Clinicopathological and prognostic analysis of 429 patients with intrahepatic cholangiocarcinoma

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AIM: To understand the clinicopathological characteristics and treatment selections and improve survival and provide valuable information for patients with intrahepatic cholangiocarcinoma (ICC).

METHODS: We retrospectively evaluated 5311 liver cancer patients who received resection between October 1999 and December 2003. Of these, 429 (8.1%) patients were diagnosed with ICC, and their clinicopathological, surgical, and survival characteristics were analyzed.

RESULTS: Upper abdominal discomfort or pain (65.0%), no symptoms (12.1%), and hypodynamia (8.2%) were the major causes for medical attention. Laboratory tests showed 198 (46.4%) patients were HBsAg positive, 90 (21.3%) had α-fetoprotein > 20 µg/L, 50 (11.9%) carcinoembryonic antigen > 10 µg/L, and 242 (57.5%) carbohydrate antigen 19-9 (CA19-9) > 37 U/mL. Survival data was available for 329 (76.7%) patients and their mean survival time was 12.4 mo. The overall survival of the patients with R0, R1 resection and punching exploration were 18.3, 6.6 and 5.6 mo, respectively. Additionally, CA19-9 > 37 U/mL was associated with lymph node metastases, but inversely associated with cirrhosis. Multivariate analysis indicated that radical resection, lymph node metastases, macroscopic tumor thrombi and size, and CA19-9 were associated with prognosis.

CONCLUSION: Surgical radical resection is still the most effective means to cure ICC. Certain laboratory tests (such as CA19-9) can effectively predict the survival of the patients with ICC.

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Key words: Intrahepatic cholangiocarcinoma; Diagnosis; Pathology; Surgery; Survival

INTRODUCTION

Patients with intrahepatic cholangiocarcinoma (ICC) are typically at an advanced pathological stage at the time of diagnosis, and are therefore associated with very poor prognosis. The incidence of ICC is increasing worldwide. The cause for this increase remains unknown and may be related to predisposing genetic and environmental factors. The incidence rate of ICC is approximately 0.5-2.0/100000 in males and slightly lower in females. In Europe and North America, ICC accounts for 10%-25% of liver cancers in males and even a higher proportion in females. The etiology and pathogenesis of ICC are not known and remain to be defined, although many potential factors may contribute to it. For example, chronic biliary tract infection is generally recognized as the most common risk factor for ICC. A multidisciplinary synthetic therapy combining surgical resection with chemotherapy is the most widely used treatment protocol. Surgical resection is the therapeutic aspect with a capacity of curing ICC, while chemotherapy is mainly used for the
patients with unresectable or recurrent disease. Moreover, no conclusion has been reached as to whether adjuvant chemotherapy is effective in the control of ICC\cite{5}. This may be because there are no standard chemotherapeutic protocols for ICC. Recently, Gemcitabine or Gemcitabine-based treatment has been a preferable choice to treat some ICC patients. Whether the patients with unresectable and non-metastatic ICC should be given liver transplantation treatment remains controversial, although the effect of liver transplantation for these patients was much better than that of palliative treatment\cite{6}.

ICC often shows higher malignant grades and poorer prognosis than those of hepatocellular carcinoma (HCC). The 5-year survival rate of ICC is still less than 5\%\cite{7}. As a result, improving patients’ survival with early detection and more aggressive treatment of ICC has been a focus of our research. Since ICC is a relatively rare neoplasm, to date, very few large-scale studies have been reported. In the current study, we have retrospectively assessed 429 cases of ICC that have undergone surgical treatment in the Eastern Hepatobiliary Surgery Hospital in Shanghai, China. We statistically evaluated the clinical characteristics, pathology, treatment, and prognosis of these patients to determine whether these parameters could contribute to a better prediction of patient survival.

MATERIALS AND METHODS

Patients
The study was approved by our institutional review board, and an informed consent was obtained from each patient. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. We retrospectively surveyed a total of 5311 patients with primary liver cancer who underwent surgical treatment in our hospital between October 1999 and December 2003. The pathological diagnoses of these patients included HCC, ICC, or mixed liver neoplasm. As a result, we obtained 429 cases of ICC from the total cases (8.1\%). Clinicopathological characteristics for these patients were retrieved, including age, gender, the existence of choledochoolithiasis, chronic viral hepatitis, tumor size, number of lesions, existence of satellite lesions, lymph node metastases, extrahepatic metastases, cirrhosis, pathology (grade), tumor invasion, some routine tumor marker expressions (\(\alpha\)-fetoprotein (AFP), carbohydrate antigen 19-9 (CA19-9), and carcinoembryonic antigen (CEA)), surgical procedures, and survival data. For surgical procedures, R0 resection was defined as the en bloc resection with all margins histologically free of tumor, while R1 resection was defined as one in which the tumor mass was removed but section margins may not necessarily be tumor-free. Other patients underwent exploratory laparotomy for unresectable lesions. All patients were graded according to International Union Against Cancer (UICC) TNM classification, 1997 version. We attempted to follow all 429 patients, but only 329 were available for data analysis. The lost follow-up data in the 100 patients may be due to their death, loss of contact, or other unknown reasons.

Statistical analysis
Statistical calculations and analyses were performed using SPSS11.0 software. Overall survival rate was plotted by the Life Table method. The univariate and multivariate predictors of prognosis were determined using univariate Cox regression analysis and the Cox proportional hazard model, respectively (Backward). The following variants were taken into account: age, gender, curative resection, lymph node metastases, number of intrahepatic lesions, satellite lesions, extrahepatic metastases, macroscopic tumor thrombi, pathology, cirrhosis, tumor size, encapsulation, microscopic tumor thrombi, tumor invasion, hepatitis B Virus (HBV) infection, AFP, CEA, and CA19-9. The Wilcoxon (Gehan) test was used to evaluate pair-wise comparisons between groups. The association between CA19-9 expression and clinicopathological parameters was analyzed using the \(\chi^2\) test and a logistic regression model. \(P < 0.05\) was considered statistically significant.

RESULTS

Clinical features
The 429 ICC patients consisted of 301 men and 128 women, with ages ranging from 22 to 81 years, with a median age of 52 years. The main clinical manifestations included upper abdominal discomfort or pain (65.0\%), an asymptomatic presentation (12.1\%), hypodynamia (8.2\%), abdominal distension (4.0\%), jaundice (3.0\%), nausea (2.8\%), lower back pain (2.6\%), abdominal mass, emaciation, and other symptoms (2.3\%). Laboratory evaluations showed that 198 patients (46.4\%) were HBsAg positive, 1 (1/321, 0.3\%) was hepatitis C virus positive, 90 (21.3\%) had AFP \(> 20 \mu\)g/L, 50 (11.9\%) CEA \(> 10 \mu\)g/L, and 242 (57.5\%) CA19-9 > 37 U/mL, as detected with an electrochemiluminescence immunoassay (Table 1).

Furthermore, 285 (66.4\%) patients had only a single tumor mass, while additional 144 (33.6\%) had multiple lesions. Tumor sizes were between 1.5 cm and 20 cm, with a mean size of 7.1 ± 3.8 cm. Macroscopic satellite lesions were found in 99 cases, of these, 40 cases had \(\leq 3\) lesions and 59 cases had more than 3 lesions. In addition, there were 47 cases of macroscopic tumor thrombi with 32 intravascular thrombi (27 portal vein thrombi and 5 hepatic vein thrombi), 10 cases of bile duct thrombi, and 5 cases of concurrent thrombi. Lymph node metastases were found in 88 (20.5\%) cases. Tumors metastasizing to lymph nodes at the porta hepatitis and hepatoduodenal ligament accounted for 59.1\% (52/88) while retroperitoneal metastases accounted for 27.2\% (24/88). Extrahepatic metastases usually invaded into the diaphragm, abdominal wall, omentum, stomach, or duodenum (Table 1). TNM classifications are shown in Table 1.

Surgical procedures and complications
All patients were preoperatively assessed and their operability was evaluated using computed tomography (CT), magnetic resonance imaging (MRI), or both. As a
Table 1  Clinicopathological characteristics of 429 ICC patients

|                              | No. of cases | Total No. of cases | Percentage (%) |
|------------------------------|--------------|--------------------|----------------|
| Gender                       |              |                    |                |
| Male                         | 301          | 429                | 70.2           |
| Female                       | 128          | 429                | 29.8           |
| Age (yr)                     |              |                    |                |
| < 53                         | 220          | 429                | 51.3           |
| ≥ 53                         | 209          |                    | 48.7           |
| Choledocholithiasis          |              |                    |                |
| No                           | 383          | 429                | 89.3           |
| Yes                          | 46           |                    | 10.7           |
| Pathology T                  |              |                    |                |
| T1                           | 11           | 429                | 2.5            |
| T2                           | 159          |                    | 37.1           |
| T3                           | 112          |                    | 26.1           |
| T4                           | 147          |                    | 34.3           |
| Pathology N                  |              |                    |                |
| N0                           | 341          | 429                | 79.5           |
| N1                           | 88           |                    | 20.5           |
| Pathology M                  |              |                    |                |
| M0                           | 408          | 429                | 95.1           |
| M1                           | 21           |                    | 4.9            |
| Pathology stage              |              |                    |                |
| I                            | 11           | 429                | 2.5            |
| II                           | 126          |                    | 29.4           |
| III                          | 133          |                    | 31.0           |
| IV                           | 159          |                    | 37.1           |
| Maximum tumor diameter (cm)  |              |                    |                |
| ≤ 5                          | 145          | 429                | 33.8           |
| > 5, ≤ 10                    | 186          |                    | 43.4           |
| > 10                         | 76           |                    | 17.7           |
| Diffuse type                 | 22           |                    | 5.1            |
| Macroscopic satellite lesions|              |                    |                |
| No                           | 330          | 429                | 76.9           |
| ≤ 3                          | 40           |                    | 9.3            |
| > 3                          | 59           |                    | 13.8           |
| Macroscopic tumor thrombi    |              |                    |                |
| No                           | 382          | 429                | 89.0           |
| In blood vessel              | 32           |                    | 7.5            |
| In bile duct                 | 10           |                    | 2.3            |
| In both                      | 5            |                    | 1.2            |
| Serum HBsAg and HbcAb        |              |                    |                |
| HBsAg (+)                    | 198          | 427                | 46.4           |
| HBsAg (+) and HbcAb (+)      | 60           |                    | 14.0           |
| HBsAg (+) and HbcAb (-)      | 169          |                    | 39.6           |
| Serum AFP (µg/L)             |              |                    |                |
| No                           | 332          | 422                | 78.7           |
| > 20, ≤ 100                  | 70           |                    | 16.6           |
| > 1000                      | 20           |                    | 4.7            |
| Serum CEA (µg/L)             |              |                    |                |
| No                           | 370          | 420                | 88.1           |
| > 10, ≤ 100                  | 36           |                    | 8.6            |
| > 100                        | 14           |                    | 3.3            |
| Serum CA19-9 (U/mL)          |              |                    |                |
| No                           | 179          | 421                | 42.5           |
| > 57, ≤ 507                  | 143          |                    | 34.0           |
| > 507                        | 99           |                    | 23.5           |

ICC: Intrahepatic cholangiocarcinoma; AFP: α-fetoprotein; CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9.

result of preoperative assessment, 319 (74.3%) received R0 liver resection, 76 (17.7%) received R1 liver resection, and 34 (7.9%) received the exploratory laparotomy. Liver resection was performed using finger fracture and clamp crushing with intermittent Pringle’s maneuver under room temperature. In all 395 patients (including R0 and R1 resections), 237 underwent partial hepatectomy (172 tumors located within two or fewer segments and 65 within three or more segments), 51 segmentectomy or bisegmentectomy, 8 trisegmentectomy, 55 left hepatectomy, 26 right hepatectomy and 18 extended hepatectomy. Fifty-four patients also received common bile duct exploration for choledolithiasis or thrombus resection, 12 patients received Roux-en-Y cholangiojejunostomy, and 19 patients received resection of invading tissues or of organs surrounding liver. Thirty-five patients underwent lymph node dissection, among them 25 patients with and 10 patients without lymph nodes metastasis. Thirty-four patients were excluded from liver resection due to intrahepatic or extrahepatic metastasis and hepatic duct system invasion by tumor metastases or metastatic lymph node.

Five (1.2%) patients died within 1 mo after surgery, 3 of them died of hepatic failure, 1 died of intraperitoneal hemorrhage, and 1 died of adult respiratory distress syndrome (ARDS). Twenty-six (6.1%) patients had surgical complications, i.e. biliary leakage (13 cases), infection of pneumonia, subphrenic or, incision infection (7 cases), bleeding (4 cases), ARDS (1 case), and intestinal obstruction (1 case).

Pathological features

After surgery, tumors were inspected macroscopically and microscopically, and the data indicated that poorly differentiated tumors accounted for 62.0%, while moderately and well differentiated tumors accounted for 36.7% and 1.3%, respectively. Microscopic tumor thrombi were found in 34.7% of the patients, and 89.4% of tumors did not have a pseudocapsule. One hundred and forty-six patients had cirrhosis in the liver, and of these 92 cases had small-nodule liver cirrhosis. Moreover, bile duct stones were observed in 10.7% (46/429) of patients.

Prognosis and prognostic factors

The longest follow-up period is 8 years, but only 329 (76.7%) patients were available for data analysis, the rest patients were lost to follow-up after operation. Most the reasons for the lost follow-up is unknown but may be due to lost contact, death, or unspecified causes. Among these 329 patients, the mean survival time was 12.4 mo with 1-, 3- and 5-year survival rates of 50.9%, 22.2%, and 17.4%, respectively. The overall survival period for the patients with R0 resection was 18.3 mo with 1-, 3-, and 5-year survival rates of 62.5%, 30.2%, and 23.6%, respectively. The overall survival for the patients with R1 resection and punching exploration were only 6.6 and 5.6 mo. The 3- and 5-year survival rates of 50.9%, 22.2%, and 17.4%.

 Furthermore, the data from the univariate analysis found that prognostic factors included radical resection, lymph node metastases, satellite lesions, extrahepatic metastasis, tumor size, number of tumor lesions, and expression of CEA and CA19-9. The multivariate analysis further confirmed that radical resection, lymph node metastases, macroscopic tumor thrombi, tumor size, and
CA19-9 were prognosis factors (Table 3). In addition, Chi-square tests showed that CA19-9 was associated with gender, age, tumor size, HBsAg positivity, and liver cirrhosis (Table 4). The logistic regression analysis revealed that CA19-9 was associated with lymph node metastases and inversely with liver cirrhosis (Table 5).

**DISCUSSION**

### Risk factors of ICC

A recent review\(^2\) showed the acknowledged risk factors in only a few cases of cholangiocarcinoma, which seem to be associated with chronic inflammation of the biliary epithelium (such as cholangiolithiasis, parasitic infection, intrahepatic biliary stones, and viral infection\(^6-10\)). Primary sclerosing cholangitis is the most common known predisposing condition for cholangiocarcinoma in Western countries\(^1\). In follow-up, or in examination of tissue specimens of cholangiocarcinoma, primary sclerosing cholangitis was found to account for 8%-40% of cholangiocarcinoma. In the current study, 198 patients were HBsAg-positive, accounting for 46.4% of cases, which is significantly higher than the estimated 10% HBV

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**Table 2** Surgery selection and prognosis

| Surgical procedures      | n  | Ratio (%) | Median survival time (mo) | Survival rate (%) | P value | 1-yr | 3-yr | 5-yr |
|--------------------------|----|-----------|--------------------------|-------------------|---------|------|------|------|
| R0\(^a\)                 | 319| 74.3      | 18.3                     | 62.5              | 0.000   | 30.2 | 23.6 |
| R1\(^b\)                 | 76 | 17.7      | 6.6                      | 25.4              | 0.000   | 0    | 0    |
| Exploratory laparotomy   | 34 | 7.9       | 5.6                      | 3.6               | 0.000   | 0    | 0    |
| Total                    | 429| 100       | 12.4                     | 50.9              | 0.000   | 22.2 | 17.4 |

\(^a\)R0 vs R1 or exploratory laparotomy, P = 0.000; \(^b\)R1 vs exploratory laparotomy, P = 0.360.

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**Table 3** Multivariate analysis of patient survival

|                      | Regression coefficient | Standard error | P value | Relative risk | 95% CI      |
|----------------------|------------------------|----------------|---------|---------------|-------------|
| Curative resection   | 0.658                  | 0.173          | 0.000   | 1.931         | 1.375-2.713 |
| Lymph node metastases| 0.432                  | 0.218          | 0.048   | 1.540         | 1.004-2.361 |
| Macroscopic tumor thrombi | 0.455               | 0.206          | 0.027   | 1.576         | 1.053-2.360 |
| Tumor size (cm)      | 0.159                  | 0.080          | 0.046   | 1.173         | 1.003-1.372 |
| CA19-9               | 0.191                  | 0.085          | 0.024   | 1.210         | 1.025-1.428 |

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**Table 4** Association of CA19-9 with clinicopathological parameters of the patients

| CA19-9 expression | Gender | Male | Female | Age (yr) | > 53 | < 53 | Age (yr) | P value |
|-------------------|--------|------|--------|----------|------|------|----------|---------|
| > 37 U/mL         |        | 159  | 135    |          |      |      |          | 0.032   |
| ≤ 37 U/mL         |        | 85   | 44     |          |      |      |          | 0.040   |

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**Table 5** Logistic regression analysis in relationship between CA19-9 expression, lymph node metastases, and liver cirrhosis

|                      | Regression coefficient | Standard error | P value | Relative risk | 95% CI      |
|----------------------|------------------------|----------------|---------|---------------|-------------|
| Lymph node metastases| 0.637                  | 0.295          | 0.031   | 1.891         | 1.060-3.374 |
| Cirrhosis            | -0.539                 | 0.230          | 0.019   | 0.584         | 0.372-0.915 |
| Constant             | 0.336                  | 0.146          | 0.021   | 1.340         | 1.000-1.904 |
carrier rate in Chinese population. This data indicate that HBV infection may be one of the risk factors for ICC. Moreover, an additional 60 patients were found to be serum positive for anti-HBc antibody, although they were negative for HBsAg, which is indicative of a past HBV infection. Combining HBsAg and anti-HBc expression, our study population had 60.4% patients with HBV or a history of HBV infection. However, it is unclear how HBV infection contributes to development of ICC. The association of cirrhosis with cholangiocarcinoma development may illuminate HBV infection as a risk factor for cholangiocarcinoma. HBV infection causes the majority of liver cirrhosis in Asian countries. Although other studies showed that hepatitis C virus infection was a risk factor for ICC\[8-9\], our study did not confirm it because of very low infection rate (0.3%) in our patients.

**Diagnosis**

Initial and early diagnosis of ICC could be very difficult to achieve due to the wide range of differential diagnoses. Features identified in CT or MRI evaluations are not typical for ICC, as minimal contrast may occur after enhancement. Therefore, some tumor markers, such as CA19-9, CEA, and AFP, may add to the differential diagnoses or diagnostic guide for ICC, although these biomarkers may not be specific for ICC. In the current study, elevated CA19-9, CEA, and AFP occurred in 57.5%, 11.9%, and 21.3% of the patients, respectively, and 70.9% patients were found to express at least one of these markers. Previous studies did report expression of these biomarkers in association with ICC\[11-13\]; however, due to lack of a large number of patients, the exact rate of positive expression of these markers remained unrevealed until the information reported in this current study.

Nevertheless, it is well known that detection of AFP expression is routinely used for early diagnosis of HCC, and given the high infection rate of HBV in the Chinese population, HCC should be first considered in a patient with elevated AFP. In the present study, 23 patients exhibited an increased AFP (> 200 µg/L but ≤ 1000 µg/L), while highly increased AFP (> 1000 µg/L) was found in 20 patients, accounting for 5.4% and 4.7% of cases, respectively. Therefore, ICC should also be taken into account for patients with elevated AFP. In addition, for patients with high levels AFP but negative in CA19-9 and CEA, ICC should also be considered before operation.

Furthermore, Positron Emission Computed Tomography (PET)/CT could be an alternative method for differential diagnoses of ICC, as it is superior to the enhanced CT in the diagnosis of extrahepatic or lymph node metastases\[8\].

**Relationship between CA19-9 levels and clinical features**

CA19-9 or known as sialylated Lewis antigen is a blood tumor marker and was discovered in patients with colon cancer and pancreatic cancer in 1981\[8\]. Previous studies found that CA19-9 expression was also prevalent in ICC\[8\]. In the current study, CA19-9 (> 37 U/mL) was found in 57.5% of ICC patients. Further analyses found that CA19-9 positivity was significantly associated with gender, age, tumor size, cirrhosis, and HBsAg expression, while logistic regression analysis indicated that expression of CA19-9 was significantly associated with cirrhosis and lymph node metastases. ICC patients with CA19-9 (> 37 U/mL) presented a higher incidence of lymph node metastases. Other studies demonstrated association of positive CA19-9 and lymph node metastases of gastric and colorectal cancers\[16-20\].

In addition, our study revealed that CA19-9 (> 37 U/mL) rate was lower in cirrhosis patients with positive HBsAg. The underlying mechanism for this remains unknown and needs further investigations. However, Schöniger-Hekele et al.\[21\] reported that the combined elevation of CA19-9 and CA 125 was useful for diagnosis of the advanced fibrosis or cirrhosis. Their observation is definitely not compatible with the results of this current study.

**Surgical resection and prognosis**

To date, surgical resection is still the primary and most effective means to cure ICC. Nevertheless, the selection methods used to determine a patient’s suitability for surgery will directly affect the patient’s chances of survival. In this study, the mean survival of patients receiving R0 resection was 18.3 mo, whereas the mean survival rate for patients with R1 resection was only 6.6 mo, indicating that radical resection is the most important factor in prolonging patient survival. Comparing R1 resection and exploratory laparotomy, the former exhibited a slightly better prognosis; however, this is not statistically significant (P = 0.36).

Several other studies\[22-27\] showed that the 1-year survival rate of patients receiving R0 resection was between 61% and 83%, and the 5-year survival rate was between 22% and 63% (Table 6), indicating that their survival rates were much higher than those of our patients. Besides the different patient population and severity of the diseases, we proposed that this might be due to the different surgical methodology. For example, segmental resection is extensively used in Western countries, while non-anatomic resection is primarily used in China. The former is a more curative procedure owing to wider resection margins. The low rate of radical resection may be due to the invasion of local and portal hepatic ducts by ICC. Lymph node metastases and distant metastasis were often observed in patients with ICC.

However, it remains debatable whether extended radical operation in combination with lymph node dissection could improve survival rates. Some studies have reported that 1- and 3-year survival rates were 94% and 82%, respectively, after extended hepatectomy (including vessel resection and reconstruction) in patients with solitary tumors but without vascular invasion or extrahepatic or lymph node metastases\[28\]. However, rather than positive effects, increased morbidity was observed in patients with extended surgery that included anatomic hepatic resection, vessel resection and reconstruction, and extended lymph node dissection\[29\].
Table 6  Comparison of post-operative survival after R0 resection

| Author | No. of total | No. of R0 | Ratio (%) | Survival (%) |
|--------|-------------|-----------|-----------|--------------|
|        |             |           | 1-yr      | 3-yr         | 5-yr         |
|        |             |           |           |              |              |
| Ohtsuka et al et al, 2003 | 50          | 34        | 68        | 61.6         | 37.6         | 22.5     |
| Morimoto et al et al, 2003 | 51          | 35        | 68.6      | 68.2         | 44.1         | 32.4     |
| Nakagawa et al et al, 2005 | 53          | 44        | 83.0      | 66.2         | 38.3         | 26.3     |
| Lang et al et al, 2006 | 54          | 30        | 55.5      | 83           | 58           | 48       |
| DeOliveira et al et al, 2007 | 44          | 34        | 77.3      | NR           | NR           | 63       |
| Konstadoulakis et al et al, 2008 | 72          | 54        | 75        | 80           | 49           | 25       |
| Our current study | 429         | 319       | 74.3      | 62.5         | 30.2         | 23.6     |

Two cases of death were excluded. NR: Not reported.

**Prognostic factors**

The present study showed that favorable prognostic factors for ICC are: radical resection, no metastasis of lymph nodes, a small tumor diameter, no macroscopic tumor thrombi, and low levels of CA19-9. Among these favorable factors, radical resection, no metastasis of lymph nodes, and a small tumor diameter are consistent with previous studies [22,24,30,31]. This study also showed that macroscopic tumor thrombi and CA19-9 expression were prognostic factors for ICC. In addition, ICC with CA19-9 (> 37 U/mL) exhibited a higher grade of malignancy and prevalence of lymph node metastases. Ohtsuka et al[22] also reported that CA19-9 was a prognostic factor of ICC. Other studies demonstrated that macroscopic tumor thrombus is a key factor for poor prognosis of hepatocellular carcinoma [33-35]. As the incidence of macroscopic tumor thrombus is relatively low in ICC (only 11% in our current study), it could be easily missed, especially studies with a small sample size.

**Liver transplantation**

Originally, the prognosis of ICC patients who received liver transplantation treatment was not satisfactory. In particular, Pascher et al [36] reported that 5-year survival rate reached 29% in a study, but did not exceed 18% in other four studies. However, most recent studies showed an improving 5-year survival rate between 33% and 42% [32,33]. Multivariate analysis revealed that single tumor, tumor-free margins, no lymph node metastasis, no jaundice, or no perineural invasion, and early TNM stage were associated with better prognosis [4,36,39]. Nevertheless, due to restricted resources of liver donors and poor prognosis after liver transplantation, it is still controversial whether the patients with unresectable and non-metastasis ICC should undergo liver transplantation. Further studies are needed to determine the criteria for selecting the patients who can benefit from liver transplantation. In addition, the effectiveness of adjuvant radiotherapy and chemotherapy both before and after transplantation remains to be defined.

In conclusion, our present study demonstrated that hepatitis B infection, CA19-9, CEA, and AFP are associated with ICC development. CA19-9 levels are associated with lymph node metastases, but inversely with cirrhosis. Radical resection (R0) is the key prognostic factor for ICC. Future studies should focus on evaluation of the molecule-targeted therapy, and whether it can efficiently control this deadly disease so as to improve the survival of the patients.

**COMMENTS**

**Background**

Incidence of intrahepatic cholangiocarcinoma (ICC) is increasing worldwide and its prognosis is very poor. Thus, further studies on its clinical characteristics for early detection and on surgical treatment for better prognosis are urgently needed.

**Research frontiers**

Early detection of ICC could focus on defining clinical characteristics and biomarker study. Surgery with radical resection always is the key factor to improve the survival of the patients. The effectiveness of chemotherapy is currently limited and novel approaches are needed.

**Innovations and breakthroughs**

This study demonstrated that carbohydrate antigen 19-9 (CA19-9) is commonly elevated in ICC and associated with lymph node metastases, but inversely associated with liver cirrhosis, indicating that CA19-9 could further be evaluated for early detection and prognosis of ICC. In addition, hepatitis B virus infection is associated with cholangiocarcinoma and increased α-fetoprotein (AFP) levels may also be considered for ICC, although AFP is a routinely used biomarker for hepatocellular carcinoma.

**Applications**

This study provides an initial assessment of ICC and further studies are needed to confirm the findings, which can apply to future early detection, prediction of prognosis, treatment election, and differential diagnosis of ICC.

**Peer review**

This is an interesting paper, with a large number of patients involved, which might be of benefit for future studies of ICC.

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