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Original Article

Surgical outcome and prognostic factors in intrahepatic cholangiocarcinoma: a single-center experience of 114 cases

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Abstract: Objectives: Intrahepatic cholangiocarcinoma (ICC) remains a rare tumor, although its incidence is increasing. The surgical outcome and prognostic factors of ICC are not fully understood. This study aimed to examine surgical outcomes for patients and prognostic factors for survival in patients with ICC. Patients and methods: We retrospectively studied 114 patients with ICC who underwent hepatectomy from January 2001 to December 2012 at the Hepatobiliary Surgery Center, Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China. Survival outcomes were analyzed using Cox hazard models and the Kaplan-Meier method. Results: Genarally, of the 114 patients, median age was 56.3 years, and 53.1% were male. Most patients (74.7%) had a solitary tumor, and median tumor size was 5.92 cm. Patients were treated with an extended hepatectomy, a hemihepatectomy (180 [35.0%]), or a minor liver resection. 87.9% of patients underwent R0 resection, and 35.7% of patients had N1 disease. For prognosis, using backward selection of clinically relevant variables, lymph node metastases (hazard ratio [HR]: 3.887; P = 0.033), vascular invasion (HR: 2.848; P = 0.046), multiple tumors (HR: 7.069; P = 0.001), elevated preoperative CA19-9 level (HR: 4.165; P = 0.006) were selected as factors predictive of survival. Conclusions: Predictive factors, including lymph node metastases, vascular invasion, multiple tumors, and an elevated preoperative CA19-9 level were associated with poor survival.

Keywords: Intrahepatic cholangiocarcinoma, hepatectomy, prognosis

Introduction

Intrahepatic cholangiocarcinoma (ICC) arise from bile duct epithelium within the liver, and it is the second most common primary liver cancer in humans, after hepatocellular carcinoma (HCC) [1]. Although it is an uncommon malignancy, several reports have documented a significant rise in incidence, not only in the United States, but worldwide over the last several decades, though this may be due-at least in part-to improved diagnosis and pathological confirmation [2, 3]. The age-adjusted worldwide incidence of ICC has increased from 0.32 per 100,000 to 0.85 per 100,000 over a 30-year period-an increase of 165% [3]. Using the National Cancer Institute (NCI) Surveillance, Epidemiology and End Results (SEER) program data, Basile Njei reported that ICC incidence was 0.07 cases per 100,000 in 1973, whereas in 2010 ICC incidence was 0.73 cases per 100,000 in the United States [4]. Although many etiological factors have been characterized, the cause and pathogenesis of ICC remain speculative in many cases. Opisthorchis viverrini infestation is a major risk factor in Thai patients, while Cirrhosis, chronic hepatitis B and C, alcohol use, diabetes, and obesity are major risk factors for intrahepatic cholangiocarcinoma in the other countries [5, 6]. The peak incidence for ICC is between ages 55 and 75 years; ICC is rare before the age of 45, with this age group accounting for less than 10% of cases. Unlike HCC, which is 5 to 6 times more prevalent in men, ICC appears to have only a slight male predominance, with a male: female ratio of 2:3 [3].

Table 1. Clinical characteristics of the 114 ICC patients

Variates	n	Proportion (%)
Age in years		
< 60	78	68.42
≥ 60	36	31.58
Sex, male/female		
Male	66	57.89
Female	48	42.11
The presenting complaints		
Abdominal discomfort or pain	39	34.21
Incidentally founding on imaging	32	28.07
Hypodynamia	13	11.40
Abdominal distension	9	7.89
Jaundice	7	6.14
Nausea	5	4.39
Lower back pain	4	3.51
Abdominal mass	3	2.63
Emaciation	2	1.75
Liver cirrhosis		
Absent	37	32.46
Present	77	67.54
Cholangiolithiasis		
No	108	94.74
Yes	6	5.26
PSC/UC		
No	110	96.49
Yes	4	3.51
Diabetes mellitus		
No	95	83.3
Yes	19	16.7
HBsAg		
Negative	90	78.95
Positive	24	21.05
HCVAb		
Negative	113	99.12
Positive	1	0.88
AFP		
Normal (< 20 ng/ml)	103	90.35
Abnormal (≥ 20 ng/ml)	11	9.65
CEA	95	
Normal (< 10 ng/ml)	82	86.32
Abnormal (≥ 10 ng/ml)	13	13.68
CA199	81	
Normal (< 37/ml)	46	56.79
Abnormal (≥ 37 ng/ml)	35	43.21
FER	88	
Normal (< 150 ng/ml)	55	62.50
Abnormal (≥ 150 ng/ml)	33	37.50

The prognosis of intrahepatic cholangiocarcinoma is very poor, with median survival for patients who do not undergo surgery being 6 months, and the 5-year survival rate for patients following complete resection being only 20%-40%. Complete surgical resection is the only potentially curative approach for patients with ICC. However, locoregional extension of these tumors is usually advanced with intrahepatic and lymph-node metastases at the time of diagnosis. In spite of the many other modes of treatment, such as radiofrequency, transarterial therapy, chemotherapy and radiotherapy, that are frequently recommended and have been used to treat ICC patients, complete surgical resection is the only potentially curative approach for patients with ICC. Study objectives aimed to determine the risk factors, clinical features, treatment outcome and prognostic factors for survival in patients with ICC.

Patients and methods

Patients

All ICCs cases that underwent complete surgical resection at Cancer Hospital, Chinese Academy of Medical Sciences between January 1, 2004 and December 31, 2013 were included in this study. Only completely resected tumors were included in this study and all needle and wedge biopsies were excluded. All patients were confirmed pathologically by at least two pathologists. The characteristics and medical data of the patients, including sex, age, liver status, etiology of chronic liver disease, pathology results, serum biochemistry, and treatment, were obtained from the patient medical records. The distribution of the selected patient characteristics is shown in **Table 1**. Written informed consent was obtained from all patients, and this study was approved by the Institutional Review Board of the Chinese Academy of Medical Sciences Cancer Institute.

Management

All 114 patients first underwent surgery in our center. During the surgery process, four types of surgical methods, including curative hepatectomy, radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), and palliative hepatectomy, were performed. Curative hepatectomy and RFA were performed to either remove or ablate all lesions with a tumor-free

Table 2. Pathologic characteristics of the 114 ICC patients

Variates	n	Proportion (%)
Tumor size (cm)		
≤ 5	61	53.51
> 5	53	46.49
Tumor number		
Single	88	77.19
Multiple	26	22.81
Surgical margin		
R0	80	70.18
R1	34	29.82
Lymph node dissection		
No	46	40.35
Yes	52	45.61
Sampling	16	14.04
Lymph node metastasis		
No	31	48.44
Yes	33	51.56
Tumor grade		
Well differentiated	14	12.28
Moderately differentiated	59	51.75
Poorly or undifferentiated	41	35.96
Vascular invasion		
No	85	75.56
Yes	29	25.44
Invasion		
No	84	73.68
Yes	30	26.32
Lymph node status		
PNx	50	43.86
PN0	31	27.19
PN1	33	28.95
T stage		
T1	56	49.12
T2	24	21.05
T3	29	25.44
T4	5	4.39

margin. Palliative hepatectomy and PEI were performed to stanch the blood by tumor rupture or reduce the tumor burden. Other adjuvant therapies, including transarterial chemotherapy (TACE), chemotherapy/target therapy/placebo therapy, or radiotherapy, were applied to selected patients with preserved liver function and distant tumor metastasis after surgery.

Follow-up

All postoperative patients were followed for the first year with 3-monthly intervals and thereafter with at 4- to 6-monthly intervals. The follow-up included serum CA 19-9 level, liver function tests, abdominal ultrasonography, and chest X-rays. Enhanced computed tomography or magnetic resonance imaging was performed every 6 months for surveillance of recurrence. Bone scanning was undertaken when necessary. In cases where a suspicious recurrent or metastatic lesion was detected, magnetic resonance imaging or hepatic angiography was employed to consolidate the diagnosis. The diagnosis of tumor recurrence was based on typical imaging features or development of extrahepatic metastasis. Fine needle aspiration/biopsies were not necessarily undertaken to assess recurrences.

Statistical analysis

Statistical significance of difference between means of quantitative variables was tested using the independent t-test. Chi-square test was used for comparing categorical variables. A p value of 0.05 was held as significant. The Kaplan-Meier method was used to estimate survival, and the duration of survival was derived from the survival curves. Survival of patients in this study was calculated from the time of diagnosis. Survival curves were compared using the log-rank test. Multivariate analysis was performed using Cox proportional hazards method with backward Wald. The factors found to be significant on univariate analysis were included in the regression model and a p value of 0.10 was used to determine if the variable would go next step. All statistical analyses were performed using the packages in Statistical Product and Service Solutions (Version. 17.0, SPSS).

Results

Patients and clinical data

The demographic and clinical features of the patients in the study group were described in **Table 1**.

Surgical procedures and complications

All patients underwent preoperative examination to evaluate the operability using computed tomography (CT), magnetic resonance imaging (MRI), or both. Liver resection was performed using clamp crushing and/or cavitron ultrasonic surgical aspirator (CUSA) with intermittent Pringle's maneuver or selective and dynamic region-specific vascular occlusion (SDRVO)

Table 3. Predictors of overall survival: univariate and multivariate analysis

Variate	Survival Rate, %			Univariate Analysis		Multivariate Analysis	
	1 y	3 y	5 y	X^2	*P* Value	HR (95% CI)	*P* Value
Sex							
Male	65.2	32.6	30.1				
Female	77.1	43.8	25.5	0.717	0.397		
Age (range)							
< 60	74.4	39.3	33.9				
≥ 60	61.1	31.2	20.2	2.847	0.092		
CA199							
Normal	73.9	46.9	37.1				
Elevated	57.1	24.9	8.3	7.834	0.005	4.165 (1.509-11.497)	0.006
CEA							
Normal	75.3	39.9	29.2				
Elevated	57.9	33.8	27.0	1.181	0.277		
FER							
Normal	76.4	36.7	29.1				
Elevated	69.7	36.7	30.6	0.053	0.818		
HBsAg							
Normal	67.8	36.0	31.4				
Elevated	79.2	42.4	24.2	0.120	0.729		
Liver cirrhosis							
Absent	71.4	38.4	33.3				
Present	67.6	34.2	21.4	0.748	0.387		
Adjuvant therapy							
No	67.1	39.9	32.0				
Yes	75.6	31.2	22.8	0.022	0.883		
Tumour number							
Single	83.0	46.0	35.5				
Multiple	26.9	5.6	0.0	39.964	0.000	7.069 (2.244-22.267)	0.001
Tumour size (cm)							
≤ 5	78.7	45.2	40.2				
> 5	60.4	26.0	10.8	6.196	0.013	1.423 (0.512-3.951)	0.499
extrahepatic extension							
No	83.3	47.3	38.4				
Yes	33.3	8.5	4.2	33.659	0.000	1.231 (0.413-3.688)	0.710
Lymph node metastasis							
No	87.1	68.6	47.9				
Yes	36.4	4.2	0.0	35.017	0.000	3.887 (1.116-13.534)	0.033
Histological grade							
Well	90.9	75.8	56.8				
Moderately	74.6	46.6	30.6				
Poorly undifferentiated	53.7	6.0	0.0	35.044	0.000	2.367 (0.891-6.288)	0.084
Vascular invasion							
No	78.8	47.9	37.5				
Yes	44.8	5.3	0.0	34.484	0.000	2.848 (1.017-7.973)	0.046
Surgical margin							
R0	83.5	52.7	41.2				
R1	42.9	4.0	0.0	39.748	0.000	1.075 (0.330-3.500)	0.904

under room temperature to block hepatic inflow. The median blocking time was 14 min (range: 5-24 min) and the mean intraoperative blood loss was 220 mL (range: 50-2,000 mL).

Tumors were located in left lobe (55 patients), right lobe (48 patients), left & right lobe (9 patients) and caudal lobe (2 patients). 63 underwent partial hepatectomy (44 tumors located within two or fewer segments and 19 within three or more segments), 18 Minor resections (5 segmentectomy, 13 bisegmentectomy), 31 Major resections (14 left hepatectomy, 10 right hepatectomy, 5 mesohepatectomies, 1 left hepatectomies+S1 and 1 left hepatectomies+S1 and S5) and 2 extended hepatectomy (1 left trisectionectomy and 1 right trisectionectomy). 4 patients also received common bile duct exploration for cholelithiasis resection, 3 patients received Roux-en-Y cholangiojejunostomy, 2 patients received thrombectomy for portal vein tumor thrombus, and 3 patients received gallbladder resection.

Lymph node dissection (LND) was not routinely performed in this center especially in early stage. Fifty-two (52/114; 45.61%) patients underwent lymph node dissection, among them 21 patients with and 31 patients without lymph nodes metastasis. Lymph node dissection was performed routinely around the hepatoduodenal ligament involved hilar, common bile duct, hepatic artery, portal vein, cystic duct, periduodenal, and peripancreatic LNs. 5 patients received lymph node dissection including the area of the coeliac trunk and the retropancreatic region additionally, according to intra-operative findings (enlarged lymph nodes in those areas), while the enlarged lymph nodes in those areas in the 5 patients were not metastasizing pathologically. 16 patients underwent lymph node sampling (1 or 2 lymph nodes were dissected), among them 12 patients with lymph nodes metastasis. So, in all 114 patients, lymph nodes metastasis (N1) were present in 33 patients, not present (N0) in 31 patients, and lymph node metastasis could not be assessed (NX) in 50 patients (46 patients did not underwent any form of lymph node dissection, 4 patients received lymph node sampling without metastasis proved pathologically).

During the postoperative period, 27 patients (23.68%) experienced a total of 38 adverse events. The surgical complications were primarily related to the liver, including hepatic dysfunction/hepatic insufficiency (16 and 2 patients, respectively) and biliary fistula (5 patients). Infectious complications were the second most common cause of morbidity, the most common being pneumonia (6 patients), subphrenic abscess (2 patients), and sepsis (2 patients). 5 patients had right-sided pleural effusion postoperatively and two received mini invasive chest catheter closed drainage. In all, one patient (0.88%) died of hepatic failure within 1 month after surgery.

The median length of hospital stay was 9 days (range, 6-34 days) from the day of surgery. After resection, 41 patients (35.96%) received adjuvant treatments, either chemotherapy (6 patients), transarterial chemotherapy (21 patients) or radiotherapy (14 patients).

Pathologic findings

After surgery, tumors were inspected macroscopically and microscopically, and the descriptive pathologic characteristics of the study cohort are detailed in **Table 2**.

Tumor thrombi were found in 25.4% (29/114) of the patients (12 macroscopic tumor thrombi, 17 microscopic tumor thrombi). 37 patients had cirrhosis in the liver, and of these 26 cases had small-nodule liver cirrhosis. Moreover, bile duct stones were observed in 5.3% (6/114) of patients. Poorly differentiated tumors accounted for 36.0%, while moderately and well differentiated tumors accounted for 51.8% and 12.3%, respectively.

On final pathologic analysis, 34 patients (29.8%) had a positive resection margin. The overall incidence of LN metastases was 48.5% (33/68) in patients who had undergone some form of LN dissection. The median number of the lymph nodes dissected was 7 (range: 5-31). While the median number of the positive lymph nodes was 3 (range: 1-22), and patients had 1-3 positive lymph nodes, patients had more than 3 ($\geq$ 4) positive lymph nodes.

Overall survival and prognostic factors

At the time of analysis, 72 of 114 patients (63.2%) had died. After a median time point of follow-up of 19 months (range, 3-134 months), overall median survival was 25 months (95% CI, 19.06-30.15 months), and the 1-, 3-, and 5-year overall survival rates were 70.2%, 37.0%, and 26.7%, respectively. The longest living survivor was alive and disease-free at 11.2 years, with 13 patients were actual 5-year survivors.

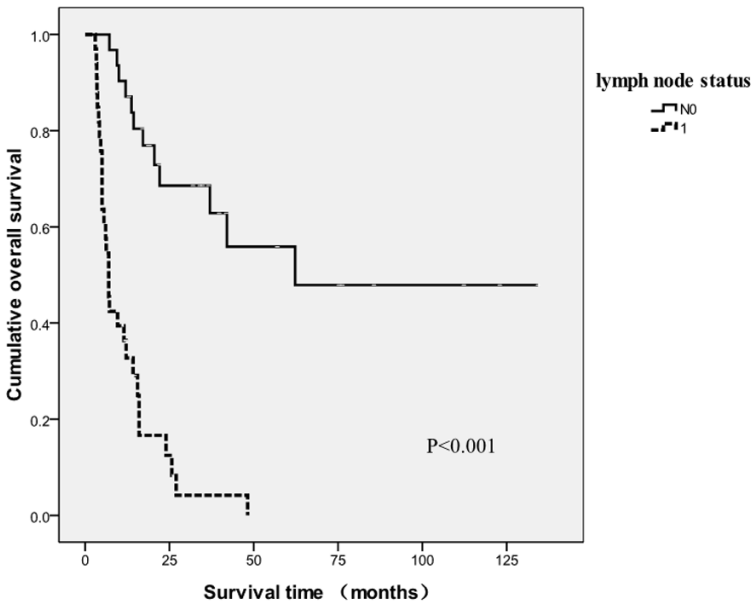

Figure 1. Overall survival for LNM-positive and LNM-negative groups.

Of these patients, 9 patients had no evidence of disease recurrence.

The data of univariate and multivariate predictors of overall survival are reported in **Table 3**. On univariate analysis, an elevated preoperative CA19-9 level, all pathologic tumor factors including lymph node metastases, tumor size, tumor number, histological grade, extrahepatic extension, vascular invasion, and the radicality of resection proved to correlate with survival. The multivariate analysis further confirmed that lymph node metastases, vascular invasion, multiple tumors, and an elevated preoperative CA19-9 level were independent predictors of poor survival.

The impact of lymph node metastasis and lymph node dissection on survival

Furthermore, we investigated the prognostic significance of lymph node metastases and the value of lymph node dissection.

The survival results of the LNM-positive group were clearly worse than in the negative group ($P < 0.001$, **Figure 1**). The overall survival period for the LNM-positive patients was 78.9 months with 1-, 3-, and 5-year survival rates of 87.1%, 68.6%, and 47.9%, respectively. And the overall survival period for the LNM-negative patients was 11.7 months with 1-, 3-, and 5-year survival rates of 36.4%, 4.2%, and 0%, respectively. However, no survival benefits between the LND (+) and LND (-) group was found.

Discussion

The incidence of ICC is on the rise, generating clinical interest in improving outcomes and identifying prognostic factors. The following factors have been studied for their effect on outcomes: solitary vs. multiple tumors, lymph node status, margin status, vascular invasion, tumor size, bilobar tumors, capsular invasion, histologic subtype, mucobilia, and CA19-9 levels [7, 8].

Lymph node metastasis (LNM) has been reported to be a significant poor prognostic factor in ICC [9-11]. survival results of LNM-positive groups which were evaluated by the 5-year survival rate, median survival time, or disease free survival time were clearly worse than in the LNM-negative groups, and in several reports, the 5-year survival rate of LNM-positive patients was a disappointing 0% [12-14]. In one study, Clancy and colleagues using SEER-Medicare data, identified 4,893 patients with ICC, 733 patients underwent major liver resection, in the 733 patients, positive vs. negative LN status was associated with worse 5-year OS of 8.4% vs. 25.9%, respectively (hazard ratio = 1.8; $P < 0.001$) [12].

In addition to prognostic value, some groups have suggested that LND may have therapeutic benefit. Weber and associates reported 3 of 20 recurrences in the hilar LNs and suggested that LND may have prevented these recurrences [15]. While, Morine et al. suggested that surgery alone with LND could not control ICC because the extent of surgery, including radical LND, did not improve patient survival, moreover, the recurrence rate did not differ according to the LND strategy. Based on their results, they concluded that the routine use of LND would not be recommended [16]. In sum, the data strongly suggest that LND should be performed at the time of surgery for staging purposes due to its strong prognostic ability, and it may lower the risk of loco regional recurrence.

The most commonly described reason for omission of LND is the absence of pre-or intraoperative finding of LNM or preoperative diagnosis of HCC for the original tumor.

Some studies showed that vascular invasion including micro and major vascular invasion was a key factor for poor prognosis of intrahepatic cholangiocarcinoma [17-19]. The presence of multifocal disease has been shown to be an independent predictor of poor outcome and is believed to represent intrahepatic metastasis [11, 20]. Endo and associates 50 found solitary vs multifocal disease to be an independent predictor of disease specific and disease-free survival for ICC, with a median survival of 87 months vs. 19 months ($P < 0.0001$), respectively.

In this study, the survival results of the solitary tumor group were clearly worse than multifocal disease ($P = 0.000$, **Table 2**). The overall survival period for the LNM-positive patients was 59.34 months with 1-, 3-, and 5-year survival rates of 83.0%, 46.0%, and 35.5%, respectively. And the overall survival period for the LNM-negative patients was 13.18 months with 1-, 3-, and 5-year survival rates of 26.9%, 5.60%, and 0%, respectively.

CA199 known as sialylated Lewis antigen is a blood tumor marker and was discovered in patients with colon cancer and pancreatic cancer in 1981 [21]. Previous studies found that CA19-9 expression was also prevalent in ICC [22]. And the presence of CA19-9 expression had been shown to be an independent predictor of poor outcome for ICC [9, 19]. Other studies have noted that preoperative CA 19-9 values greater than 100 U/mL were also associated with worse recurrence-free survival after surgical resection [23].

In conclusion, intrahepatic cholangiocarcinoma is associated with poor prognosis and resection remains the best option for long term survival. Lymph node metastases and multiple tumors are associated with decreased survival rates, but they should not be considered selection criteria that prevent other patients from undergoing a potentially curative resection. In this series the survival rate in patients with four or more positive nodes was significantly lower than in those with fewer than four. However, lymph node dissection did not improve survival. And an elevated preoperative CA19-9 level and presence of vascular invasion were also independent predictors of poor survival after ICC resection. The present study also revealed that use of chemotherapy, transarterial therapy or radiotherapy in the adjuvant setting failed to improve survival. The pathogenesis, treatment and prognostic factors of ICC demands further study and elucidation to improve the guarded prognosis associated with this disease.

Disclosure of conflict of interest

None.

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