organs. The echoes produced by most tumors differ from those of normal tissue. The patterns of echoes can help distinguish between some types of benign and malignant tumors. The sensitivity and specificity of ultrasound is poor in the diagnosis of cholangiocarcinoma, and staging generally relies on other imaging modalities(47, 48).

CT scan: the CT scan is an x-ray procedure that produces detailed cross-sectional images of your body. Instead of taking one x-ray, a CT scanner takes many pictures as it rotates around you. A computer then combines these into images of slices of the part of your body that is being studied. CT can be helpful in the staging, preoperative planning, and evaluation of vascular encasement. However, evaluation of intraductal spread and detection of lymph node and peritoneal metastases are also suboptimal. The sensitivity for N2 metastases detection has been reported to be 50% and the overall accuracy in the assessment of resectability 60% to 75%(49).

MRI scans: It provides detailed images of soft tissues in the body. But MRI scans use radio waves and strong magnets instead of x-rays. The energy from the radio waves is absorbed and then released in a pattern formed by the type of body tissue and by certain diseases. A computer translates the pattern into very detailed images of parts of the body. A contrast material called gadolinium may be injected into a vein before the scan to better see details. At present, MRI with magnetic resonance cholangiopancreatography (MRCP) is the best available imaging modality(50). It provides information regarding tumor extent, biliary and hepatic parenchymal anatomy, and intrahepatic metastases.

Cholangiogram: The imaging test that looks specifically at the bile ducts to see if they are blocked, narrowed, or dilated (widened). They can be used in people who may have bile duct cancer to look for abnormalities and to help plan surgery. There are several types of cholangiogram including Endoscopic retrograde cholangiopancreatography (ERCP), Magnetic resonance cholangiopancreatography (MRCP) and Percutaneous transhepatic cholangiography (PTC). MRCP has the advantage of being noninvasive and the possibility of obtaining additional information about other intra- and extrahepatic anatomic structures, whereas ERCP and PTC have the advantage of allowing bile duct sampling for diagnostic analysis as well as the possibility of relieving biliary obstruction by the insertion of stents.

Positron emission tomography (PET) scan: A scanner which can spot the radioactive deposits. This test can help spot small collections of cancer cells. It may also help tell if a tumor is benign or malignant. The radioactive glucose is injected into the patient's vein to look for cancer cells. The radioactivity will tend to concentrate in the cancer.

Angiography: An x-ray procedure for looking at blood vessels. For this test, a small amount of contrast dye is injected into an artery to outline blood vessels before x-ray images are taken. The images allow the doctors to see if blood flow in an area is blocked or affected by a tumor, and they can show any abnormal blood vessels in the area. Angiography can also show whether a bile duct cancer has grown through the walls of certain blood vessels. This information is mainly used to help surgeons decide whether a cancer can be removed and to help plan the operation.

Laparoscope: A thin tube with a light and a small video camera on the end which is inserted through the abdominal wall to view the bile duct, gallbladder, liver, and other organs and tissues in the area. The tube is inserted through a small incision (cut) in the front of the abdomen. (Sometimes more than one cut is made.) This procedure is typically done in the operating room while you are under general anesthesia.

Cholangioscope: A very thin fiber-optic tube which is passed into the bile duct through the mouth after routine ERCP or through a needle placed into a liver bile duct through the abdominal wall. From there it can be maneuvered into the bile duct. This allows the doctor to see any tumors and even biopsy them.

2.6 Intrahepaticcholangiocarcinoma (ICC)

The ICC was known as cholangiocellular carcinoma or peripheral bile duct carcinoma. It occurred in bile duct from intra-hepatic area to secondary branch of hepatic duct, not included the tumor at right or left hepatic bile duct, hepatic confluence (Klatskin's tumor) and distal common bile duct. Intrahepatic cholangiocarcinoma (ICC) is the 2nd most common of primary cancer after hepatocellular carcinoma. The incidence of ICC around the world is 10% in

average(51) of all kinds of primary cancer. In Thailand, the northeastern region has the highest incidence of ICC, about 300 cases per year. Among those cases, the ratio of male to female equal 1.8 : 1, the age range is 45 – 64 years old(18). The prognosis of the cases is not good because many of them visit the hospital during late stage of disease(52).

The ICC can be categorized into 2 groups; hilar type and peripheral type. Pathogenesis of ICC is likely from the chronic inflammation of bile duct (chronic cholangitis), chronic injury and regenerative hyperplasia of epithelium of bile duct result to malignant transformation. Macroscopic classification(53) according to the classification of primary liver cancer from the liver cancer study group of Japan was divided into 3 types is Mass-forming type, periductal infiltrating type and intraductal growth type. The malignancy spreading of mass-forming type correlates with hepatocellular invasion, periductal infiltration type relates with periportal invasion and intraductal growth type has the tumor spreading via intraductal part. The intraductal growth type gives the relatively best treatment result(52).

Uttaravichien. T categorized the ICC according to pathological finding into 4 types(18)

- Type I: A peripheral mass without intrahepatic duct dilatation and without jaundice
- Type II: An intermediate mass with intrahepatic duct segmental dilatation and still no jaundice
- Type III: A central mass with intrahepatic duct lobar dilatation and with or without jaundice. Admittedly, to have jaundice both right and left lobes intrahepatic duct will be involved.
- Type IV: Diffuse tumor masses of various sizes are found on both lobes and may be the combination of either one, two or all of the above three types (I, II, and III). This diffuse type therefore can have either one with or without intrahepatic duct dilatation, and also with or without jaundice.

2.7 Extrahepaticcholangiocarcinoma (ECC)

Extra-hepatic type (central type) is the tumor defined that occur from hepatic hilar until the end of common bile duct. This type normally leads to biliary obstruction. In early stage of disease, the symptoms are not obvious because tumor is still small but whenever the tumor became larger, bile duct would be obstructed (25). Typically, the larger tumor will come together with the near organ and lymph node metastasis, so most patients visiting hospital are in stage III – IV that is why the prognosis of the disease is relatively poor compare with the other cancers.

There are 3 common ways to classify the ECC including from the gross appearance, histological finding and the location of tumor at the hilar area. Using the gross appearance, the ECC can be divided into 4 types; papillary type, nodular type, nodular-infiltrating type and diffusely infiltrating type. The papillary type gives the best prognosis compare with the others. From the microscopic, the ECC can be categorized according to the histological finding to 5 types; grade cannot be assessed, well differentiated, moderately differentiated, poorly differentiated and undifferentiated. The perihilar type can be classified from the location of tumor at the hilar area according to the Bismuth-Corlette classification (figure 2.2)

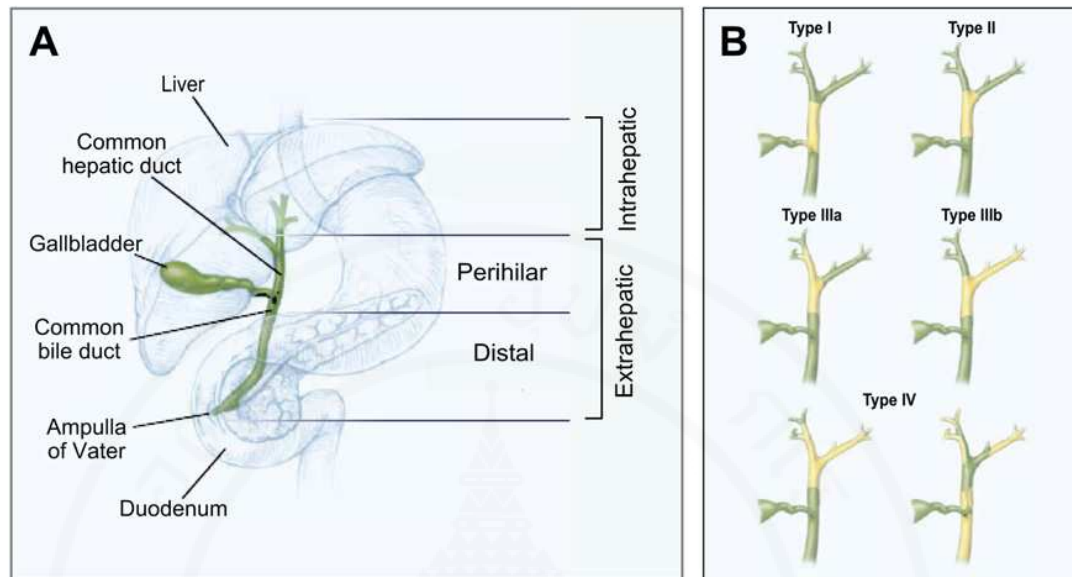


Figure 2.2 Bismuth – Corlette classification

Type I : lesion of the main hepatic duct not involving the main confluence.

Type II : lesion involving the confluence but clear of the right and left hepatic ducts.

Type IIIa : lesion involving the right hepatic duct.

Type IIIb : lesion involving the left hepatic duct.

Type IV : lesion involving the right and left hepatic ducts.

2.8 Staging

The major system used to describe the stages of cholangiocarcinoma is the American Joint Committee on Cancer (AJCC) TNM system (TNM; American Joint Committee on Cancer: AJCC, 2002). There are actually 3 different staging systems for CCA, depending on where they start. ICC is staged separately from ECC. Also, ECC are split into 2 groups: perihilar tumors and distal tumors. The TNM system for all bile duct cancers contains 3 key pieces of information:

T describes whether the main tumor has invaded through the wall of the bile duct and whether it has invaded other nearby organs or tissues.

N describes whether the cancer spread to nearby (regional) lymph nodes

M indicates whether the cancer has metastasized to other organs of the body.

2.9 Treatment

There are 2 general types of surgical treatment for bile duct cancer -- potentially curative surgery and palliative surgery. Potentially curative surgery is used when imaging tests indicate a good chance that the surgeon will be able to remove all of the cancer. Doctors may use the term 'resectable' to describe cancers they consider can be removed completely and 'unresectable' to describe those they think have spread too far or are in too difficult a place to be entirely removed by surgery or the health status of the patient is not proper to get surgery. In fact, only a small portion of cholangiocarcinoma are resectable at the time they are first diagnosed. Palliative surgery may be conducted to relieve symptoms or treat (or even prevent) complications, such as blockage of the bile ducts. This type of surgery is performed when the tumor is too widespread to be completely removed. Palliative surgery is not expected to cure the cancer, but it can sometimes help someone feel better and sometimes can even help them live longer. Palliative surgery is described in more detail in the section "Palliative therapy for bile duct cancer." Surgery to remove cancer can have obvious side effects and, depending on how extensive it is, may require several weeks for recovery. Patients whose cancer is not curable may want to carefully weigh the benefit and drawback of surgery or treatments that require significant recovery time. Unless there is clear evidence that such treatments will improve the patient's chance for longer survival or improved quality of life, some patients with very advanced stages of cholangiocarcinoma may choose to avoid them.

Treatment the cholangiocarcinoma by surgery with complete cancer moving out (negative margin) is only one way to cure it; however it depends on stage of disease. In case of patient who cannot be excised the cancer totally, the supporting care, ablative therapy together with cryotherapy and radiofrequency may be considered but there were no the role of chemotherapy. So far, there is no definitive adjuvant regimento expand the survival time(12). Meanwhile, the research from Japan demonstrates conversely that repeated surgery, combined with new effective regimens of chemotherapy could benefit the survival of Intrahepatic CCA patients(13). The CCA is notoriously difficult to diagnose and is usually fatal because of its late clinical presentation and the lack of effective non-surgical therapeutic modalities(14).

2.9.1 The surgical treatment for ICC

Hepatic resection, tumor removal with liver part resection is only one way to cure the patient. Some of patient needs more operational technique after hepatic resection depending on type and stage of cancer. Mass-forming type will be treated by anatomic and extensive hepatectomy with lymph node dissection. Periductal infiltrating type will be treated by hepatectomy with extrahepatic duct excision, hilar lymph node resection and skeletonization at hepatoduodenal ligament. Intraductal growth type should be operated as en bloc at affected hepatic segment and bile duct to get free margin. The previous studies about the result after hepatic resection were shown in the table 2.1.

Table 2.1 The treatment result after hepatic resection among intrahepatic cholangiocarcinoma patient

Authors/Year	Countries	No. of patients	% survival		
			1 st Yr	3 rd Yr	5 th Yr
Yamamoto et al/1992	Japan	20	66	36	36
Cherqui et al/1995	France	14	100	-	-
Pichlmayr et al/1995	Germany	32	56	16	13
Berdah et al/1996	France	31	67	-	32
Lieser et al/1998	USA	61	85	60	22
Harrison et al/1998	USA	32	78	58	42
Kim et al/1999	Korea	25	67	36	-
Chu et al/1999	Hong Kong	48	60	29	22
Valverde et al/1999	France	30	86	63	-
El Rassi et al/1999	France	19	83	17	-
Isaji et al/1999	Japan	36	44	24	24
Shimada et al/2001	Japan	49	66	-	-
Uenishi T et al/2001	Japan	28	57	27	27
Suzuki et al/2002	Japan	19	63	35	28
Tajima et al/2003	Japan	12	75	58	58

Yamamoto, 1999 summarized that in case of lymph node metastasis, the extended lymph node resection cannot improve the treatment result. The use of lymph node dissection is just to confirm histological diagnosis which will support the treatment plan(54). If the lymph node metastasis can be seen grossly, the extended lymph node resection was not recommended, giving adjuvant chemotherapy should be considered(52).

2.9.2 The surgical treatment for ECC

The treatment for extra-hepatic cholangiocarcinoma (ECC), In case that the tumor is in proximal third of bile duct, hilar resection with lymphadenectomy should be considered. Sometimes, liver resection is supposed to be done as well if only hilar resection was not enough. For chronic jaundice cases that total bilirubin level more than 10 mg%, bile drainage should be applied through skin by technique Percutaneous Transhepatic Biliary Drainage (PTBD) before surgery. A tumor at middle third of bile duct, the major duct resection and frozen section were recommended. Pancreaticoduodenectomy and lymphadenectomy were recommended for the distal third. The patient having positive margin or positive lymph node or carcinoma in situ at margin, adjuvant radiation or chemotherapy may be considered. However, there was no any clinical trial proving the success of treatment by radiation or chemotherapy. The palliative care or supportive treatment is useful and sometimes give the better result than the others. For the patient with metastatic disease, only bile drainage by using stent should be done, there still be no any other treatment is appropriate at the moment, although some techniques were accepted in some studies (55, 56)

2.9.3 Palliative therapy

Palliative therapy is treatment given to help control or reduce symptoms caused by advanced cancer. It is not meant to be a curative treatment. If the cancer has spread too far to be completely removed by surgery, doctors may focus on palliative operations, palliative radiation, and other palliative therapies. Because these cancers tend to advance quickly, doctors try to use palliative therapies that are less likely to affect a person's quality of life, when possible.

2.9.3.1 Chemotherapy

Chemotherapy is treatment with anti-cancer medicine which is given through intravenous or oral route. These medicines enter the bloodstream and reach all areas of the body, making this treatment useful in some cancers that have spread to organs beyond the bile duct. However, chemo has not been found to be effective against CCA, so the use has been somewhat limited. For CCA that is resectable, chemotherapy may be used after surgery to try to reduce the risk that the cancer will return. This is known as adjuvant chemotherapy. Some doctors may use it before surgery for borderline resectable cancers to try to improve the odds that surgery will be successful. This is called neoadjuvant treatment. Chemotherapy may also be used (with or without radiation therapy) for more advanced cancers. But it is not clear if chemotherapy used in this situation helps people live longer (25, 26).

Several drugs can be used to treat bile duct cancer. In some cases, 2 or more of these drugs may be combined to try to make them more effective. The drugs that have been used most often to treat bile duct cancer include:

- 5-fluorouracil (5-FU)
- Gemcitabine (Gemzar®)
- Mitomycin C
- Doxorubicin (Adriamycin®)
- Cisplatin
- Capecitabine (Xeloda®)
- Oxaliplatin

2.9.3.2 Biliary bypass

Once the surgery is started it becomes clear that the cancer is too advanced to be removed completely. At this point the surgeon may do a biliary bypass to allow the bile to flow into the intestines to reduce symptoms such as jaundice or itching. In this palliative procedure, the surgeon creates a bypass around the tumor blocking the bile duct by connecting part of the bile duct before the blockage with a part of the duct that lies past the blockage. Often, the gallbladder is used to provide some of the bypass. There are several different biliary bypass operations, and the decision on which one to use is based on the location of the

blockage. This option is more likely to be used if a patient is already having surgery and the cancer turns out to be unresectable. While a bypass is clearly more invasive than placing a stent or catheter, it has some advantages in that the effects may last longer and infection is less likely to be a problem(4).

2.9.3.3 Biliary stent or biliary catheter

If cancer is obstructing the bile duct, the doctor may insert a small tube (called a stent or catheter) into the duct to help keep it open. This may be done as part of a cholangiography procedure such as Percutaneous Transhepatic Cholangiography (PTC) or Endoscopic Retrograde Cholangiopancreatography (ERCP) or, in some cases, during surgery. A stent opens the duct to allow the bile to drain into the small intestine, while a catheter drains into a bag outside the body that can be emptied when needed. The stent or catheter may need to be replaced every few months if it becomes clogged and to reduce the risk of infection and gallbladder inflammation.

2.9.3.4 Palliative radiation therapy

Radiation therapy is treatment with high-energy rays. It may be used to help relieve pain and other symptoms by killing some cancer cells that are causing blockage of the bile duct or are pressing on nerves. Radiation therapy is treatment with high-energy rays or particles that destroy cancer cells. There are 2 different kinds of radiation therapy; external and internal radiation therapy.

2.9.3.5 Tumor ablation

Tumors in the liver that can't be resected can sometimes be ablated by placing a long metal probe through the skin and into the tumor. The tip of the probe is then heated (in radiofrequency ablation) or frozen (in cryotherapy) to kill the cancer cells.

2.9.3.6 Photodynamic therapy (PDT)

For this technique, a light-activated drug is injected into a vein. A few days later, an endoscope is passed down the throat and into the bile duct. A special red light on the end of the bronchoscope is aimed at the tumor, causing the

cells to die. The combination of PDT and stenting can help patients with bile duct cancer whose tumors aren't resectable live longer(56).

2.9.3.7 Alcohol injection

To relieve pain, doctors may deaden the nerves that convey sensations of pain from the bile duct and intestinal area to the brain by injecting these nerves with alcohol. This can be done during surgery or later under the guidance of a CT scan.

2.9.3.8 Pain medicines

Doctors can prescribe strong pain-relieving drugs if needed. Some people with cancer may hesitate to use opioid drugs (such as morphine) for fear of being sleepy all the time or becoming addicted to them. But many people get very effective pain relief from these medicines without serious side effects. It's very important to let your cancer care team know if you are having pain so that it can be treated effectively.

2.10 Survival analysis of CCA

Generally, survival analysis can use to calculate descriptively and analytically. The term of survival that normally use is survival rate and survival time

Survival rate is a part of survival analysis, indicating the percentage of people in a study or treatment group who are alive for a given period of time after diagnosis. The 5-year survival rate refers to the percentage of patients who live at least 5 years after their cancer is diagnosed. Certainly, many people live much longer than 5 years. In order to get 5-year survival rate, doctors have to look at people who were treated at least 5 years ago. In the same way, survival rate can be calculated at any point of time such as 1-year, 3 –year survival rate. Improvements in treatment since then may result in a more favorable outlook for people now being diagnosed with. Survival rates are often based on previous outcomes of large numbers of people who had the disease, but they cannot predict what will happen in any particular person's

case. Besides stage, many other factors may affect a person's outlook, such as the location of the cancer, whether or not it is resectable (removable by surgery), and a person's general health.

There were several studies in the past discussing on the survival rate and survival time under the effects of different factors they studied on. Some discussed on the overall survival among all kinds of CCA and shows the different survival rate by cancer stage. From the study by Shaib and El-Serag in 2004, most CCA patients have unresectable disease at presentation and die within 12 months from the effects of cancer cachexia and a subsequent rapid decline in performance status. Overall survival rate, including resected patients, is poor, with less than 5% of patients surviving to 5 years, a rate which has not changed significantly over the past 30 years(6). The statistics from the National Cancer Institute's SEER program in USA illustrate the percentage of 5 years survival rate among intrahepatic/extrahepatic CCA patient is 15%/30% for stage I, 6%/24% for stage II and III and 2%/2% for stage IV(17). One study from Thailand by Uttaravichien.T published in year 1999 considering the 1, 3 and 5 years survival rate according to stage of ICC shows that the 1, 3 and 5 years survival rate after surgery among stage III is 100%, 33%, 3 persons respectively. Stage IV-A patient's is 80%, 30% and 0% respectively. Stage IV-B's is 26%, 12% and 0% respectively(18). The study in Malaysia during 1997 -2007 found the overall median survival time was 4 months, whereas the median survival of R0 resected patients was 16 month Theoverall 1-,2- and 3-year cumulative survival rates were 67%,17% and 17%,respectively (57). However, many other factors may affect a person's outlook, such as the location of the cancer, whether or not it is resectable, and a person's general health. The 10 year (1997 – 2007) study among 69 patients in Malaysia also shows that the survival rates were significantly associated with curative resection, intrahepatic tumor, negative margin status, early tumor stage, higher degree of tumor differentiation and absence of jaundice. In contrast to previous reports, regional lymph node metastasis(58) and perineural invasion(59) were not associated with survival in resected patients. Moreover, we found that age, gender, race and risk factors were not predictors of survival(18, 57). Multivariate analysis showed that tumor location was a significant independent predictor of patient survival. Most patients have unresectable disease at the time of diagnosis and usually die within 6-12 mo from the cancer

cachexia, liver failure and biliary sepsis(57). The 5-year survival rate of CCA is quite low (about 5%).

2.11 Survival of ICC

The study by Seong Yeon Cho in 2010 illustrated that the cumulative 1-, 3- and 5-year survival rates were 68.2, 50.5 and 31.8 respectively and also show that old age patient, high preoperative CA 19-9 level, lymphatic invasion, and narrow resection margin has worse prognosis(15). The study by Cheng-Hsi Su and et al in year 1996 shows that the cumulative 5-year survival rate after resection for the 44 surviving ICC patients (hilar type) was 14.9% with a median survival of 14 months. The 5-year survival rate for the curative resection was 34.5%, and its median survival was 19 months, whereas the palliative resection gave no 5-year survivors and a median survival of 9 months(58). However, there is no established consensus on the prognostic significance of lymph node dissection. The previous study in Japan(54) studied about the survival time among the patients with lymph node metastasis who received 3 different operative techniques including hepatectomy or hepatectomy with extrahepatic bile duct and lymphnode resection, extended surgery or standard surgery together with vessel resection and the last group is supportive care (no operation). The 5th year survival rate among patient getting standard surgery is 30%, extended surgery is 10%. The fatality rate at 1 year after extended surgery among infiltrating-spread type patient is higher than noninfiltrating-spread type. The 5yr-survival rate of using adjuvant radiation is 39%, higher than patient receiving only surgery of which 5yr-survival rate is 13%(60). However there were several studies on adjuvant radiotherapy showing not effective treatment result, so adjuvant radiation has no obvious role for the current ICC treatment. For palliative treatment in unresectable cholangiocarcinoma, in case of biliary obstruction was suggested to apply biliary endoprosthesis rather than bypass surgery. Radiotherapy does not increase survival time among advance state of unresectable cholangiocarcinoma, in the other hand it will increase morbidity. Meanwhile, chemotherapy does not have a role to treat the patient.

There were several factors which determine the prognosis of ICC, for example the area that tumor invaded, intraductal growth gives the best prognosis, followed by mass-forming type, the worst prognosis type is periductal infiltrating type(22). The 5--year and 10-year survival rate of Intraductal growth is 58%. The 3 and 5 year survival rate of mass-forming type is 40% and 21% respectively. The 3 and 5 year survival rate of periductal infiltration type is 26% and 7% respectively. The prevalence of portal vein thrombus and lymph node metastasis were found in mass-forming with periductal infiltration type more often than in mass-forming type alone. Inoue et al conducted the research among mass-forming type 52 cases who received the operation curative resection in year 1980 – 1998, the factors influencing to overall survival time is surgical margin, lymph node metastasis, lymph node dissection and vascular invasion(61).

2.12 Survival of ECC

Population-based studies indicate that the overall 5-year survival rates of ECC in United State of America in 1973-1977 was 11.7% and in 1983 – 1987 was 15.1%(62). J. J. Kloek. et al conduct the review of the English-language literature (January 1995 – September 2007) concerning resectable extrahepatic cholangiocarcinoma by considering clinical and surgical prognostic factors and pathological prognostic factors shows evidences that female, low initial plasma bilirubin level, adjuvant therapy, concomitant pharmacotherapy, portal vein resection and no blood transfusion are beneficial for survival time from multivariate analysis study, whereas younger age patients have better result from univariate analysis. Furthermore, tumor location was suspicious whether it was influent the prognosis. The pathological prognostic factors were also studied, several research support that early stage of TNM staging system, Ro resection, early stage of tumor invasion, no lymph node metastasis, good differentiation grade, no vascular invasion and no perineural invasion advantage the survival time, the result was show in table 2.2

Table 2.2 Clinical and surgical prognostic factors and pathological prognostic factors in extrahepatic CCA, studied conducted by Kloek JJ. et al in January 1995 – September 2007(63)

Factor	Prognostic impact	Favouring survival benefit
<p>Clinical/surgical factor</p> <ul style="list-style-type: none"> • Age • Sex • Level of jaundice • Hepatolithiasis • Tumor location • Bismuth-Corlette staging • Chemoradiation therapy • Type of operation • Portal vein resection • Surgical complication 	<p>Minor</p> <p>Considerable</p> <p>Considerable</p> <p>None</p> <p>Dubious</p> <p>Dubious</p> <p>Considerable</p> <p>Considerable</p> <p>Considerable</p> <p>Considerable</p>	<p>Younger age</p> <p>Female</p> <p>Low initial plasma bilirubin level</p> <p>Distal lesion</p> <p>Type I, II lesion</p> <p>(Neo) adjuvant therapy</p> <p>Concomitant partial hepatectomy</p> <p>Portal vein resected</p> <p>No blood transfusion</p>
<p>Pathologic factor</p> <ul style="list-style-type: none"> • TNM staging systems • Tumor invasion • Lymph node metastases • Differentiation grade • Vascular invasion • Perineural invasion 	<p>Considerable</p> <p>Considerable</p> <p>Strong</p> <p>Strong</p> <p>Considerable</p> <p>Considerable</p>	<p>Early stage</p> <p>Early stage</p> <p>Metastases absent (N0)</p> <p>Good differentiation</p> <p>No invasion</p> <p>No invasion</p>

Note: Prognostic impact on clinical and surgical factors is scored as none (no evidence), dubious (conflicting evidence), minor (evidence from univariate analysis), considerable (evidence from uni- and multivariate analysis) and strong (evidence from several multivariate analyses)

2.13 The factor influencing the prognosis of CCA in Thailand

Thailand have encountered with the problem of CCA for many years by focusing on the risk prevention(27, 28), early diagnosis and treatment but the factors which may influence the prognosis of disease during treatment in Thailand were hardly studied. Survival time of each stage of CCA does not only represent the severity of the disease but also reflect the quality of treatment guideline whereas there were few survival studies in the past several years in Thailand despite Thailand is the endemic area of CCA(29, 30). One study from Thailand by Uttaravichien.T published in year 1999 considering the 1, 3 and 5 years survival rate according to stage of ICC shows that the 1, 3 and 5 years survival rate after surgery among stage III is 100%, 33%, 3 persons respectively. Stage IV-A patient's is 80%, 30% and 0% respectively. Stage IV-B's is 26%, 12% and 0% respectively(18)

2.14 Global CCA situation

From WHO's annual compilation of health-related data in year 2012 (World Health Statistics 2012) demonstrate that 7.8 million people worldwide died from cancer in the year of 2008(1). The mortality from cancer is 13% of all cause of death in the world(2). About 70% of all cancer deaths in 2008 occurred in low- and middle-income countries. Lung, stomach, liver, colon and breast cancer cause the most cancer deaths each year. Cholangiocarcinoma (CCA) accounts for about 10–25% of the primary liver cancers in most parts of the world with age-standardized incidence rates (ASRs) between 0.3 and less than 1.5 per 100 000 in Western countries(3-5). An increasing trend of CCA incidence has been reported in many parts of these countries(6). Furthermore, CCA rates increased more than 120% in black and white American men recruited in the Surveillance, Epidemiology and End Results program during 1976–2000(7, 8). The incidence of CCA in Eastern Asia is also low, such as in Korea and Japan (ASRs less than 1.5) (8).

2.15 CCA situation in Thailand

Thailand is the middle income countries that also face the problem of cancer. The data from Hospital-Based Cancer Registry of National Cancer Institute in Thailand in year 2010 shows that top five of cancer prevalence is colon cancer, hepato-biliary cancer, lung cancer, breast cancer and cervical cancer respectively(10). Among liver and bile duct cancer can be classified into 3 types of cancer by histological study namely hepatocellular carcinoma (HCC), cholangiocarcinoma (CCA) and others. The results from histological study in 7 cancer centers and 3 universities in year 2001 – 2003, more than 75% of hepato-biliary cancer in Northeast region was from Cholangiocarcinoma and around 20% was from hepatocellular carcinoma. The incidence of CCA in Northeast region of Thailand is highest among all regions of Thailand and also in the world(64). In other regions the percentage proportion of hepatocellular carcinoma was about 50-70%, cholangiocarcinoma was about 25 – 40%(11). The CCA incidence in Thailand is, however, exceedingly high with ASRs of 33.4 per 100 000 in men and 12.3 per 100 000 in women(9).

2.16 CCA control strategy in Thailand

The national policy in Thailand to control the problem of CCA, the prevention strategy was highlighted. From the scientific evidences showing that the major cause of developing CCA in Thailand is from *Opisthorchis viverrini* infestation, the CCA control strategy focused on the raw fresh fish eating behavior and liver fluke screening. History of opisthorchiasis control started in 1950 as a small scale helminthiasis control program in some high risk areas. Following a number of studies and trial projects of the Faculty of Tropical Medicine, Mahidol University, the national liver fluke control program has been developed and operated under several National Public Health Development Plans. Presently, the program is being operated in some provinces of the Central, and all provinces of the Northeast and North of Thailand.

In year 1987, Thailand launched the big campaign “Esan Mai Kin Pla Dib” (translated in English; Northeastern region people reject eating raw fresh fish), to build the proper attitude on eating behavior among Thai people, but the program lack s of

the continuity. Therefore, the impact of the program is not very effective. Nowadays, the incidence of CCA still burdens the country. The Ministry of Public Health realized the problem, so they declared the new strategy to encounter with CCA comprehensively in year 2012. The main issue in the strategy not only deal with the CCA prevention but also covered all area of the disease management including focusing on community participation, multisectoral coordination, improving CCA diagnosis and treatment, developing the quality of life, strengthening research on CCA and evaluation

2.17 Roi-et hospital

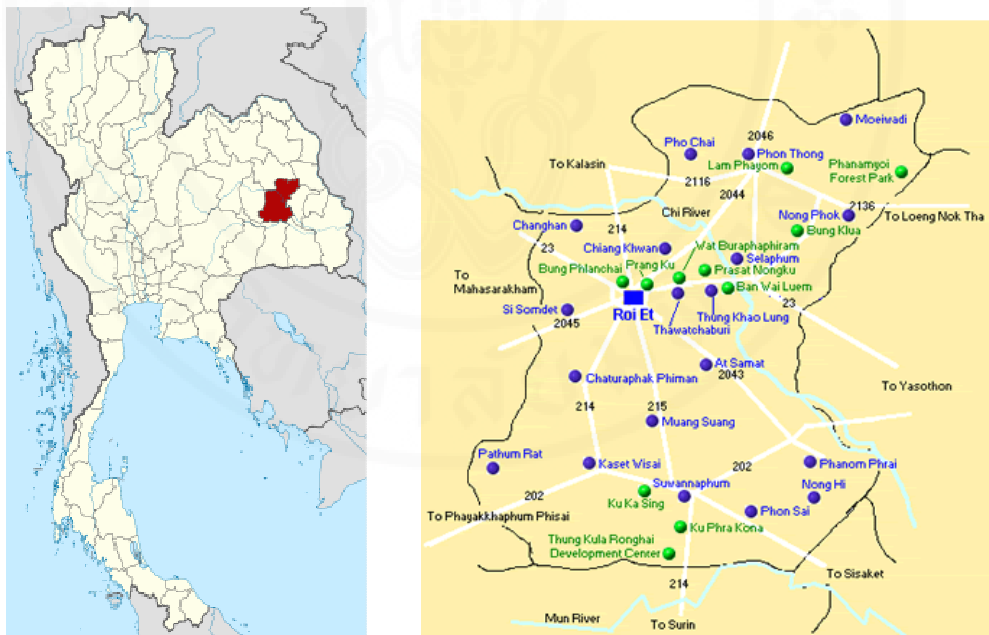


Figure 2.3 Map of Thailand and the location of Roi-et province (right picture), and Roi-et map (left picture)

Roi-et province is in the Northeast region where the endemic area of CCA is (10, 64). Roi-et province also has the high prevalence of CCA. There are 20 districts in Roi-et province. Total number of population at December 2006 was 1,310,047 and at December 2010 was 1,309,708 which compose of 653,903 males and 655,805

females. In each district, there is one public hospital in each district. The Roi-et hospital is the provincial hospital which is in Mueang District. Roi-et hospital is only one public hospital which can give the diagnosis and treatment to the patient with malignancy, so CCA patients from every district in Roi-et province have to be referred to Roi-et hospital. All CCA patients in service system will be registered into Roi-et cancer registry. Because of some nearby provinces around Roi-et province had no the tertiary care hospital where can treat the CCA patient, so not only the patient living in Roi-et province were registered, the patients from the nearby provinces were also in the cancer registry.

From Roi-et Hospital Based Cancer Registry 2006 – 2010 shows that the number of new case of CCA and Liver cancer in year 2006 – 2010 is 421, 458, 386, 438 and 302 respectively(30, 65-68). In year 2010, there were 302 new cases of CCA and Liver cancer, among those 0.66% is stage I, 1.66% is stage II, 1.32% is stage III, 28.48% is stage IV and 67.88% is unknown. From pathological result from biopsy, there were 53 cases of CCA and Liver cancer having the biopsy result. Twenty three from 53 cases (43%) are Cholangiocarcinoma(30). However, from data of Roi-et Hospital Based Cancer Registry shows some limitation of data including unknown the number of CCA, many unknown staging of CCA.

CHAPTER III

RESEARCH METHODOLOGY

3.1 Study design

A retrospective cohort study was designed to illustrate the characteristic of CCA patients and to demonstrate the survival analysis among CCA patients having different findings and receiving treatment procedures.

3.2 Place of study

Roi-et hospital, Roi-et province, Thailand was selected purposively as the study area

3.3 Studied population

The studied population included all charts of patients who were diagnosed as CCA according to ICD10 code of C221 in Roi-et hospital during January – December 2010.

3.3.1 Sample size

The whole study population was included in the study. For log-rank test with power 80%, significant level 0.05 and hazard ratio 2.0, the needed sample size was 72 cases. For cox proportional hazard regression with power 80%, significant level 0.05 and hazard ratio 2.0, the needed sample size was 66 cases. To calculate both log-rank test and cox proportional hazard regression in this study, at least 72 cases was needed to collect. Due to incomplete data, all CCA cases in year 2010 were recruited in the study.

3.3.2 Inclusion criteria

- A patient who was diagnosed as CCA according to ICD10, C221, during 1st January – 31st October 2010 by using at least 1 technique as following
 - Computed tomography (CT) scan
 - Magnetic resonance imaging (MRI) scan
 - Cholangiography
 - Endoscopic retrograde cholangiopancreatography (ERCP)
 - Magnetic resonance cholangiopancreatography (MRCP)
 - Percutaneous transhepatic cholangiography (PTC)
 - Positron emission tomography (PET) scan
 - Angiography, CT angiography and MRI angiography
 - Endoscope
 - Laparoscopy
 - Cholangioscopy

3.3.3 Exclusion criteria

The CCA patients who were not diagnosed during January 1st – October 31st (figure 3.1)

3.4 Ethical consideration

- The permission to use the data from the cancer center board in Roi-ed Hospital was asked for. Consent was taken from the organization where the study will be conducted
- Confidentiality of the information provided in the hospital-based data was maintained. The patients' name and hospital number was omitted; code number were used instead.
- All of the study process were reviewed and asked for the permission from the ethical committee of Mahidol University

3.5 Research instrument

A structured data collection form was used as research instrument for data collection. It was developed by the researcher through the consultation from the experts including the surgeon and statistician in Roi-et Hospital. The information filled in the form was extracted from the patients' charts, computer-based data, operative note and laboratory record which were kept at Registration Unit of Roi-et Hospital.

3.6 Validity and reliability test of instrument

- The purpose of the study were informed and clarified to all assistants.
- All assistants who join the retrieving patients' record were trained how to collect and record the patients' data. The skill which should be trained to assistance is
 - The definition of variables
 - The way to find the essential information from OPD, IPD chart and operation room record
- The pretest were conducted with the 30 patients' records and cross checking will be done after data collection
- All data collected by assistants were re-examined and cleaned by the main researcher.
- Surgeon and radiologist were recruited to be the consultants for the specific technical term the hospital used in each case

3.7 Data collection procedure

The patients' data were recruited from several sources as following.

- The profile and demographic data of CCA patients were collected from Hos-XP program using ICD10 code C221 by using the date of applying CT scan to know patient profile at diagnosis date.
- The date of applying CT scan or MRI that shows the result as suspected or suggested cholangiocarcinoma was assigned to be the diagnosis date.

- Patients' symptom and laboratory results were reviewed from OPD and IPD chart. Only a laboratory test done within 30 days before or after the date of applying CT scan or MRI was considered.

- The intervention given to the patients were reviewed from Hos-XP program, OPD and IPD chart by considering only the procedure done in Roi-et hospital were accounted to be the intervention which patient received regardless an alternative treatment patients seek outside the hospital.

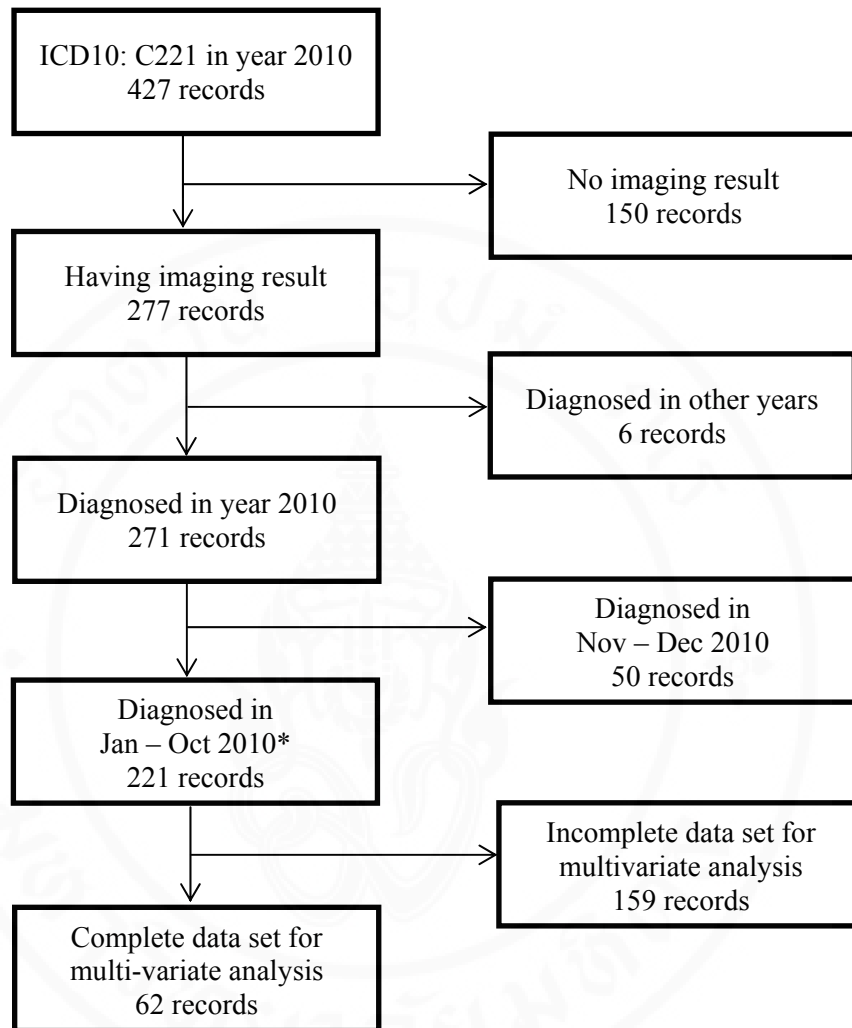
- All results of the imaging each patient was interpreted by medical radiologist from Roi-et hospital.

- Patient death status was collected from Patient death status was merged from collected data from 2 sources.

- Hospital-based data in Roi-et hospital.

- The National Health Security Office's (NHSO) record, name and ID were concealed, so to identify the dead people, the date of birth, sex and sub-district were matched. However, the death information retrieved from NHSO was available only in between 1st January 2010 – 31st October 2011. Therefore, to calculate 1-year survival among these patients, only the patients diagnosed as CCA during 1st January 2010 – 31st October 2010 were considered.

The whole process of data collection will be done by trained health officers, nurses and medical doctors. Hospital numbers of patients who diagnosed as CCA in Roi-et Hospital during January – December 2010 will be retrieved from computerized database of registration unit of the hospital. The diagnosis will be found out from ICD 10 code; the code for CCA is C221. The patients' charts were thereafter identified from the unit by the nurses or statistician working in the hospital. Those patients' charts will be copied with concealing the name, hospital number. Information will be extracted by the researcher and filled into the data collecting form. The data were collected during November 2012 and January 2013. Missing charts will be traced again within 7 days. All patients in studied period will be followed up for 1 years; the end point is at 31st October 2011. Only 221 patients having imaging result diagnosed during 1st January 2010 – 31st October 2010 were considered for descriptive study, whereas there were only 62 patients having data complete enough for cox-proportional hazard regression (The flow of recruited patient and number of patients were shown in figure 3.1).



*The period January to October 2010 was selected because death information was available in that period.

Figure 3.1 Diagram showing recruitment of CCA cases and death status among 221 studied CCA patients, Roi-et hospital.

3.8 Data processing and analysis

The collected data was checked for completeness, coded and entered into computerized database using Excel version 2003. Error in data entry was minimized by using CHECK (for minimization of intra-data-entry error) and VALIDATE (for minimization of inter-data-entry error) of Epi Info program version 3.5.4. Data analysis was performed by using STATA program, version 11.0.

3.8.1 Descriptive analysis

Descriptive analysis will be conducted to describe the characteristic of 221 cholangiocarcinoma patient in Roi-et hospital during January – October 2010. The incidence rate among CCA patient each factor was described. The 25th, 50th (median survival time) and 75th percentile of survival time at 12th month following diagnosis of CCA patient were calculated by the Kaplan-Meier method. Moreover, all independent factors of each type of CCA were described as well.

3.8.2 Bivariate analysis

Bivariate analysis was used to compare the survival curve of variables in each group by the log-rank test. A significant level was set at $p\text{-value} = 0.05$.

3.8.3 Multivariate analysis

Multivariate analysis was applied to calculate hazard ratio by Cox-proportional hazard regression that can be explained how many times of risk to get the event between the patients who exposed the given factors and the patients who did not exposed the factor at significant level at $p\text{-value} < 0.05$ by using the statistics program STATA/SE version 11.

3.8.3.1 Model selection procedure

- Identify factor to be considered to create fit model by reviewing literature and related medical knowledge of cholangiocarcinoma.
- The given assumption is no patient who loss-follow up during 1 years, even if some patient drop off hospital visit from several reasons.

- Because the death information were surveyed annually, so the study accounted that the intervention a patient got from hospital when they visit the hospital is the factor to study in this study.

- The assumption for cox-proportional hazard regression is the hazards for persons with different patterns of covariates are constant over time. The model assumption was checked by both graphical and statistical approach.

- Graphical approach using log-minus-log plots of the baseline survival function. The criteria to conclude that those factors met assumption was the curve from log-minus-log plot of each variable of the same factor looks parallel

- Statistical approach using Schoenfeld's global test. The p-value from wald test was more than 0.05 to meet the assumption.

- All independent factors meeting assumption were selected to put in cox-proportional hazard regression model. Stepwise backward elimination was performed for variable selection with p to eliminate 0.2.

3.8.4 Goodness of fit of final model

- We evaluate the fit of the model by using the Cox-Snell residuals. If the model fits the data well then the true cumulative hazard function conditional on the covariate vector has an exponential distribution with a hazard rate of one. This translates into fitting the model using the `stcox` command and specifying the `mgale` option which will generate the martingale residuals. Then we use the `predict` command with the `csnell` option to generate the Cox-Snell residuals for the model. The p-value of the test should be greater than 0.05 to summarize that the model is suitable. We then use the `sts generate` command to create the Nelson-Aalen cumulative hazard function. Finally, we graph the Nelson-Aalen cumulative hazard function and the `cs` variable so that we can compare the hazard function to the diagonal line. If the hazard function follows the 45 degree line then we know that it approximately has an exponential distribution with a hazard rate of one and that the model fits the data well.

CHAPTER IV

RESULTS

In the result chapter, the findings of the study were presented includes the following topic:

- Descriptive study
 - Characteristic of cholangiocarcinoma patient
 - Survival time
- Analytic study
 - Bivariate analysis by Log-rank test
 - Among 221 CCA patients
 - Among 62 CCA patients
 - Multivariate analysis by Cox-proportional hazard regression
 - Model assumption testing
 - Backward elimination stepwise
 - Goodness-of-fit test

4.1 Descriptive study

4.1.1 Characteristic of CCA patient

There were total 427 patients diagnosed as CCA according to ICD 10 from Roi-et hospital's data base in year 2010. From those, only 271 patient records have imaging result (269 CT scan, 1 MRI and 1 MRCP) in either OPD or IPD chart showing suspected or confirmed CCA. The number of male case was 180 and female case was 91, therefore an incidence rate among male and female was 27.5 and 13.9 per 100,000 populations in year 2010. The number of case by occupation; jobless = 0, government officer = 13, agriculture = 157, monk = 6 and general employee = 16. The median age at diagnosis date among 271 patient was 64 years old (range = 40 – 90).

Roi-et hospital has started the operation of hepatic resection by one surgeon working in Roi-et hospital since the beginning of 2010 so some patients were referred to receive a treatment from another tertiary-care hospital. During 1-year follow up, there were 140 cases receiving any kinds of treatment from only Roi-et hospital (not referred). Among those, 105 cases got supportive care and another 35 cases got any interventions including 4 hepatic resections, 5 cholecystectomy, 5 explore laparoscopy, 1 core needle liver biopsy and 20 palliative surgeries (ERCP, PTBD, by pass and wearing stent). There was only 1 patient getting chemotherapy as adjuvant therapy. Most patients referred to another hospital were referred to Khonkaen Province (62%).

Due to death information from National Health Security Office was retrieved only duration of 1st January 2010 – 31st October 2011. Thus, to study 1-year survival outcome only the CCA patients diagnosed during 1st January – 31st October 2010 were considered. Among all 271 imaging of those CCA patients treated at Roi-et hospital, there were 221 CCA patient diagnosed during 1st January 2010 – 31st October 2010. Therefore the 221 CCA patient was selected to study descriptive analysis. However, of those 221 CCA patients, the completeness or coverage of data each particular factor was different (table 4.1), the data of sex, age, occupation, underlying disease DM, clinical abdominal pain, referral information and treatment technique were complete 100%, the laboratory result including alkaline phosphatase, bilirubin level, CA 19-9 and CEA were 70%, 71%, 49% and 47% respectively. The laboratory results were not 100% because not all patients were tested. Nevertheless, all laboratory results were selected to study both descriptive and analytic part. The factors excluded were Body mass index due to very low completeness of height record (9.6%). The underlying disease bile duct stone, choledocal cyst, cirrhosis, primary sclerosing cholangitis, and liver fluke infestation were excluded since those diseases were hardly screened. The median age of those 221 CCA patients was 62 years old (range 40 – 90). According to conceptual frame work, those factors can be grouped into 3 groups including patients factor, treatment technique and disease classification, but the disease classification information cannot be collected because almost all CCA patients in Roi-et hospital were not explored pathologically and grossly. Therefore, only the factor of demographic, clinical presentation, laboratory and treatment technique were considered.

Table 4.1 The source of data which the data was retrieved from and the completeness of the data to be accepted into the model

Factor	Source of data	Completeness	Acceptance
Sex	Hos-XP data base	100%	Accepted
Age	Hos-XP data base	100%	Accepted
Occupation	Hos-XP data base	100%	Accepted
Body mass index • Height • Weight	OPD and IPD chart review	9.6% 36.5%	Not accepted Not accepted
Underlying disease • Bile duct stone • Cirrhosis • Choledocal cyst • Primary sclerosing cholangitis • Diabetes mellitus (DM) • Liver fluke infestation	Hos-XP data base, OPD and IPD chart	Only diabetes mellitus information was reliable. The completeness was 100%	Accepted (only DM)
Clinical presentation Jaundice • Abdominal pain	OPD and IPD chart review	100%	Accepted
Tumor marker • CA 19-9 • CEA	Hos-XP data base, OPD and IPD review	49% 47%	Accepted Accepted

Table 4.1 The source of data which the data was retrieved from and the completeness of the data to be accepted into the model (cont.)

Factor	Source of data	Completeness	Acceptance
Bilirubin level	Hos-XP data base, OPD and IPD review	70%	Accepted
Alkaline phosphatase level	Hos-XP data base, OPD and IPD review	71%	Accepted
Referral information	Hos-XP and OPD and IPD review	100%	Accepted
Treatment technique	Hos-XP and OPD and IPD review	100%	Accepted

The case distribution by other demographic data, clinical presentation and treatment procedure were shown in table2. Most CCA cases in the study were male (66%), age > 60 years old (65%) and farmer (61%). Only 10% of all cases were diabetes mellitus. Most cases presented the CCA without clinical of abdominal pain (81%). Looking at the tumor marker CA 19-9 and CEA, more than 50% of all CCA cases were tested for tumor marker. Among patient having tumor marker results, 56% of them had CA 19-9 ≤ 200 U/ml and 44% of them were greater than 200 U/ml whereas 59% of them had CEA $\geq 5\mu\text{g/l}$ and 41% had CEA $< 5\mu\text{g/l}$. The level of total bilirubin (TB) and alkaline phosphatase (ALP) were tested over 70%; most of them have TB level $< 5\text{ mg/dl}$ (60%) and ALP level 150 – 400 IU/l (41%).

Following the matched data-base of National Health Security Office's record in during 1st January 2010 – 31st October 2011, there were 121 CCA patients already died without any injuries. The fatality rate among 221 CCA patients during 1 year follow-up was 54.8%.

Table 4.2 Number, and percent proportion of CCA patients diagnosed in year 2010 in Roi-et hospital stratified by demographic, clinical presentation and treatment procedure and incidence rate of each factor

Factors	Number of CCA case (%)	Number of death (% SFR)	Death rate (person-month)
Sex			
• Male	146 (66)	84 (58)	0.08
• Female	75 (34)	37(49)	0.06
Age (year)			
• ≤60	77 (35)	37 (48)	0.06
• >60	144 (65)	84 (58)	0.08
Occupation			
• No job	61(28)	32 (52)	0.07
• Government officer	9 (4)	5 (56)	0.08
• Farmer	134 (61)	77 (57)	0.07
• Monk	5 (2)	2 (40)	0.04
• General employee	12 (5)	5 (42)	0.05
Underlying disease			
• No diabetes mellitus	198 (90)	107 (54)	0.07
• Diabetes mellitus	23 (10)	14 (61)	0.08
Clinical			
• No abdominal pain	41 (19)	29 (71)	0.11
• Abdominal pain	180 (81)	92 (51)	0.06

Table 4.2 Number, and percent proportion of CCA patients diagnosed in year 2010 in Roi-et hospital stratified by demographic, clinical presentation and treatment procedure and incidence rate of each factor (cont.)

Factors	Number of CCA case (%)	Number of death (% SFR)	Death rate (person-month)
Tumor marker			
• CA 19-9 (U/ml)			
○ <200	61 (28)	29 (48)	0.06
○ >200	47 (21)	28 (60)	0.08
○ No result	113 (51)	64 (57)	0.07
• CEA (µg/l)			
○ < 5	42 (19)	13 (31)	0.03
○ > 5	61 (28)	41 (67)	0.10
○ No result	118 (53)	67 (57)	0.07
Total bilirubin level (mg/dl)			
○ < 5	93 (42)	44 (47)	0.06
○ > 5 – 10	19 (9)	11 (58)	0.08
○ > 10	42 (19)	26 (62)	0.09
○ No result	67 (30)	40 (60)	0.08
ALP level(IU/L)			
○ < 150	42 (19)	16 (38)	0.04
○ >150 – 400	64 (29)	34 (53)	0.07
○ > 400	50 (23)	33 (66)	0.11
○ No result	65 (29)	38 (58)	0.08

Table 4.2 Number, and percent proportion of CCA patients diagnosed in year 2010 in Roi-et hospital stratified by demographic, clinical presentation and treatment procedure and incidence rate of each factor (cont.)

Factors	Number of CCA case (%)	Number of death (% SFR)	Death rate (person-month)
Referral to other hospital			
• Not referred	140 (9)	76 (54)	0.07
• Referred	81 (11)	45 (56)	0.07
Intervention among not referred group (N=140)			
• Surgery	15 (11)	7 (47)	0.06
○ Hepatic resection	4		
○ Cholecystectomy	5		
○ Explore laparotomy	6		
• Palliative care	20 (14)	9 (45)	0.05
○ Applying ERCP, PTBD, by pass or stent	20		
• No intervention (supportive care)	105 (75)	60 (57)	0.08

Note: SFR = specific fatality rate

* P-value was calculated among tested patient having laboratory result, not included the patients without result of laboratory.

4.1.2 Survival time

The Kaplan-Meier survival estimation showed that the median of overall survival time was 10 months and 25% of the cases died within first 3 months after date of diagnosis (figure 4.1) and no one died after receiving a surgery within 1-month follow up.

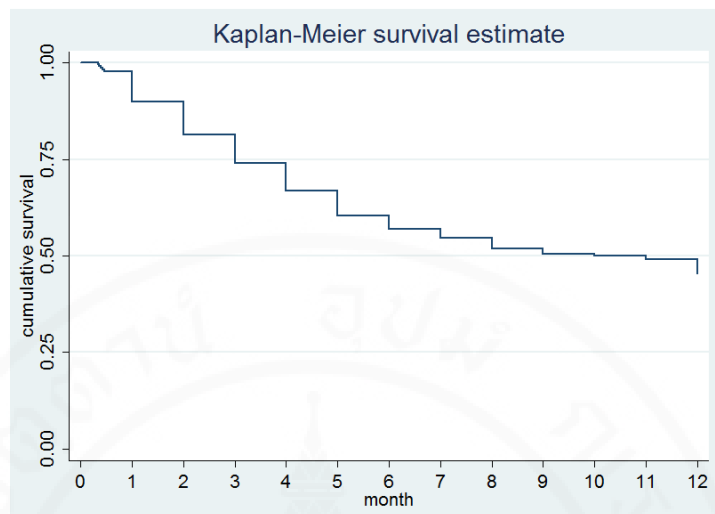


Figure 4.1 Kaplan-Meier survival curve among 221 CCA patients who were followed up for 12 months after getting imaging diagnosis in Roi-et Hospital in year 2010 (N=221)

4.2 Analytic study to identify risk factors

4.2.1 Bivariate analysis by log-rank test

4.2.1.1 Among 221 CCA patients

According to log-rank test (table 4.3), the factor of having abdominal pain, CEA ≥ 5 $\mu\text{g/l}$ and ALP level were significantly associated with disease prognosis. Looking at the median survival each factor, the median survival was more than 1 year among these factors including, female gender, age group, monk and general employee, and patient without any health insurance, CA 19-9 level ≤ 200 U/ml, CEA < 5 $\mu\text{g/l}$, total bilirubin < 5 mg/dL, ALP level < 150 IU/L, and getting palliative care. The diabetes mellitus was only one underlying disease which could be retrieved from data base. The BMI could not be described because most of record was incomplete.

Table 4.3 CCA patients diagnosed in year 2010 in Roi-et hospital stratified by demographic, clinical presentation and treatment procedure with median survival time and the significant level (p-value) from the log-rank test each factors

Factors	Number of available data	Median survival (month)	p-value (Log-rank test)
Sex	221		0.26
• Male	146	8	
• Female	75	≥12	
Age (year)	221		0.10
• ≤60	77	≥12	
• >60	144	8	
Occupation	221		0.84
• Government	9	10	
• Non-government	212	6	
Underlying disease	221		0.74
• Non-diabetes	198	12	
• Diabetes	23	≥12	
Health insurance	221		0.96
• Universal coverage	182	8	
• Non-Universal coverage	39	10	
Clinical	221		0.01*
• No abdominal pain	180	4	
• Abdominal pain	41	12	

Table 4.3 CCA patients diagnosed in year 2010 in Roi-et hospital stratified by demographic, clinical presentation and treatment procedure with median survival time and the significant level (p-value) from the log-rank test each factors (cont.)

Factors	Number of available data	Median survival (month)	p-value (Log-rank test)
CA 19-9 (U/ml)	108		0.22
• <200	61	>12	
• >200	47	8	
CEA (µg/l)	103		<0.001*
• < 5	42	>12	
• > 5	61	5	
Three level of TB (mg/dL)	154		0.07
○ < 5	93	>12	
○ > 5	61	6	
Three level of ALP(IU/L)	156		<0.01*
○ < 150	42	>12	
○ >150 – 400	64	8	
○ > 400	50	5	
Referral to other hospital	221		0.76
• Not referred	140	11	
• Referred	81	9	
Intervention among not referred group	140		0.40
• Surgery	15	12	
• Palliative care	20	≥12	
• No intervention (supportive care)	105	6	

4.2.1.2 Among 62 CCA patients

Among those 221 patients, there was only 62 CCA cases treated having completed all variables. Therefore, to do multivariate analysis by cox-proportional hazard regression, only 62 CCA cases were put in the model. The number of CCA case, CCA case proportion, specific fatality rate and log-rank test by factor were checked again to study representativeness with 221 CCA patients (table 3). There was small difference of case distribution and fatality rate in each factor between the group of 62 and 221. Only the factor of health insurance which the difference of case proportion was greater than 10%. Considering the log-rank test in both 62 CCA cases and 221 CCA cases, p-value of each factor among both groups was similar. The power of the test at significant level 0.05 and hazard ratio 2 for the sample size 221, 156, 150, 108, 62 was 0.99, 0.99, 0.99, 0.95 and 0.78 respectively.

Table 4.4 The number of CCA case of each factor among 62 CCA cases who were treated at Roi-et hospital having completed all variables

Factors	62 CCA cases		221 CCA cases	
	Number (%)	p-value (Log-rank test)	Number (%)	p-value (Log-rank test)
Sex	62 (100)	0.31	221(100)	0.21
• Male	42 (68)		146 (66)	
• Female	20 (32)		75 (34)	
Age (year)	62	0.84	221(100)	0.1
• ≤60	18 (29)		77 (35)	
• >60	44 (71)		144 (65)	
Occupation	62	-	221(100)	0.84
• Government	0 (0)		9 (4)	
• Non-government	62 (100)		212 (96)	

Table 4.4 The number of CCA case of each factor among 62 CCA cases who were treated at Roi-et hospital having completed all variables (cont.)

Factors	62 CCA cases		221 CCA cases	
	Number (%)	p-value (Log-rank test)	Number (%)	p-value (Log-rank test)
Underlying disease	62 (100)	0.74	221(100)	0.74
• Non-DM	55 (89)		198 (90)	
• DM	7 (11)		23 (10)	
Clinical	62	0.49	221(100)	0.01*
• No abdominal pain	55 (89)		180 (81)	
• Abdominal pain	7 (11)		41 (19)	
CA 19-9 (U/ml)	62	0.05	108(100)†	0.22
• <200	35 (56)		61 (56)	
• ≥200	27 (44)		47 (44)	
CEA (µg/l)	62	<0.001*	103(100) †	<0.001*
• < 5	31 (50)		42 (41)	
• ≥ 5	31 (50)		61 (59)	
Level of TB (mg/dL)	62	0.02*	154(100) †	0.07
• < 5	40 (65)		93 (60)	
• > 5	22 (35)		61 (40)	

Table 4.4 The number of CCA case of each factor among 62 CCA cases who were treated at Roi-et hospital having completed all variables (cont.)

Factors	62 CCA cases		221 CCA cases	
	Number (%)	p-value (Log-rank test)	Number (%)	p-value (Log-rank test)
Clinical	62	0.49	221(100)	0.01*
• No abdominal pain	55 (89)		180 (81)	
• Abdominal pain	7 (11)		41 (19)	
CA 19-9 (U/ml)	62	0.05	108(100)†	0.22
• < 200	35 (56)		61 (56)	
• ≥ 200	27 (44)		47 (44)	
Level of TB (mg/dL)	62	0.02*	154(100) †	0.07
• < 5	40 (65)		93 (60)	
• > 5	22 (35)		61 (40)	
Level of ALP(IU/L)	62	0.03*	156(100) †	0.01*
• < 150	19 (31)		42 (27)	
• >150 – 400	21 (34)		64 (41)	
• > 400	22 (35)		50 (32)	

Table 4.4 The number of CCA case of each factor among 62 CCA cases who were treated at Roi-et hospital having completed all variables (cont.)

Factors	62 CCA cases		221 CCA cases	
	Number (%)	p-value (Log-rank test)	Number (%)	p-value (Log-rank test)
Intervention	62	0.94	140(100) ‡	0.4
• Surgery	9 (15)		15 (11)	
• Palliative care	11 (18)		20 (14)	
• No intervention (supportive care)	42 (68)		105 (75)	

*p-value was less than 0.05; statistical significance

†the number of studied population was not 221 because some CCA patients were not tested

‡ the number of studied population was not 221 because some patients were referred to another hospital, the study focused on the patients who received treatment only in Roi-et hospital.

4.2.2 Multivariate analysis by cox-proportional hazard regression

4.2.2.1 Model assumption testing

To do multivariate analysis by cox-proportional hazard regression, the 62 CCA cases treated having completed all variables were recruited. Then the assumption was tested. The result of assumption test was shown in figure 4.2 – 4.11. Graphical considering log-minus-log plot together with statistical considering by Schoenfeld's global test, the variable of age, ALP level, CEA level, CA19-9 level, abdominal pain, total bilirubin level, type of intervention were selected to test the assumption. The factor of occupation was excluded because all patients were non-government employee. All those factors except sex met the assumption, the difference between the curves remain proportional over time and p-value from statistical test was greater than 0.05.

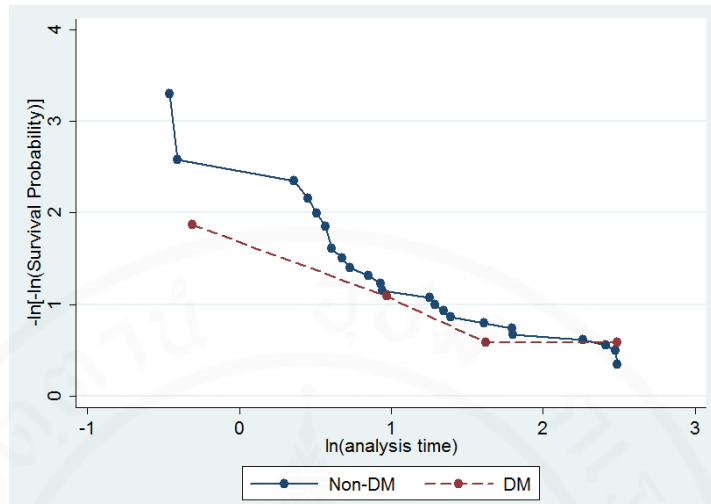


Figure 4.2 Log-minus-log plots of the baseline survival function of CCA patients with factor of underlying disease diabetes mellitus (DM). The difference between 2 graphs, DM and Non-DM looks constant over time. (N=62)

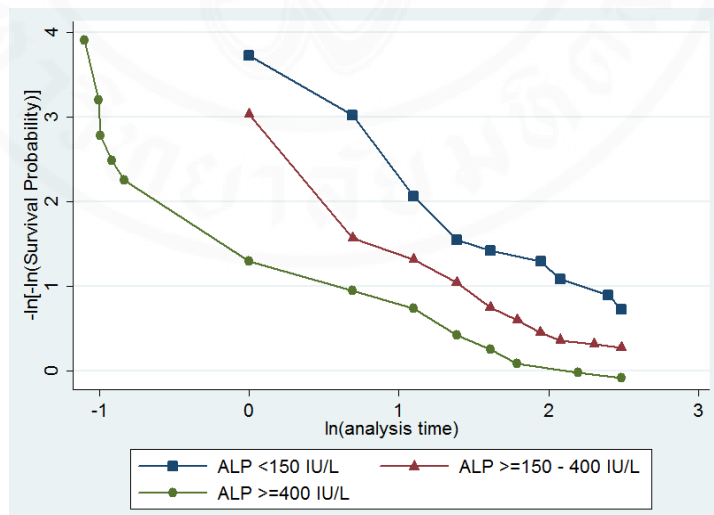


Figure 4.3 Log-minus-log plots of the baseline survival function of CCA patients with factor of ALP level, <150 IU/L, 150 -400 IU/L and \geq 400 IU/L. The difference between 3 graphs looks constant over time. (N=62)

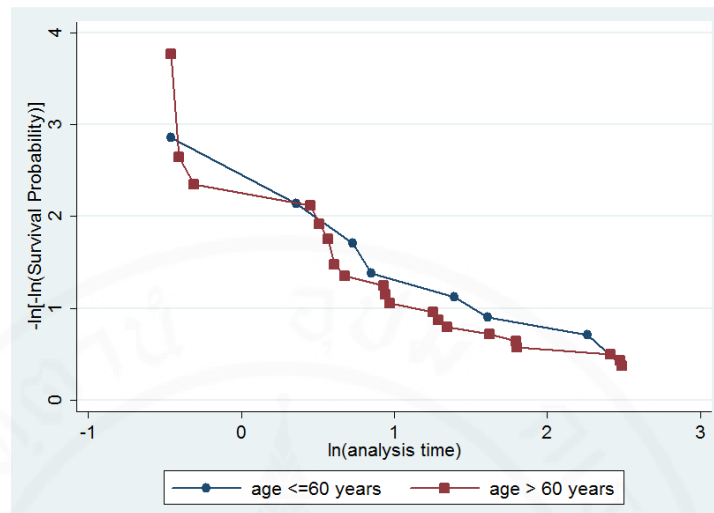


Figure 4.4 Log-minus-log plots of the baseline survival function of CCA patients with factor of age. The difference between 2 graphs, age < 60 years old and > 60 years old looks constant over time. (N=62)

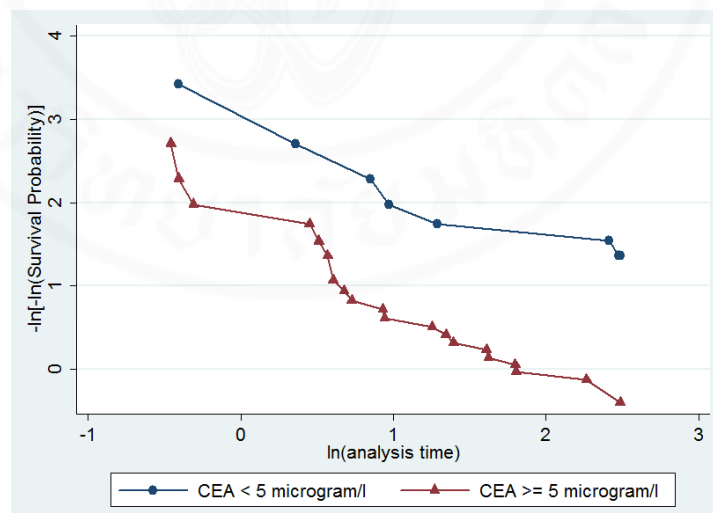


Figure 4.5 Log-minus-log plots of the baseline survival function of CCA patients with factor of CEA level. The difference between 2 graphs, CEA < 5 micrograms/l and CEA \geq 5 micrograms/l looks constant over time. (N=62)

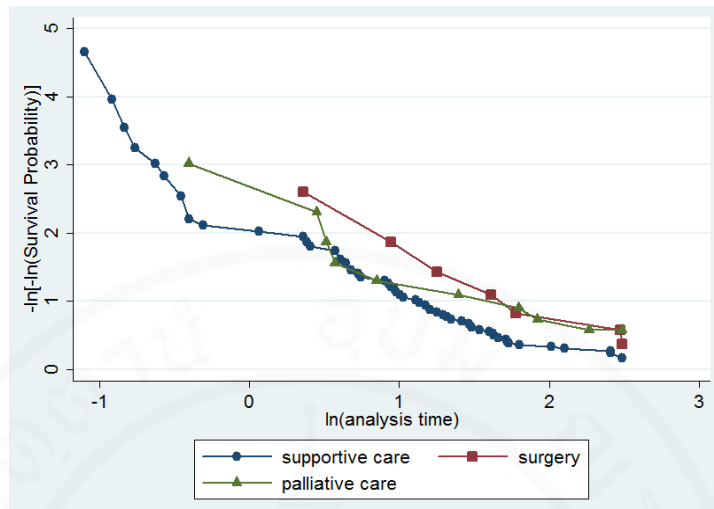


Figure 4.6 Log-minus-log plots of the baseline survival function of CCA patients with factor of intervention given to the CCA patient. The difference between 3 graphs, supportive care, palliative care and surgery looks constant over time. (N=62)

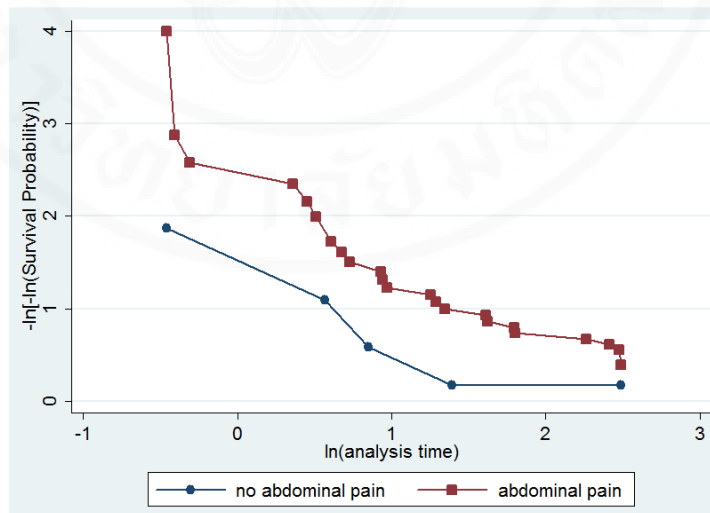


Figure 4.7 Log-minus-log plots of the baseline survival function of CCA patients with factor of having abdominal pain. The difference between 2 graphs, having abdominal pain and no abdominal pain looks constant over time. (N=62)

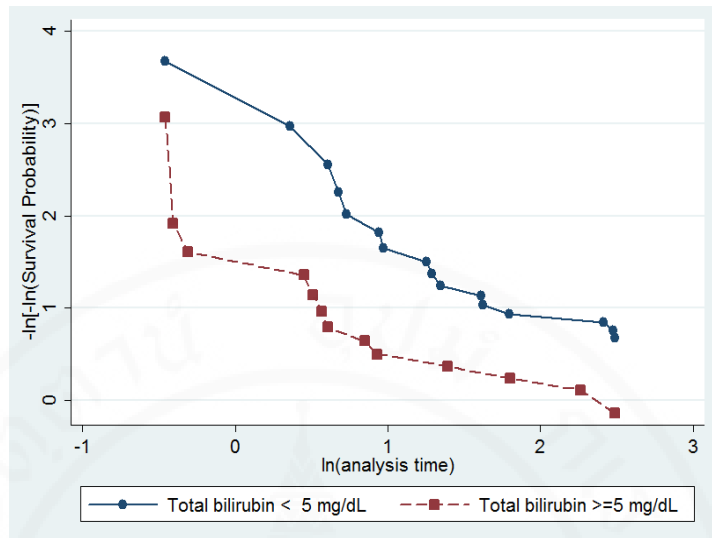


Figure 4.8 Log-minus-log plots of the baseline survival function of CCA patients with factor of total bilirubin level (TB level). The difference between 2 graphs, TB level < 5 mg/dl and TB level \geq 5 mg/dl looks constant over time. (N=62)

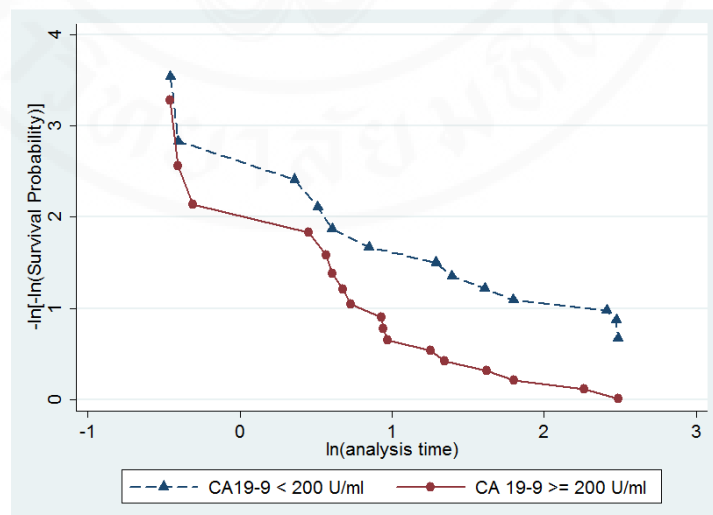


Figure 4.9 Log-minus-log plots of the baseline survival function of CCA patients with factor of CA 19-9 level. The difference between 2 graphs, CA 19-9 level < 200 U/ml and CA 19-9 level \geq 200 U/ml looks constant over time. (N=62)

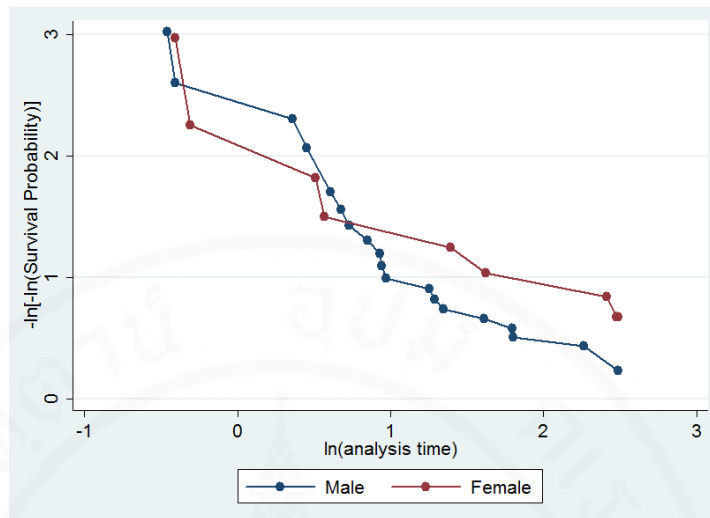


Figure 4.10 Log-minus-log plots of the baseline survival function of CCA patients with factor of total bilirubin level (TB level). The difference between 2 graphs, TB level < 5 mg/dl and TB level ≥ 5 mg/dl looks constant over time. (N=62)

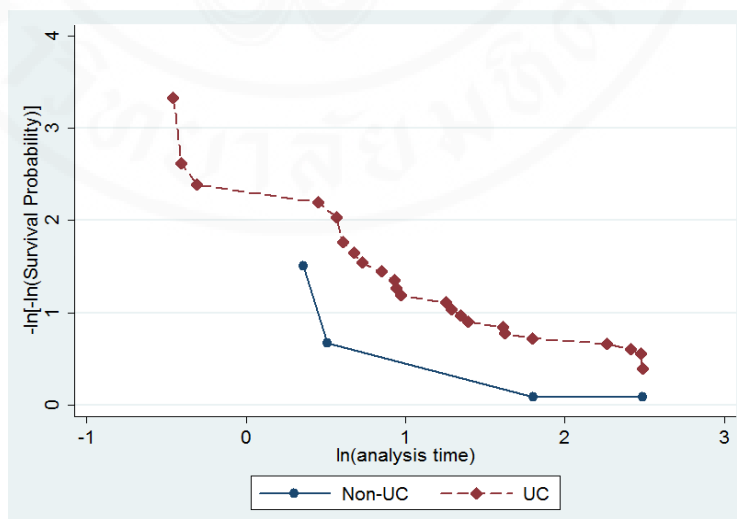


Figure 4.11 Log-minus-log plots of the baseline survival function of CCA patients with factor of health insurance classified into 2 groups, universal coverage (UC) and non-universal coverage (Non-UC). The difference between 2 graphs looks constant over time. (N=62)

The statistical test to prove the model assumption by Schoenfeld’s global test shows that all factors gave p-value higher than 0.05, so all factors met statistical assumption. However, considering both graphical and statistical test, the factor of sex did not meet graphical assumption so the factor of sex was excluded from the model (table 4.12).

Table 4.5 Schoenfeld’s global test to test the proportional hazards assumption in the Cox proportional hazards model each factor among 62 CCA patients

Factor	Statistical test		Assumption, (Graphical test)	Putting into the model
	p-value	Assumption		
Sex	0.72	met	not met	No
Age group	0.65	met	met	Yes
Diabetes	0.11	met	met	Yes
Universal coverage	0.81	met	met	Yes
Abdominal pain	0.61	met	met	Yes
CA 19-9 (U/ml)	0.93	met	met	Yes
CEA (µg/l)	0.37	met	met	Yes
Level of TB (mg/dL)	0.44	met	met	Yes
ALP(IU/L)				
○ < 150	Reference	met	met	Yes
○ ≥150 - 400	0.08			
○ ≥ 400	0.02			
Intervention		met	met	Yes
• Surgery	0.08			
• Palliative care	0.24			
• No intervention (supportive care)	reference			
Global test	0.59	met	-	-

4.2.2.2 Backward elimination stepwise

After applying back-ward elimination technique to select the proper variable into the regression, only the factor of CEA level, total bilirubin level and age were kept in regression due to p-value was less than 0.2. Even though, CEA level was only one factor which statistically significantly associate with 1-year survival outcome. The CCA patient with CEA level $\geq 5 \mu\text{g/l}$ have the hazard 5.21 times greater than the CCA patients who have CEA level $< 5 \mu\text{g/l}$. (Hazard ratio = 5.21, P-value < 0.001) (table 4.6). At significant level 0.05, hazard ration 2.0 and sample size 62, the power of the model was 0.78

Table 4.6 Hazard ratio of having the factor of CEA level, age and total bilirubin (TB) level level among patient diagnosed as CCA in Roi-et Hospital during 1st January - 31st October 2010 by multiple cox-proportional hazards regression

Factors	Hazard ratio	P-value
• CEA $\geq 5 \mu\text{g/l}$	5.21	$<0.001^*$
• Age > 60 years old	1.75	0.18
• TB $> 5 \text{ mg/dl}$	1.85	0.10

Note: log-likelihood ratio = -107.88 p-value = 0.0001

4.2.2.3 Goodness-of-fit test

The goodness-of-fit test of the model shows that the p-value of both quantile of risk were greater than 0.05 (table 4.7), so there was no statistical difference between an expected value and observed value gotten from the model. Similarly, the graphical test to compare Nelson-Aalen cumulative hazard function and the Cox-Snell residual also show the similar pattern, the hazard function follows the 45 degree line then it approximately has an exponential distribution with a hazard rate of one and that the model fits the data well (figure 4.12). Therefore, according to two tests, the model was fit.

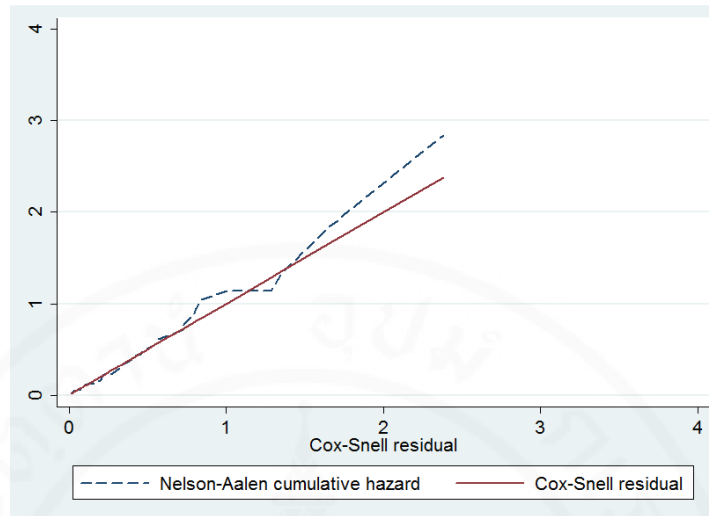


Figure 4.12 Graph of the Nelson-Aalen cumulative hazard function and the Cox’s Snell residuals variable to test the goodness-of-fit of the cox-proportional hazard model containing variable of age, CEA level, and bilirubin level

Table 4.7 Goodness-of-fit test for the inclusion of design variables based on 2 quantiles of risk (Added variables version of the Groennesby and Borgan test) to test the goodness-of-fit of the cox-proportional hazard model containing variable of age, CEA level, and bilirubin level

Quantile of Risk	Observed	Expected	p-value	Observations
1	21	23.567	0.597	31
2	10	7.433	0.346	31
Total	31	31		62

CHAPTER V

DISCUSSIONS

This retrospective cohort study was conducted in Roi-et cancer center in Roi-et hospital. The studied population was the CCA patients diagnosed during 1 January - 31 October 2010. The 221 CCA patient's record recruited in the descriptive study and log-rank test. 62 CCA patients having complete all studied variable was considered to do cox-proportional hazard regression.

The study aimed to describe the epidemiological characteristic of CCA patient diagnosed in Roi-et cancer center in Roi-et hospital during January - October 2010, to describe the survival outcome among studied CCA patient with the different factors and to determine the factors that influence of the survival time of studied CCA patient treated in Roi-et cancer center in Roi-et hospital.

5.1 Descriptive study with median survival time

There were 427 CCA cases according to ICD10 code, but only 271 cases having evidence of computerized tomography or any imaging as inclusion criteria. In other words, there were 156 cases (36.5%) diagnosed without any imaging support. It may reflect that case definition to report to hospital-based data was not clear and also the guideline to test tumor marker, ALP and total bilirubin was not done.

Considering those 271 cases, CCA morbidity rate in Roi-et in year 2010 was 20.7 per 100,000 populations whereas the incidence in other part of Northeastern from other studies shows that the incidence in Udonthani during 2001 – 2003 was 115 cases per 100,000 populations in male and 52.7 cases per 100,000 populations in female. The incidence in Khonkaen's during 1990 – 2001 was 85 cases per 100,000 populations (69, 70).

This study was conducted to figure out the overall 1-year survival outcome among any types and stages of CCA patient in Roi-et hospital. The fatality rate in 1-year follow up was 55%. In other words, the 1-year overall survival rate was 45% which was higher than the study in ClujNapoca, 2005 - 2009(71) but lower than the study in Malaysia about 22%. However, most CCA patients (83%) in Malaysia's study in 1997 - 2007 were extrahepatic CCA whereas most CCA patients in Thailand were intrahepatic type, over 99% of all CCA in Thailand was intrahepatic CCA(72). The median survival time was 10 months that was greater than the median survival time in 10-year study in Malaysia (57). The number of death after surgery within 30 days was considered as the mortality from a complication the operation(73), nevertheless no CCA patient in this cohort who died within 30 days after getting operation.

5.2 Analytic study to identify risk factor influencing the survival outcome

5.2.1 Bivariate analysis using log-rank test

Considering the factor of demographic data including sex, age, occupation and health insurance, all of those did not statistically associate to the survival outcome from Log-rank test. Meanwhile, considering the factor of clinical and laboratory presentation composing of abdominal pain, total bilirubin level, alkaline phosphatase level and tumor marker, CEA level and CA 19-9 level, only the factor of having abdominal pain, CEA level and ALP level statistically affect to the survival outcome. Looking at treatment technique, getting surgical or palliative intervention were not statistically associated to survival outcome. Actually, another factor which may affect the death outcome of CCA was nutritional status that can be measured by Body Mass Index (BMI) but the information of height and weight at diagnosis date could not be retrieved so BMI could not be calculated. According to the Log-rank test, CCA patient having different type of health insurance and occupation had the same chance to get dead within 1 year. Those can reflect the equality to access to care in government hospital among different occupation. Using the level of CA19-9 and bilirubin cannot

forecast the prognosis of CCA in 1 year in this study which is not consistent to the meta-analysis study in China.(31)

Prognosis of cholangiocarcinoma is generally poor with a 5-year survival of less than 5% (6, 74). Median survival for patients with intrahepatic cholangiocarcinoma is expected to be 18-30 months. A slightly shorter survival has been reported for patients with perihilar cholangiocarcinoma (12-24 months). Cure can be expected from only surgical resection of early stage tumors(75). After surgery, the 5-year-recurrence rate is in the range of 60% to 90%. Because most patients initially present with advanced disease, they are not amenable to primary surgical resection; 75% of patients die within 1 year of diagnosis. Focusing on the intervention patient got, they there was no difference between surgery and palliative care from log-rank test in this study shows that. However, considering the median survival from descriptive part, the patient with no intervention (supportive care) had a shortest median survival time, it can be explained by late stage of the disease at the diagnosis date that physician normally will not provide surgery, just only supportive care and sometimes palliative care(50). The shorter survival time among patient getting surgery needs further investigation on how to diagnose the disease staging and considering the surgery. When getting surgery and palliative intervention were grouped to compare to the supportive care, the difference was still not significant statistically (P-value = 0.18). However, the sample size to study affect from intervention was small so the benefit of intervention that physician gave to CCA patient in Roi-et Hospital to prolong their life within 1 year still need further investigation including surgeon interview and more complete data collection. Most studies supported that CCA patients who underwent surgical resection had a definite survival advantage over those who did not, however the median survival time among all types of CCA patients who got curative resection from other studies depends on a margin or residual of tumor after resection, the median overall survival time for R0, R1 and R2 were 58, 28 and 19 months respectively(76). Therefore, these results support that to improve the prognosis of CCA patient, the early diagnosis and early screening are very important for CCA. However, the result may be changed if those patients are followed continuously for few years after diagnosis. Furthermore, because the study did not include an intervention patient got from outside hospital, some changes or additional

interventions after diagnosis date may be missed. The factor of age could not be included in cox-proportional hazard regression due to the hazard curve of age ≤ 60 years and > 60 years were not parallel overtime, however the curve showed that at the first 6 months after diagnosis the hazard of the patient with age > 60 years were more than the patient's with age < 60 years. Then, the hazard of both age groups became parallel with similar rate after 6th month of diagnosis.

5.2.2 Multivariate analysis (Cox-proportional hazard regression)

The sample size in multivariate analysis was decreased to 62 cases because of incomplete data; the high number of incomplete data can distort the real situation. However, the comparison of case distribution by each factor between 221 cases and 62 cases show that the distribution was not much different, and also the result from log-rank test was show in the same way. So it can be explained that the 62 cases left was randomly selection apart from 221 cases.

According to cox-proportional hazard regression, there were 3 factors put in the model including age, CEA level, and total bilirubin level. But the CEA level was the only one factor that was statistically significantly associate to the survival outcome which can be concluded that every month the CCA patient with CEA level $> 5 \mu\text{g/l}$ have the hazard 5.26 times greater than the CCA patients who have CEA level $\leq 5 \mu\text{g/l}$. It is possibly explained by positive correlation between tumor stage and CEA level(77). Thus, CEA level of $5 \mu\text{g/l}$ can help the surgeon for treatment planning, the higher cancer staging possibly associate with higher CEA level. Having abdominal pain, total bilirubin level, and age > 60 years and ALP level may be the proxy of disease severity at diagnosis date(26), but the result shows that they were not associated to the death outcome. However, due to the low number of studied CCA cases, some factors might show not significant association in the study

5.3 Limitations

Because of the retrospective cohort study, some data were missed from records. Cancer staging and microscopic classification could not be retrieved because they will normally be confirmed after surgery which there was only 19 patients

operated. The cancer staging was the important confounder of survival study to evaluate an effect of intervention since a surgeon would not perform surgery among advance stage CCA patient. Once a patient came to hospital with late stage of CCA, physician will decide to give a palliative or supportive care rather than surgery according to the treatment guideline. Consequently, survival outcome among patients getting surgery tend to be better than palliative care. However, the result in this study shows that there was no different survival outcome between interventions. The sensitivity and specificity of using CT scan to tell cancer staging was not high, 10% sensitivity to detect extrahepatic invasion and 65% sensitivity to detect ductal dilatation (78), so the pathological finding of cancer should be collected properly to study survival time of applying an intervention each stage of cancer. Only 9.6% patients had recorded their weight and height at the date of diagnosis, so BMI of most patients cannot be calculated. The date patient got interventions was not accounted in the study, so the different date on when physician applied the intervention might affect the survival time. Some patients received both hepatic resection and PTBD, but the study categorized them in the hepatic resection group. Therefore the effect from each individual particular intervention should be studied more, prospective data collection with well design was recommended. Some alternative treatment that patient might get from another place was not considered in the study which can affect the survival time as well. However, a treatment patient got from outside the hospital is likely to affect the hazard ratio not much, since the patients' decisions to select outside-hospital treatment were random. The underlying disease bile duct stone, choledocal cyst, cirrhosis, primary sclerosing cholangitis, and liver fluke infestation were excluded since those diseases were hardly screened, the effect of those underlying disease could not be explored. The numbers of cases who have complete factor to perform multivariate analysis were small, only 62 cases in cox-proportional hazard regression analysis which can affect to the power of test.

CHAPTER VI

CONCLUSION AND RECOMMENDATION

The retrospective cohort study to describe and analyze the 1-year overall survival outcome among 221 CT imaging-diagnosed CCA patients in Roi-et Hospital shown that the median survival time was 10 months and survival rate of 1st year following diagnosis was 45%. The high fatality rate in 1st year following diagnosis implied that diagnosis was late, so early screening and diagnosis should be emphasized. There was not different between survival time among particular factor including age greater and lower than 60 years, male and female, occupations, type of health insurance, bilirubin level > 5 mg/dL, CA 19-9 level and getting surgery or palliative intervention from cox proportional hazard regression among 62 cases having completed data . Only the factor of CEA level > 5 µg/l was statistically significant to survival time in first year following diagnosis. Therefore, the physician might be suggested to consider the level of CEA to make a decision for treatment, the higher cancer staging possibly associate with higher CEA level.

However, some variables which were not able to be collected may relate to the outcome such as BMI, tumor classification (ICC or ECC) and tumor staging, therefore the specific survival outcome by those factors cannot be figured out. To complete the study of effects from those factors, a prospective cohort study few more years with proper data collecting system should be considered. The more complete data collection system did not only benefit to the future research but also be useful for disease prognosis consideration of individual CCA case.

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BIOGRAPHY

NAME Auttakit Karnjanapiboonwong

DATE OF BIRTH July 27, 1980

PLACE OF BIRTH Bangkok Thailand

INSTITUTION ATTENDED Mahidol University,
Ramathibodi Medical Faculty, 1998 - 2004
Medical Doctor
Bureau of Epidemiology
Field Epidemiology Training Program,
2009 - 2011
Preventive Medicine (Epidemiology)
Mahidol University
ASEAN Institute for Health Development,
Thailand, 2012 - 2013
Master of Primary Health Care
Management

**FELLOWSHIP/
RESEARCH GRANT** Bureau of Epidemiology, Ministry of
Public Health

PRESENT POSITION Medical Physician Senior Professional
Level

HOME ADDRESS 19/21 Bangkunnong Rd. Bangkoknoi,
Bangkok
Tel. 6681-820-1894
E-Mail: auttakit@yahoo.com

EMPLOYMENT ADDRESS FETP, Bureau of Epidemiology
Ministry of Public Health