

RESEARCH ARTICLE

Survival Rate of Intrahepatic Cholangiocarcinoma Patients after Surgical Treatment in Thailand

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Abstract

Intrahepatic cholangiocarcinoma (ICC), one of the primary liver cancers, is frequent in the northeastern part of Thailand. Surgical resection remains the best method of treatment, but patients suffering from ICC usually present at a late stage of the disease. Studies of survival and prognostic factors after surgery remain rare. The aim here was to evaluate the survival rate and factors affecting the survival of patients with intrahepatic cholangiocarcinoma after surgery. The study used a retrospective cohort design. The subjects were 73 consecutive patients with ICC, who were admitted for surgery to Srinagarind Hospital, Khon Kaen University, during the period 2005-2009. The censoring date was 31 December, 2011, data being evaluated using uni- and multivariate analyses. Postoperative survival analysis was performed by the Kaplan-Meier method, and the Cox proportional hazard model was used to identify independent prognostic factors. The total follow-up time was 99 person-years. The total number of deaths was 59, giving a mortality rate of 59 per 100 person-years. The cumulative 1-, 3-, and 5-year survival rates were 52.1%, 21.7%, and 11.2%, respectively. The median duration of survival after resection was 12.4 months. Univariate analysis revealed stage of disease, lymph node metastasis, histological type, histological grade and macroscopic classification to be statistically significant (p -value<0.05) prognostic factors. In the multivariate analysis, only macroscopic classification was statistically significant (p -value<0.05). In conclusion, macroscopic classification was the only independent factor found to be significantly associated with survival following surgical treatment of ICC.

Keywords: Intrahepatic cholangiocarcinoma - surgical treatment - survival time - Thailand

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Introduction

Cancer is a major health problem around the world; in 2010, there were 789,620 new cancer cases in males and 739,940 new cancer cases in females. In the same year, the estimated number of deaths from cancer was 299,200 in males and 270,290 in females (American Cancer Society, 2010). Cholangiocarcinoma (CCA), including both the intrahepatic and extrahepatic bile duct forms of the disease, is the most common cancer in Thailand, especially in the northeastern region where the incidence rate has been the highest in the world. In the northeast province of Khon Kaen, where 89% of liver cancers are CCA (Vatanasapt et al., 1995), the age-adjusted incidence rates for liver cancer have been 89.2 and 35.5 per 100,000 in males and in females, respectively (Vatanasapt et al., 1990).

Intrahepatic cholangiocarcinoma (ICC) is one of the primary liver cancers. Surgical resection remains the best method of treatment, but patients suffering from ICC usually present at a late stage of the disease. Studies of

prognostic factors and survival after surgery remain rare, but the survival of patients suffering from this disease is low in both hospital-based and population-based studies (Sriamporn et al., 1995; Khuntikeo et al., 2008; Shen et al., 2009). The particularly high incidence of CCA in northeast Thailand is linked to high levels of infection by the liver fluke, *Opisthorchis viverrini*, and programmes for the control of infection by this parasite have played a role in the primary prevention of the disease for decades (Saengsawang et al., 2012). However, due to the large number of patients presenting with the disease, tertiary prevention is also important.

A previous study followed up patients with extrahepatic cholangiocarcinoma following surgical treatment at Srinagarind Hospital, Khon Kaen University, Thailand (Pattanathien et al., 2013). The present study aimed to evaluate the survival rates and factors affecting survival in patients with intrahepatic cholangiocarcinoma following surgical treatment at the same hospital. The outcomes are expected to be useful for improving the treatment modality and the quality of life of patients.

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Materials and Methods

A retrospective cohort study was conducted with 73 patients, who were diagnosed with intrahepatic bile duct cancer (histologically confirmed) and treated by surgical excision by one surgeon during the period 1 January, 2005, to 31 December, 2009, at Srinagarind Hospital, Khon Kaen, Thailand. The patients were followed up until death or the end of the study (31 December, 2011).

The independent variables were age at diagnosis, gender, stage of disease, resection margin, histological type, histological grade, and macroscopic type. The dependent variable was the survival time of patients with ICC. In order to calculate the survival time, the starting point was identified as the date of surgery, and the follow-up period ended when a patient died or on completion of the study. Censored data were used for those still alive at the end of the study or lost to follow-up. The follow-up status of each patient was checked from medical records and by linkage with the death registry of the national statistics database.

Descriptive statistics were used for exploratory data analysis. The observed survival rate was calculated by the Kaplan-Meier method. Median survival times with 95% confidence intervals (CIs) and the log-rank test were used for comparisons between groups. The Cox proportional hazard regression model was used to assess associations between the various independent variables (covariates) and survival, and the adjusted hazard ratios were tested for significance with the partial likelihood test. The level of significance was set as $p < 0.05$. All analyses were performed using STATA version 10.0 (StataCorp, 2007).

The research was approved by the Khon Kaen University Ethics Committee for Human Research (reference no. HE541334).

Results

Table 1 shows the characteristics of subjects included in the study. There were 73 patients with ICC (43 males and 30 females), and their mean age was 56 years. Most patients (52%) presented themselves at the hospital at a late stage (stage IV), 58.9% received what was essentially palliative surgery (47.9% R1 plus 11.0% R2), and 80.8% had died by the end of the study. The total follow-up time was 99 person-years, and the total number of deaths was 59. The mortality rate was therefore 59 per 100 person-years (95%CI: 0.45-0.77).

Table 2 and Figures 1A-D present the survival rate data. After surgical treatment, the cumulative survival rate was 87.7% at 3 months (95%CI: 77.6-93.4). The cumulative 1-, 3-, and 5-year survival rates were 52.1% (95% CI: 40.1-62.8), 21.7% (95%CI: 12.9-32.1), and 11.2% (95%CI: 3.7-23.3), respectively. The median duration of survival after resection was 12.4 months (95%CI: 7.7-16.2). From the analyses to investigate the factors associated with the survival of patients after surgical treatment, the univariate analysis revealed that stage of disease, lymph node metastasis, histological type, histological grade and macroscopic classification were statistically significant (p -value <0.05) prognostic

Table 1. Characteristics of Intrahepatic Cholangiocarcinoma Patients after Surgical Treatment

Variables	No. (n=73)	%	
Gender	Male	43	58.90
	Female	30	41.10
Age (years)	<40	2	2.74
	40-49	12	16.44
	50-59	37	50.68
	≥60	22	30.14
mean (SD)	56 (7.8)		
min : max	38 : 76		
Stage of disease	I	1	1.37
	II	3	4.11
	III	9	12.33
	IVA	26	35.62
	IVB	12	16.44
	Unknown stage	22	30.14
Resection margin	R0 resection (Negative)	30	41.10
	R1 or R2 resection (Positive)	43	58.90
Histological type	Noninvasive papillary carcinoma	4	5.48
	Invasive papillary carcinoma	25	34.25
	Tubular adenocarcinoma	34	46.58
	Type cannot be assessed	10	13.70
Histological grade	Well differentiated	28	38.32
	Moderately differentiated	5	6.85
	Poorly differentiated	4	5.48
	Grade cannot be assessed	36	49.32
Macroscopic classification	Mass forming type	11	15.07
	Periductal infiltrating (PI) type	21	28.77
	Intraductal growth type	24	32.88
	Type cannot be assessed	17	23.29
Status at the end of study	Dead	59	80.82

Table 2. Cumulative Survival Rates of Intrahepatic Cholangiocarcinoma Patients after Surgical Treatment

Survival time	Median time (months) (95% CI)	Cumulative Survival rates (%)	95% CI
3 Months	2.0 (0.5-2.8)	87.7	77.6-93.4
6 Months	3.7 (2.8-4.5)	65.7	53.7-75.4
9 Months	4.2 (3.2-5.5)	54.8	42.7-65.4
1 Years	4.5 (3.5-5.5)	52.1	40.1-62.8
3 Years	8.5 (6.0-13.9)	21.7	12.9-32.1
5 Years	12.4 (6.6-16.0)	11.2	3.7-23.3

Table 3. Factors Effecting Survival Rates of Intrahepatic Cholangiocarcinoma Patients after Surgical Treatment

Variables	Median time (95% CI)	Person-IR/100 months	HR Crude	HR _{Adj.}	95% CI (HR _{Adj.})	p-value (Adj.)
Sex						0.913
Female	12.43 (5.5-23.3)	43	56	1	1	
Male	12.43 (6.6-16.6)	56	62	1.09	1.03	0.6-1.8
Age (years)						0.913
≥55	14 (6.6-23.3)	53	56	1	1	
<55	8 (5.5-14.2)	46	63	1.19	0.99	0.6-1.7
Staging						0.302
Stage I+II+III	NA (4.2-NA)	25	24	1	1	
Stage IVA+IVB	8 (6.0-13.9)	42	86	3.13	1.9	0.7-5.3
Unknown stage	13 (4.2-23.6)	32	53	2.16	1.28	0.5-3.6
Resection margin						0.17
R0	12 (7.7-44.6)	55	36	1	1	
R1, R2	13 (4.5-16.0)	44	88	2.12	1.51	0.7-2.5
Macroscopic Type						0.002
Mass forming	8 (3.2-19.6)	10	111	1	1	
Periductal infiltrating	12 (5.5-25.3)	28	68	0.63	0.54	0.2-1.2
Intraductal growth	24 (16.0-NA)	51	25	0.25	0.33	0.1-0.8
Cannot be assessed	4 (2.8-8.3)	10	159	1.46	1.44	0.6-3.3

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

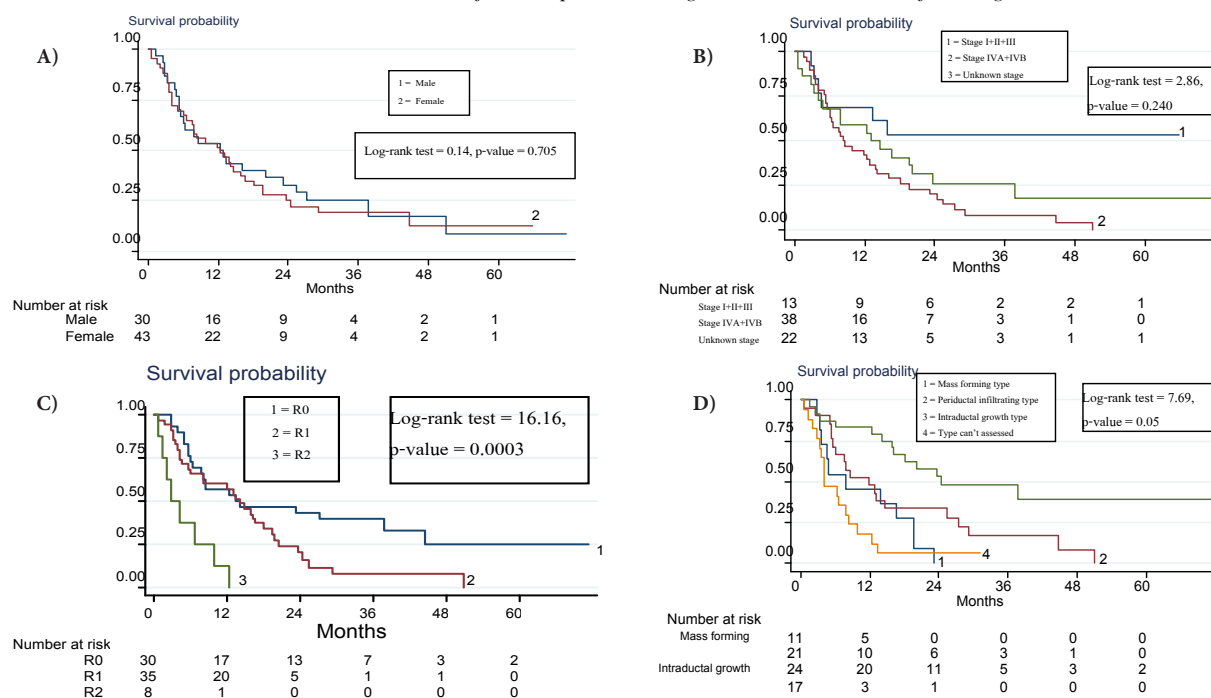


Figure 1. Survival Curve of Intrahepatic Cholangiocarcinoma Patients after Surgical Treatment. A) Gender, B) Stage, C) Resection Margin and D) Macroscopic Classification

factors. In the multivariate analysis, only macroscopic classification was statistically significant (p -value < 0.05) (Table 3).

Discussion

There have several reviews of cumulative survival rates after surgery for ICC. Gores (2003) reported that the 3-year survival rates in patients resected for cure were 40-60%, and the 5-year survival rates in patients with tumour-free margins were 20-40%. Khan et al. (2005) found 5-year survival rates of 8-47% with the highest survival in patients with negative resection margins. In a review by Morise et al. (2010), the 1-, 3-, and 5-year survival rates ranged 35%-86%, 20%-52%, and 20%-40%, respectively. The results of the present study are in line with the 1- and 3-year rates in these reviews, but the 5-year rates in the previous studies were generally higher. In recent studies (Cho et al., 2010; Ribero et al., 2012) the 1- and 3-year rates were also higher.

The inconsistencies with other studies could be explained in terms of patient and tumour characteristics and differences in the quality of treatment modality or the advanced technology; for example, if a tumour is completely removed, then the survival rates of patients after surgery should be longer. In the present study, although the 1-year survival rates were about the same for those with positive and negative resection margins (57.1% vs. 56.7%, respectively), the 3- and 5-year rates were much lower in those with a positive resection margin (8.0% vs. 40.0%, and 0.0% vs. 25%, respectively). Whereas the studies by Cho et al. (2010) and Ribero et al. (2010) included only 6.4% and 12% (respectively) with a positive resection margin, the majority of patients (58.9%) in the present study had a positive resection margin.

In the univariate analysis, factors found to be associated with the survival rates after surgery were staging of disease, lymph node metastasis, histological type, histological grade and macroscopic type. These findings are similar to those reported in previous studies (Uenishi et al., 2001; Hirohashi et al., 2002; Suzuki et al., 2002; Khuntikeo et al., 2008). Patients with lymph node metastasis had a 2.68 times (95%CI: 1.33-5.38) higher mortality risk than those with no lymph node metastasis. Similar findings were reported by Hanazaki et al. (2002) and Guglielmi et al. (2009). In the present study, macroscopic type was also found to be associated with survival rates after surgery. When compared with the mass forming type, those with intraductal growth type had a 0.25 times (95% CI: 0.11-0.57) lower risk of death, and those with the periductal infiltrating type had a 0.63 times (95% CI: 0.29-1.34) lower risk of death. These findings are almost the same as those in the study reported by Morimoto et al. (2003). However, Guglielmi et al. (2009) reported a rather different finding; patients with mass forming cancers had longer survival rates.

In the multivariate analysis, macroscopic type was the only factor significantly associated with the survival rates of ICC patients after receiving surgical treatment. When compared with patients with a mass forming type of cancer, patients with intraductal growth had a lower mortality risk, as did those with a periductal infiltrating type of malignancy. When the analysis excluded those subjects whose macroscopic type could not be assessed, the result was no longer significant, but the hazard ratios were in the same direction.

In conclusion, macroscopic classification was the only independent factor found to be significantly associated with survival of intrahepatic cholangiocarcinoma patients following surgical treatment.

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