Clinicopathologic features, diagnosis and surgical treatment of intrahepatic cholangiocarcinoma in 104 patients

Xiao-Hui Fu, Zhao-Hui Tang, Ming Zong, Guang-Shun Yang, Xiao-Ping Yao and Meng-Chao Wu

Shanghai, China

BACKGROUND: **The outcome of surgical treatment of patients with intrahepatic cholangiocarcinoma (ICC) is poor. This study was designed to analyze the relationship between clinicopathologic features and the survival time after operation.**

METHODS: **The operation was performed in 104 patients with mass-forming type ICC at our hospital between November 1996 and May 2000. Seventy-nine patients (76.0%) were followed up successfully. Sixteen clinicopathological variables including age, sex, history of chronic liver disease, HBsAg, operation, adjuvant therapy, ascites, lymph node metastasis, invasion of adjacent organs, tumor size, necrosis of tumor, envelope, intrahepatic metastasis, International Union Against Cancer (UICC) TNM staging, histology, and cirrhosis were selected for univariate and multivariate analyses to evaluate their influence on the prognosis.**

RESULTS: **The accumulative 1-, 3-, 5-year survival rates of the 79 patients were 49.4%, 17.3%, 9.6% respectively. Univariate analysis revealed that sex (P=0.0221), HBsAg (P=0.0115), operation (P=0.0042), adjuvant therapy (P=0.0389), ascites (P=0.0001), invasion (P=0.0220), intrahepatic metastasis (P=0.0000) and TNM stage (P=0.0001) were related to survival time. Multivariate analysis revealed that HBsAg, ascites and TNM stage were significantly related to prognosis.**

CONCLUSION: **Early diagnosis and treatment and major hepatectomy are essential to improving the results of surgical treatment of ICC patients.**

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KEY WORDS: **intrahepatic cholangiocarcinoma; surgery; pathology**

Author Affiliations: Department of Comprehensive Therapy of Hepatobiliary Tumors, Eastern Hepatobiliary Surgery Hospital, Shanghai 200438, China (Fu XH, Tang ZH, Zong M, Yang GS, Yao XP and Wu MC)

Corresponding Author: Xiao-Hui Fu, MD, Department of Comprehensive Therapy of Hepatobiliary Tumors, Eastern Hepatobiliary Surgery Hospital, Shanghai 200438, China (Tel: 86-21-65564166 ext 75412; Email: danlit@sina.com)

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Introduction

Intrahepatic cholangiocarcinoma (ICC) ranks the second in incidence of primary liver cancer, next to hepatocellular carcinoma; it accounts for 5% of all primary liver cancers.[1] Although primary hepatocellular carcinoma (PHC) has been well understood and the outcome of its treatment is getting better, the prognosis of ICC is still poor.[2-4] The clinicopathological features and the prognostic determinants of ICC remain obscure. Most patients with ICC are at their advanced stage by the time of diagnosis, and the strategy for therapy of ICC has not been well established. In fact, surgical treatment of the patients with ICC is still dependent on the experience in treatment of PHC in many occasions. The purpose of this study was to find an early diagnostic method and a suitable therapeutic protocol for ICC patients by analyzing the relationship between clinicopathological characteristics and prognosis.

Methods

Between November 1996 and May 2000, 104 patients with mass-forming type ICC were admitted to our hospital. All of the patients received laparotomy and were identified as having ICC after pathological examination. Seventy-nine (76.0%) of the 104 patients were followed up successfully with letters or phones after operation. For each variable, survival rate was estimated by the Kaplan-Meier method and was checked for statistical significance by the log-rank test. Cox's proportional hazard model was used in stepwise multivariate analysis to identify factors independently associated with prognosis after operation. Probability values less than 0.05 were considered significant.

Results

Only 7 patients (6.9%) were diagnosed as having ICC preoperatively (Tables 1 and 2). Among 102 patients exa-

Table 1. Clinical characteristics of the 104 patients

Age (y)	Average 52.8(25-78)
Sex (M:F)	66:38
Clinical manifestation	
Asymptomatic	14(13.5%)
Symptomatic *	90(86.5%)
Jaundice	1(1.0%)
Hepatomegaly	18(17.3%)
Associated liver disease	
Hepatitis B positive	26(25%)
Hepatolithiasis	13(12.5%)
Schistosomiasis	7(6.7%)

*: Symptoms: abdominal discomfort (62.5%), fatigue (11.5%), nausea (9.6%).

Table 2. Laboratory test results

Test	Patients	Patients with abnormal results (%)
γ-GT	61	44(72.1)
ALP	69	50(72.5)
AFP	101	56(55.4)[a]
CEA	99	58(58.6)[b]
CA19-9	58	31(53.4)

γ-GT: γ-glutamyl transpeptidase; ALP: alkaline phosphatase; AFP: α-fetoprotein; CEA: carcinoembryonic antigen; CA19-9: cancer antigen19-9. a: only 6 cases >100 ng/ml; b: only 23 cases >20 ng/ml.

Table 3. Pathological characteristics of the 104 patients

Variables	Number (%)
Cirrhosis	36(34.6)
Histologic type	
Poorly differentiated	34(39.1)
Moderately differentiated	50(57.5)
Well differentiated	3(3.4)
Tumor size	
<5 cm	25(27.2)
≥5 cm, <10 cm	45(48.9)
≥10 cm	22(23.9)
Envelope	
No	70(84.3)
Partial	11(13.3)
Intact	2(2.4)

Table 4. Immunohistochemical examinations of cancer tissues

Test	Patients	Patients with positive results (%)
AFP	44	0(0)
CK8	38	29(76.0)
CK18	23	21(91.3)
CK19	40	31(77.5)
Ki67	27	21(77.8)
PCNA	41	33(80.5)
P53	14	6(42.9)
HCV	9	1(11.1)
VI	6	1(16.7)
EMA	8	7(87.5)

PCNA: proliferative cell nuclear antigen; EMA: epithelial membrane antigen.

mined by B-type ultrasonography (BUS), 28 (27.4%) showed hyperechoic mass, and 55 (53.9%) hypoechoic mass. Cholelithiasis was found in 15 patients (14.7%). Blood vessel passing through the mass was found in 3 patients, cholangiectasis complicated by hepatolithiasis in 3, and sound halo in 5. Sixty-seven patients received CT scan. All masses appeared as low density on plain scan. Forty-three patients underwent contrast-enhanced scan, showing hyperattenuated lesions in 22 patients, capsular hyperattenuation in 8, and no enhancement in 13. Eight patients had delayed sweep results, and retained contrast medium was observed in masses of 5 patients in this period. Only 4 patients were diagnosed as having ICC, and 5 patients as having hepatolithiasis. In 34 patients examined by MRI, all masses presented with low signal intensity in T1-weighted phase and with relatively high signal intensity in T2-weighted phase, with an exception of 2 patients who had low signal intensity in both T1 and T2 phases. Proton-weighted phase was described in 12 patients with equal signal intensity (8), high signal intensity (2), and low signal intensity (2). Nine patients received enhancement scan and 6 patients had delayed sweep, and all these 6 patients presented with delayed enhancement similar to hepatoangioma, but without a typical sign of "bulb" in T2 phase. In 7 patients who underwent endoscopic retrograde cholangiopancreatography (ERCP) before operation because of hepatolithiasis, only one patient was diagnosed as having ICC.

Seven patients with extensive metastasis underwent laparotomy only, and the others received palliative or curative operation. The curative criteria included a negative margin of specimens and the absence of lymph node metastasis or extrahepatic invasion. Major hepatectomy was performed in 32 patients, and local hepatectomy in the others. Among 29 patients (27.9%) with lymph node metastasis, 19 had metastasis in the porta hepatis, 8 in the hepatoduodenal ligament, 3 in the lesser omentum, and 3 around the head of the pancreas. Lymph node dissection was performed in 4 patients. Ascites occurred in 18 patients, of whom 14 patients had lymph node metastasis or extrahepatic invasion. The diaphragm was involved in 14 patients. Thirty-five patients underwent transcatheter hepatic arterial chemoembolization (TACE) (1-3 times) after operation.

Pathological characteristics were demonstrated in less than 104 patients because of incomplete data (Table 3). With the pTNM classification (UICC, 1997 version) these 104 patients were divided into stage I (1 patient, 1%), stage II (42, 40.4%), stage III-A (7, 6.7%), stage III-B (18, 17.3%), and stage IV-A (36,

Table 5. Univariate analysis of 16 variables in relation to survival (79 cases)

Variables	Cutoff levels	Number	Median survival time (mon)	*P* value
Age (y)	<45	19	16	0.5712
	≥45, <60	32	6	
	≥60	48	9	
Sex	Male	51	15	0.0221
	Female	28	5	
History	Yes	22	9	0.5004
	No	57	10	
HBsAg	Positive	18	16	0.0115
	Negative	61	8	
Operation	Explorative	7	3	0.0042
	Palliative	37	8	
	Curative	35	16	
Adjuvant therapy	Yes	29	16	0.0389
	No	50	8	
Ascites	Present	15	3	0.0001
	Absent	64	12	
Lymph node	Positive	26	9	0.5507
	Negative	53	12	
Invasion	Present	15	5	0.0220
	Absent	64	12	
Tumor size (cm)	<5	18	14	0.8182
	≥5, <10	34	12	
	≥10	20	7	
Necrosis	Present	27	12	0.8810
	Absent	45	10	
Envelope	Present	11	7	0.3258
	Absent	61	12	
Intrahepatic metastasis	Present	24	3	0.0000
	Absent	55	14	
TNM	I	1	20	0.0001
	II	28	16	
	III-A	5	15	
	III-B	16	9	
	IV-A	29	5	
Histology	Well	2	9	0.5240
	Moderate	44	12	
	Poor	33	9	
Cirrhosis	Present	26	14	0.3970
	Absent	53	9	
	Overall	79	10	

Table 6. Results of multivariate analysis

Variable	Regression coefficient	Standard error	*P* value	Relative risk	95% confidence interval
HBsAg	-0.738	0.324	0.023	0.478	0.253-0.903
TNM	0.469	0.192	0.014	1.598	1.098-2.327
Ascites	0.938	0.401	0.019	2.556	1.164-5.611

34.6%). Cancer tissue was examined immunohistochemically in some patients (Table 4).

The mean survival time after operation was 11.9 months. The 1-, 2-, 3-, 4- and 5-year survival rates were 49.4%, 25.3%, 17.3%, 9.6% and 9.6%, respectively (Fig. 1). Univariate analysis revealed that sex, HBsAg, operation, adjuvant therapy, ascites, invasion, intrahepatic metastasis and TNM stage were significantly related to the survival time (Table 5).

Fig. 1. Cumulative survival curve of the 79 patients after surgery intrahepatic cholangiocarcinoma.

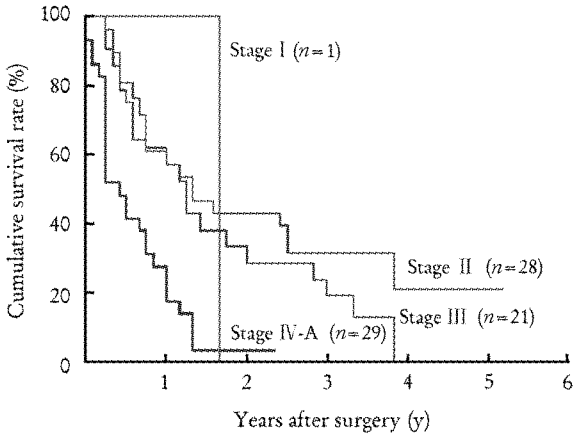

Fig. 2. Cumulative survival curve according to tumor UICC stage. Stage II versus stage IV-A: $P<0.01$; Stage III versus stage IV-A: $P<0.01$.

Multivariate analysis showed that HBsAg, ascites and TNM were significantly related to the therapeutic outcome (Fig. 2, Table 6).

Discussion

It was reported that the biological behaviors and prognosis of ICC are poor[5-9] and that the survival rates of patients with ICC are still low even after surgery. In most patients, once the disease is diagnosed it has been at its late stage, which is contraindicated for operation. In this study, the IV-A stage patients accounted for 34.6% in our series according to the UICC staging system. Better outcome was found in I-II stage patients.[10-12] Hence

early diagnosis is important to the management of ICC patients. First, it is necessary to define the criteria for early diagnosis of high risk people. Second, periodic examinations should be given to the high risk people. Nevertheless, how to define high risk people? and what kind of tests should be performed for the high risk people? Patients with hepatolithiasis are likely thought the possibility of carcinogenesis.[7-10] Tumor screening is proposed in these patients at the time of treatment of cholelithiasis, and the indication of hepatectomy should be extended in consideration of the poor prognosis of ICC. Thus early therapy can be offered to the patients who have developed ICC, while removal of the basis of carcinogenesis. Hepatitis B and C have been found to be correlated with ICC in addition to PHC[10-14] although the mechanism is not clear. Other chronic liver diseases such as schistosomiasis can also be recognized as high risk factors.[15]

BUS is useful in detecting liver mass, but not in pathological diagnosis of ICC. Similarly, ERCP is effective in the diagnosis of hilar cholangiocarcinoma, but ineffective in the detection of mass-forming type ICC. In our study, the levels of carcinoembryonic antigen, cancer antigen 19-9, alkaline phosphatase and γ-glutamyl transpeptidase were significantly elevated in ICC patients, markedly different from those in PHC patients, which serves a clue to early diagnosis of ICC. Delayed enhancement of CT or MRI as a characteristic of ICC image indicates somewhat an angioma without a typical sign of "bulb" in T2 phase.[16,17] An early diagnosis of ICC can establish according to the above findings.

Many reports focus on the operational methods of ICC. In this study although multivariable analysis indicated there was no significant correlation between operation and prognosis, which may be associated with a low diagnosis rate before operation and an inadequate surgical therapy, anatomic and extensive hepatectomy was proven to be helpful to improve the prognosis of patients without lymph node metastasis.[18-20] Pathological findings revealed that intrahepatic metastasis near the main lesion was common in mass-forming type ICC, and recurrence was seen in the adjacent liver tissue.[10,21] Major hepatectomy only accounted for 30.8% of this series, indicating the poorer prognosis of our series than that of other reports. Moreover, 84.3% of tumors were not enveloped, intrahepatic metastasis was found in 30.4% of the specimens, and most patients did not develop severe cirrhosis. The above conditions justify the necessity and feasibility of anatomic and extensive hepatectomy.

Lymph node metastasis is believed to be an important factor for prognosis after operation,[11,12] and researchers[12] even suggested that systematic lymph node dissection could improve the outcome of ICC patients. Nevertheless, metastasis is rarely limited to regional lymph nodes and it is difficult to dissect all metastatic lymph nodes, as illustrated in our study.[18,22] A Japanese study reported extended surgery for ICC,[23] including standard hepatic resection and extrahepatic bile duct resection combined with vessel and/or pancreas resection. Compared with conventional surgery, which was defined as hepatectomy alone or hepatectomy with bile duct resection, the extended surgery did not improve the curative resection rate or the surgical outcome for ICC; and a significantly higher mortality rate was observed after extended surgery than after conventional surgery. In our series only 4 patients received lymph node dissections and the survival time after operation was 37 (still alive), 8 and 5 months, respectively (one case lost to follow up). There is no consensus on the role of lymph node dissection in the operation of ICC.

It is concluded that anatomic and extensive hepatectomy is a standard operative protocol for mass-forming type ICC, but local hepatectomy is a safe and effective therapy for PHC accompanied by severe cirrhosis and chronic hepatitis. Thus, it is necessary to get a definitive diagnosis before or during operation for a better management of ICC. Misdiagnosis of PHC as liver cancer or liver mass would yield bad outcome. As mentioned above, history, laboratory test and imaging examination could help to differentiate ICC from PHC. Moreover, a fast frozen-section examination is also helpful during the operation.

Adjuvant therapy after surgery is followed by the protocol of PHC, ie, TACE after operation, radiological interventional therapy and sonographic interventional therapy after tumor recurrence. Obviously it is ignored that ICC is different pathologically from PHC. The experience in management of extrahepatic cholangiocarcinoma would be useful for the establishment of adjuvant therapy for ICC after operation. Reports indicated that routine radiotherapy and chemotherapy after operation couldn't prolong the survival time of patients with ICC.[24-27]

It is difficult to judge whether the results of immunohistochemistry test could be used to predict the outcome of operation because of a small number of cases studied.[28-31] Since clinicopathological features are still the best prognostic factors,[8] more valuable factors are expected to appear after accumulation of cases and prospective randomized study being performed.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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