

Prognostic factors in resectable cholangiocarcinoma patients: Carcinoembryonic antigen, lymph node, surgical margin and chemotherapy

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Abstract

AIM: To evaluate outcomes in resectable cholangiocarcinoma patients and to determine prognostic factors.

METHODS: A retrospective study was conducted among newly-diagnosed cholangiocarcinoma patients from January 2009 to December 2011 who underwent curative resection in Srinakarind Hospital (a 1000-bed university hospital). Two hundred and sixty-three cholangiocarcinoma patients with good performance were enrolled. These patients had pathological reports with clear margins or microscopic margins. Prognostic factors which included clinical factors, serum liver function test as well as serum tumor makers at presentation,

tumor data, and receiving adjuvant chemotherapy were determined by uni- and multivariate analysis.

RESULTS: The median overall survival time was 17 mo (95%CI: 13.2-20.7); and 1-, 2-, and 3- year survival rates were 65.5%, 45.2% and 35.4%. Serum albumin levels, serum carcinoembryonic antigen (CEA) levels, staging classifications by American Joint Committee on cancer, pathological tumor staging, lymph node metastases, tumor grading, surgical margin status, and if adjuvant chemotherapy was administered, were shown to be significant prognostic factors of resectable cholangiocarcinoma by univariate analysis. Multivariate analysis, however, established that only abnormal serum CEA [hazard ratio (HR) 1.68; $P = 0.027$] and lymph node metastases (HR 2.27; $P = 0.007$) were significantly associated with a decrease in overall survival, while adjuvant chemotherapy (HR 0.71; $P = 0.067$) and surgical margin negative (HR 0.72; $P = 0.094$) tended to improve survival time.

CONCLUSION: Serum CEA and lymph node metastases which were associated with advanced stage tumors become strong negative prognostic factors in cholangiocarcinoma.

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Key words: Cholangiocarcinoma; Prognosis; Carcinoembryonic antigen; Lymph nodes; Neoplasm metastasis; Surgical margin status; Hepatectomy; Chemotherapy; Adjuvant; Survival rate

Core tip: Cholangiocarcinoma has a high prevalence in the Asian countries, particularly Thailand. Cholangiocarcinoma patients usually have a high mortality rate and poor treatment outcomes. Curative surgery is the only treatment for early stages of this cancer. Cholan-

giocarcinoma has a high rate of recurrence. This study aimed to evaluate outcomes in resectable cholangiocarcinoma patients and to determine prognostic factors. The results demonstrated serum carcinoembryonic antigen and lymph node metastases which were associated with advanced stage tumors become strong negative prognostic factors in cholangiocarcinoma, while additional treatment including adjuvant chemotherapy and adequate surgical resection may improve survival time.

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INTRODUCTION

Cholangiocarcinoma is a malignant tumor of intrahepatic and extrahepatic bile duct epithelium^[1]. It is a second most common malignancy of primary liver tumors worldwide^[2]. The highest incidence is in the Northeast region of Thailand, while it is a rare tumor in Europe and America^[3,4]. *Opisthorchis viverrini* infestation is a major risk factor in Thai patients, while primary sclerosing cholangitis, obesity, viral hepatitis B and viral hepatitis C infection are the risk factors in Western countries^[5,6]. Cholangiocarcinoma is commonly classified into 3 groups based on the location of the tumor: intrahepatic, perihilar, or distal types^[1].

Surgery with clear surgical margin is an important treatment for patients with local disease^[7]. Standard surgery for cholangiocarcinoma depends on its location. Major hepatectomy is a surgical procedure for intrahepatic cholangiocarcinoma and perihilar cholangiocarcinoma, while pancreaticoduodenectomy is performed in distal cholangiocarcinoma^[7,8].

Although most patients receive surgical treatment, the five-year survival rate is extremely low^[9]. High locoregional recurrence and metastases are common causes of death in resectable patients^[10]. Benefits of adjuvant therapy in achieving long-term survival in resectable cholangiocarcinoma patients are controversial^[11]. Previous studies attempted to identify prognostic factors in this group^[12-15]. Surgical margin status and lymph node involvement are important prognostic factors^[9,11,16]. Other risk factors may be differentiation of tumor cells, preoperative tumor markers like carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA), and site of tumor^[13,17,18]. Data about prognosis in resectable cancer patients, however, are still limited. Moreover, only a few participants were enrolled in former reports. Therefore, this study aimed to determine prognostic factors in cholangiocarcinoma patients who underwent curative resection.

MATERIALS AND METHODS

Patients

A retrospective study was conducted among newly-diagnosed, cholangiocarcinoma patients from January 2009 to December 2011, who underwent curative surgery in Srinakarind Hospital, Khon Kaen University (a 1000-bed university hospital), Khon Kaen, Thailand. The study was reviewed and approved by the institutional review board (HE 551183). Curative resection was defined as a total excision of the entire tumor, including the primary tumor and the associated lymph node drainage fields. Two hundred and sixty-three cholangiocarcinoma patients with good performance status were enrolled. All patients with curative resection had pathological reports with a negative surgical margin or microscopic surgical margin. Demographic data including sex, age, underlying disease especially type 2 diabetes mellitus, body weight, height, and clinical manifestations were collected. Body mass index (BMI) was calculated from weight in kilograms divided by the square of the height in meters (kg/m^2). BMI cutoffs were classified according to the World Health Organization criteria for Asian and Pacific populations (underweight, $< 18.5 \text{ kg}/\text{m}^2$; healthy, $18.5\text{-}22.9 \text{ kg}/\text{m}^2$; at risk, $23\text{-}24.9 \text{ kg}/\text{m}^2$; obese I, $25\text{-}29.9 \text{ kg}/\text{m}^2$; and obese II, $\geq 30 \text{ kg}/\text{m}^2$)^[19]. Preoperative liver function status including total bilirubin, cholesterol, alanine transaminase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP), as well as serum tumor markers including CA 19-9 and CEA were evaluated.

Tumor data included tumor location, staging classification by the 7th edition of American Joint Committee on Cancer (AJCC), pathological tumor staging (pT), lymph node metastasis, tumor differentiation, and surgical margin status. All patients received the appropriate surgical procedure. Adjuvant chemotherapy was administered in patients who accepted the risk-benefit after a discussion with their physicians.

Statistical analysis

The survival time was defined as date of diagnosis to date of death from any cause. Patients' characteristics and tumor data were summarized as mean and percentage. The cumulative survival rate is presented by the Kaplan-Meier curve. The following variable factors were analyzed: sex, age, diabetic status, hepatomegaly, BMI status, serum total bilirubin level, serum cholesterol level, serum albumin level, serum ALT level, serum AST level, serum ALP level, serum CEA level, serum CA 19-9 level, AJCC staging, tumor location, pT, lymph node status, tumor differentiation, surgical margin status and adjuvant chemotherapy. Differences in survival between subgroups were compared using the log-rank test. Univariate analysis was performed using the chi-squared testing. Multivariate analysis was performed with the Cox proportional hazard model. The statistical analyses were performed by using SPSS software version 20.0. A *P*-value of less than 0.05 was considered statistically significant. The database was closed for analysis in August 2012.

Table 1 Baseline characteristics of 263 resectable cholangiocarcinoma patients *n* (%)

Age, yr	
mean ± SD	59.0 ± 8.9
Range	35-80
Male	181 (69.6)
DM	19 (6.5)
BMI (mean ± SD), kg/m ²	
< 18.5	23 ± 8.7
18.5-22.9	127 ± 48.3
23-24.9	47 ± 17.9
25-29.9	48 ± 18.3
≥ 30	13 ± 4.9
Not available	5 ± 1.9
Clinical manifestation	
Abdominal pain	164 (62.4)
Jaundice	54 (20.5)
Fever	6 (2.3)
Cholangitis	4 (1.5)
Weight loss	1 (0.4)
Asymptomatic	17 (6.5)
Hepatomegaly	153 (58.2)
Total bilirubin (mg/dL)	
< 10	213 (81.0)
≥ 10	50 (19.0)
Cholesterol (mg/dL)	
< 200	168 (63.9)
≥ 200	95 (36.1)
Albumin (g/dL)	
< 3	42 (16.0)
≥ 3	220 (83.7)
ALT (U/L)	
< 30	46 (17.5)
≥ 30	151 (82.5)
AST (U/L)	
< 30	25 (9.5)
≥ 30	238 (90.5)
ALP (U/L)	
< 100	82 (31.2)
≥ 100	180 (68.5)
CA 19-9 (U/mL)	
< 35	108 (41.1)
≥ 35	148 (56.3)
CEA (ng/mL)	
< 2.5	65 (24.7)
≥ 2.5	183 (69.6)
Receiving adjuvant chemotherapy	
Yes	138 (52.5)
No	125 (47.5)

CA 19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen; ALT: Alanine transaminase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; BMI: Body mass index; DM: Diabetes mellitus.

RESULTS

The patients' characteristics and tumor data are presented in Tables 1 and 2. Abdominal pain was the most common clinical presentation. The majority of the patients had normal a BMI, level of serum total bilirubin below 10 mg/dL, level of serum albumin above 3 g/dL, elevation of serum liver enzymes as well as abnormal serum tumor markers, CA 19-9 and CEA. Intrahepatic cholangiocarcinoma was the most common site of tumor. Most patients were in an advanced stage, *i.e.*, stage III or IV. One hundred and thirty-three patients received

Table 2 Tumor data of 263 resectable cholangiocarcinoma *n* (%)

Tumor location	
Intrahepatic	166 (63.1)
Perihilar	91 (34.6)
Distal	6 (2.3)
AJCC staging	
0	11 (4.2)
1	37 (14.1)
2	54 (20.5)
3	89 (33.8)
4	72 (27.4)
pT stage	
0	10 (3.8)
1	47 (17.9)
2	85 (32.3)
3	95 (36.1)
4	25 (9.5)
pN stage	
0	167 (63.5)
1	96 (36.5)
Tumor grading	
Well diff	198 (75.3)
Moderate diff	14 (5.3)
Not available	51 (19.4)
Margin surgical resection	
Free	134 (51.0)
Not free	129 (49.0)

AJCC: American Joint Committee on Cancer; pN: Pathologic node; pT: Pathologic tumor.

adjuvant chemotherapy of which the combination of fluorouracil and mitomycin C was the most administered regimen (60.9% of these patients). Other regimens included combination of gemcitabine and capecitabine, gemcitabine, fluorouracil, and capecitabine.

Median overall survival of the entire cohort was 17 mo (95%CI: 13.2-20.7) as shown in Figure 1. One, two, and three-year survival rates were 65.5%, 45.2%, and 35.4%. Serum albumin, serum CEA, AJCC staging, pT staging, lymph node metastases and whether or not having received adjuvant chemotherapy were significant prognostic factors in resectable cholangiocarcinoma by univariate analysis as shown in Table 3. Figure 2 revealed Kaplan-Meier survival curve regarding significant prognostic factors. Receiving adjuvant chemotherapy prolonged survival in resectable cholangiocarcinoma patients, however, the combination between fluorouracil and mitomycin C was not different other regimen to improve survival benefit [median survival time was 17.3 mo (95%CI: 12.8-21.7) *vs* 22.3 mo (95%CI: 20.3-24.3), respectively; *P* = 0.20]. Abnormal serum CEA and lymph node metastasis significantly impacted the overall survival in multivariate analysis (Table 4).

DISCUSSION

This cohort study had several similar and different characteristics from the previous reports^[3,20,21]. Most patients in this study had a BMI below 23; whereas, the majority of patients in the cited previous report were over-

Table 3 Differences of survival time among significant variable factors when analyzed by univariate analysis

Variable	Median survival (mo)	95%CI	P value
Albumin (g/dL)			0.04
< 3	12.8	7.1-18.4	
≥ 3	19.1	14.6-23.5	
CEA (ng/mL)			0.02
< 2.5	27.7	14.1-41.3	
≥ 2.5	16.5	13.0-20.0	
AJCC staging			< 0.001
0	Not reached		
1	Not reached		
2	23.5	16.9-30.1	
3	12.8	10.6-15.1	
4	12.5	9.3-15.7	
Tumor grading			0.01
Well differentiated	17.9	12.6-23.2	
Moderate differentiated	7.7	0.0-21.7	
Margin in resection group			0.001
Negative	26.7	19.6-33.8	
Positive	14.1	11.9-16.4	
pT stage			< 0.001
0	Not reached		
1	28.6	23.1-34.1	
2	19.9	12.9-26.9	
3	12.8	9.4-16.3	
4	15.5	9.9-21.1	
pN stage			< 0.001
0	25.1	20.0-30.1	
1	10.0	6.7-13.3	
Receiving adjuvant chemotherapy			0.01
Yes	21.6	16.9-26.4	
No	13.4	10.7-16.2	

CEA: Carcinoembryonic antigen; AJCC: American Joint Committee on Cancer. pN: Pathologic node; pT: Pathologic tumor.

weight^[20]. The tumor data showed that intrahepatic cholangiocarcinoma was the most common subtype, whereas, perihilar subtype was the most common location in other reports^[3]. These findings were correlated with the first clinical presentation of abdominal pain and level of serum bilirubin below 10 mg/dL. Furthermore, this study found that asymptomatic presentation was more common in patients with intrahepatic cholangiocarcinoma than in other previous studies^[21]. The authors' results demonstrated serum albumin was a significant prognostic factor by univariate analysis. Serum albumin is marker of nutritional status in cancer patients^[22]. A low level of serum albumin is usually found in malnourished patients, and associated with poor treatment outcomes such as postoperative infection and impaired wound healing^[23,24]. Advanced stages of cancers, including cholangiocarcinoma, also lead to a decrease in serum albumin level^[25]. Additionally, previous studies reported that low serum albumin was associated with an increased postoperative mortality in cholangiocarcinoma patients^[26].

AJCC staging of cholangiocarcinoma, pT staging, and the differentiation of tumor cells were an associated prognostic factor, as well and were demonstrated in our results by univariate analysis. These results were similar

Table 4 Significant prognostic factors by multivariate analysis

Variable	HR	95%CI	P value
Serum CEA (< 2.5 ng/mL vs ≥ 2.5 ng/mL)	1.68	1.05-2.66	0.027
Lymph node metastasis (yes vs no)	2.27	1.24-4.12	0.007
Receiving adjuvant chemotherapy (yes vs no)	0.71	0.49-1.02	0.067
Surgical margin (negative vs positive)	0.72	0.49-1.06	0.094

CEA: Carcinoembryonic antigen; HR: Hazard ratio.

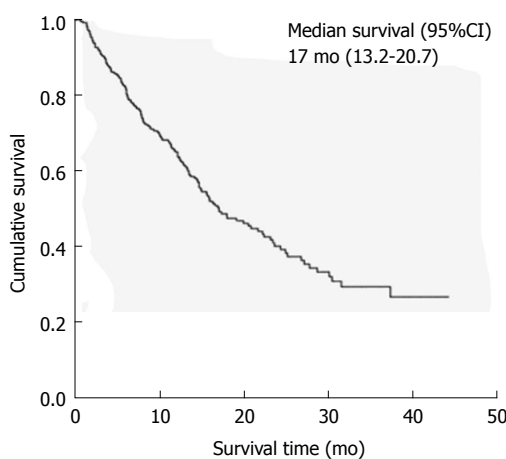


Figure 1 Kaplan-Meier survival curve used to analyze the overall survival time of 263 resectable cholangiocarcinoma.

with previous results^[18,25]. A well-differentiated tumor histology was related to early staging and was a good prognostic factor from results of the previous studies^[27,28].

The results showed that the level of serum CEA above 2.5 ng/mL and lymph node metastases were significant independent poor prognostic factors by univariate and multivariate analysis. CEA was demonstrated in fetal gut tissue and in tumors from the gastrointestinal tract^[29]. Serum CEA in cancer patients was significantly higher than in healthy controls and may be a prognostic factor in several gastrointestinal cancers, including cholangiocarcinoma^[30,31]. A previous study demonstrated that cancer patients with a high level of serum CEA was associated with an advanced stage of cancer and may signal poor prognosis^[32,33]. This study demonstrated that cholangiocarcinoma patients with high level of serum CEA were associated high risk of death (HR 1.68, 95%CI: 1.05-2.66), which is similar to previous studies^[25]. The preoperative serum CEA level in cholangiocarcinoma patients was correlated with the stage of cancer and could help determine their prognosis^[32,34].

Lymphatic dissemination is a common metastatic pathway of cholangiocarcinoma. Previous studies demonstrated that up to 55% of cholangiocarcinoma patients who underwent operations had tumor cells in the regional lymph nodes^[9]. Several studies showed that overall survival rate in cholangiocarcinoma patients with lymph node involvement was lower than other groups^[35-37]. These findings were similar in both resectable and unresectable patients^[25,26,38,39]. The findings of the present

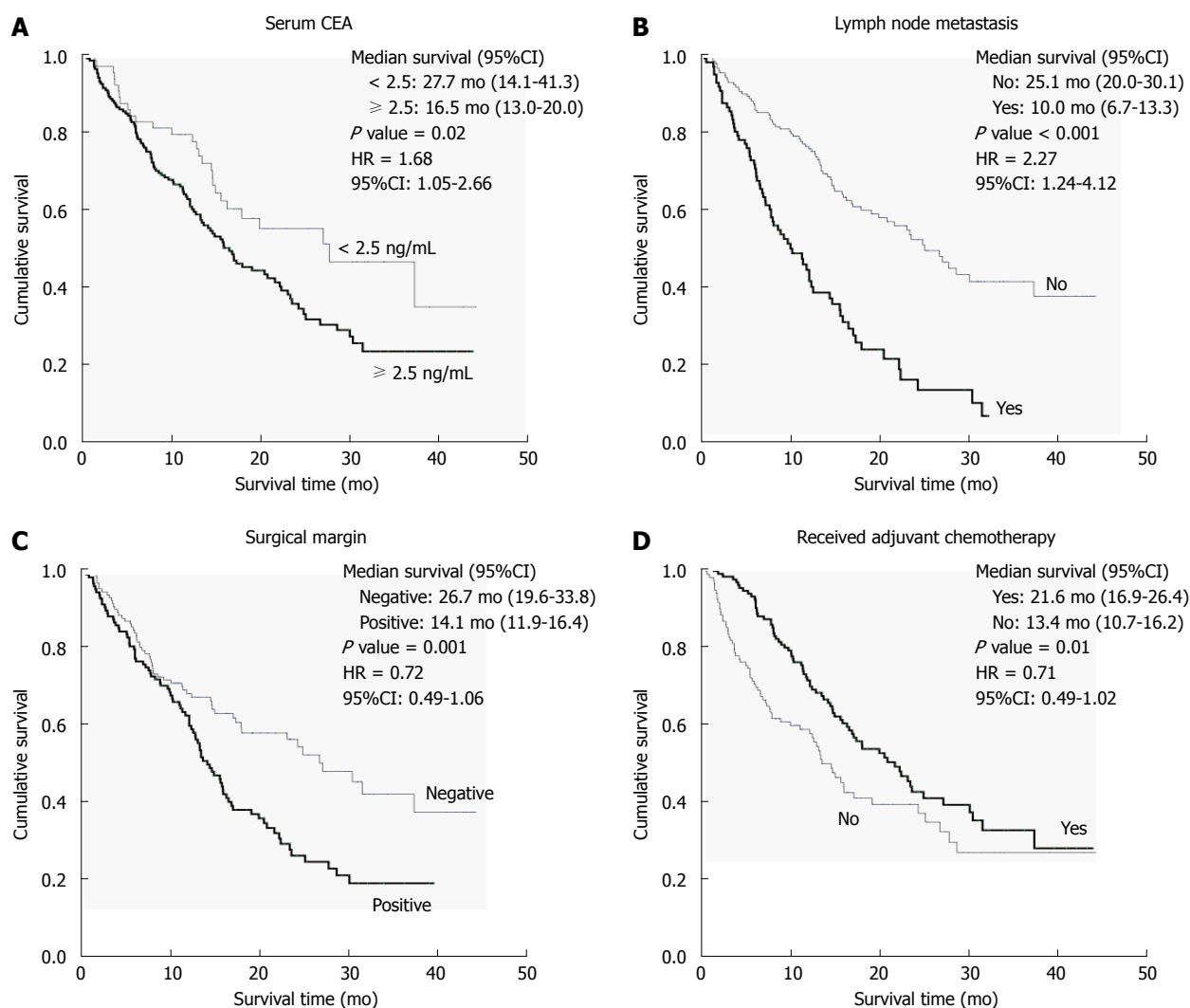


Figure 2 Kaplan-Meier survival curve showed significant difference in survival rate regarding prognostic factors. A: Serum carcinoembryonic antigen (CEA) level ≥ 2.5 ng/mL at presentation; B: Lymph node metastasis; C: Surgical margin; D: Receiving adjuvant chemotherapy. HR: Hazard ratio.

study also showed that lymph node metastases had an impact on survival.

Surgical margin status is a prognostic factor in several cancers, including cholangiocarcinoma. Previous studies showed overall survival rate in cholangiocarcinoma patients with positive surgical margin was lower than patients with negative surgical margin^[15,28,40-42]. The present results demonstrated that a negative surgical margin was associated long-term survival time.

Adjuvant chemotherapy is a controversial issue in resectable cholangiocarcinoma. The present authors' results showed that patients with adjuvant chemotherapy may have longer overall survival time than patients without adjuvant chemotherapy. Previous retrospective studies showed benefits of adjuvant chemotherapy^[12,15,43]. Randomized studies, however, did not demonstrate a definite advantage in cholangiocarcinoma^[44]. Recently, a meta-analysis showed that chemotherapy as a part of adjuvant therapy which included radiotherapy and concurrent chemoradiotherapy may be beneficial in resect-

able cholangiocarcinoma patients with high risk features, such as lymph node metastases and positive surgical margins^[45]. In our institute, combination of 5-fluorouracil and mitomycin C was the most administered regimen. However, the survival of this combination was not significantly different from the other regimens.

In conclusion, serum CEA and lymph node metastasis which are associated with advanced tumor stages become strong negative prognostic factors in cholangiocarcinoma, while additional treatment including adjuvant chemotherapy and adequate surgical resection may improve survival time.

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COMMENTS

Background

Cholangiocarcinoma has a high prevalence in the Asian countries, particularly Thailand. Cholangiocarcinoma patients usually have a high mortality rate and poor treatment outcomes. Curative surgery is the only treatment for early stages of this cancer. Cholangiocarcinoma has a high rate of recurrence. This study aimed to evaluate outcomes in resectable cholangiocarcinoma patients and to determine prognostic factors.

Research frontiers

A retrospective study included newly-diagnosed 263 cholangiocarcinoma patients from January 2009 to December 2011 who underwent curative resection and had pathological reports with clear margins or microscopic margins in Srinakarind Hospital (a 1000-bed university hospital).

Innovations and breakthroughs

The results demonstrated serum carcinoembryonic antigen and lymph node metastases which were associated with advanced stage tumors become strong negative prognostic factors in cholangiocarcinoma, while additional treatment including adjuvant chemotherapy and adequate surgical resection may improve survival time.

Applications

Adjuvant chemotherapy and adequate surgical resection may improve survival time.

Terminology

Curative resection was defined as a total excision of the entire tumor, including the primary tumor and the associated lymph node drainage fields.

Peer review

This is an interesting study aimed to evaluate outcomes in resectable cholangiocarcinoma patients and to determine prognostic factors. The results are interesting and suggest that adjuvant chemotherapy which includes combination of fluorouracil and mitomycin C and other regimens may improve overall survival in resectable cholangiocarcinoma patients.

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