

RESEARCH COMMUNICATION

Diagnosis and Cure Experience of Hepatolithiasis-Associated Intrahepatic Cholangiocarcinoma in 66 Patients

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Abstract

Background: The management of hepatolithiasis combined with intrahepatic cholangiocarcinoma (IHHCC) remains a challenge due to poor prognosis. The aim of this study was to summarize our diagnosis and cure experience of IHHCC over the recent 10 years. **Methods:** From January 1996 to January 2006, 66 patients with IHHCC were reviewed retrospectively. **Results:** Of the 66 patients, 52 underwent surgical resection (radical resection in 38 and palliative in 14) and 8 patients abdominal exploration, while the other 6 cases received endoscopic retrograde biliary internal drainage and stent implantation. In this series, correct diagnosis of advanced stage was made during operation in 8 cases (8/60, 13.3%) and all of them (underwent unnecessary abdominal exploration, among them the positive rate of CA19-9 was 100%, and the positive rate of CEA was 87.6% (7/8), incidence rate of ascites was 100% and short-term significant weight loss was 100%, with median overall survival of only 4 months. **Conclusion:** Radical resection is mandatory for IHHCC patient to achieve long-term survival, the CT and MR imaging features of IHHCC being concentric enhancement. Patients with IHHCC have significant higher CA199 and significant higher CEA and short-term significant weight loss and ascites should be considered with advanced stage of IHHCC and unnecessary non-therapeutic laparotomies should be avoided.

Keywords: Intrahepatic cholangiocarcinoma - hepatolithiasis - diagnosis - therapy

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Introduction

Since 1952, Sanes MacCallum et al. (1952) first reported that two cases Hepatolithiasis is merger Hepatobiliary cancer (IHHCC), the phenomenon of IHHCC aroused more and more people seriously enough, Hepatolithiasis is a common disease in China and 5% to 10% of hepatolithiasis is known to be associated with cholangiocarcinoma (Uenishi et al., 2005), However, it is difficult to detect early cholangiocarcinoma that occurs as a complication of hepatolithiasis. Clinically, IHHCC remains challenging because it is difficult to diagnose in its early stages, symptoms tend to be vague and insidious in development, often are diagnosed at an advanced stage. Curative resection with clear margins and without vascular or lymphatic invasion is infrequent and recurrence is common, three-to five-year survival rates even with resection remain dismal (Tischoff et al., 2007). To investigate the clinicopathologic features and advanced stage of IHHCC, we retrospectively analysed the clinical and pathologic data of resected IHHCC at our hospital and summarize diagnosis and cure experience in recent 10 years, so as to increase our understanding on IHHCC and promote effective treatment.

Materials and Methods

From January 1996 to January 2006, 66 consecutive patients with histologically proven IHHCC, underwent surgical treatment at the Department of Hepatobiliary Surgery, The Second Affiliated Hospital of Chongqing Medical University, China. Group of 66 cases patients with the male 26 cases, female 40 cases, average age 48 years old, with discovery of Calculi history 9 ~ 42 years, 46 cases had biliary surgeries, including 3 cases had 1 times biliary surgeries, 1 cases had 2 times biliary surgeries, 2 cases had 3 times biliary surgeries, 2 cases intraoperative history for pure cholecystectomy, and 1 case of bile duct exploration stone-free cut, and 1 case of bile duct and duodenum anastomosis, and 2 case of bile duct and jejunum anastomosis. 4 cases of childhood with biliary tapeworm history. 17 patients had a history of hepatitis B, 9 patients were positive with hepatitis B surface anti-(HBsAg).

IHCC was defined as carcinoma arising from second order or more distal branches of the intrahepatic ducts. Meanwhile, a radical resection was defined as negative resection margin observed during histopathological examination, that is, R0 resection.

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Table 1. Clinical Presentation of IHHCC Patients

Finding	Number of patients (%)
Right upper abdominal	52 (78.8)
Fever and chill	36 (54.5)
Jaundice	23 (34.8)
Shoulder department radiation pain	12(18.1)
Liver enlargement	42 (63.6)
Loss of appetite	28(42.4)
Ascites	8(12.1)
Short-term significant weight loss	10(15.2)

IHHCC, intrahepatic hepatolithiasis associated intrahepatic cholangiocarcinoma

Table 2. The Relation Between Operation Approaches and Surgical Resection

operation approaches	cases	surgical resection
radical resection	38	63.3%
palliative resection	14	23.3%
laparotomy and biopsy	6	8.2%
laparotomy and biopsy	2	3.3%

Clinical presentation

The clinical manifestations in patients with IHHCC were not specific. We found that the most common symptom on admission was patients who presented with right upper abdominal pain and tenderness 78.8% (52/66). This was, followed by 54.5% (36/66) of patients. with fever and chills, 34.8% (23/66) of patients with jaundiced performance, 18.1% (12/66) of patients with shoulder department radiation pain, 63.6% (42/66) of patients with liver enlargement, 42.4% (28/66) of patients with a loss of appetite, 12.1% (8/66) of patients with ascites, 15.2% (10/66) of patients with short-term significant weight loss (Table 1).

Follow-up study and statistical analysis

Follow-up was made by out-patient clinic interview, telephone or letter communication. All the IHHCC patients undergoing surgical treatment received regular postoperative follow-up until death or the study deadline. The clinicopathological database was established by SPSS14.0 software. Survival curves were calculated using the Kaplan-Meier method and compared by the log-rank test.

P value less than 0.05 was considered statistical significance.

Results

Laboratory investigations and imagine examination

All patients were routine check after admission, Laboratory tests were conducted the day before surgery, total bilirubin (TB) was elevated in 36 patients (51.2%), alkaline phosphatase(ALP) was elevated in 46 patients (69.6%), aspartate aminotranferase (AST) was elevated in 48 patients (72.7%), carbohydrate antigen (CA19-9) was elevated in 53 cases (80.3%), carcinoembryonic antigen (CEA) was elevated in 10 cases (15.2%), alpha-fetoprotein (AFP) was slightly elevated only in 6 patients (9.1%).

66 cases upper abdomen B ultrasonic examination, all found intrahepatic biliary calculi with intrahepatic

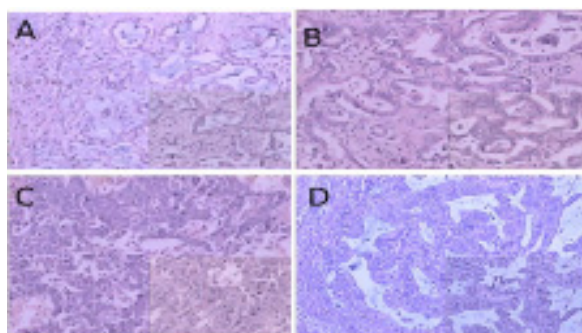


Figure 1. Pathological Classification of HC: A, well-differentiated adenocarcinoma; B, moderately differentiated adenocarcinoma; C, poorly differentiated adenocarcinoma; D, papillary adenocarcinoma. (The segment on right bottom of each pic is the HP image for them [original magnification ×20])

space-occupying lesions in 52 cases, the correct diagnosis obtained was 78.8% (52/66), 56 cases examination liver with CT, 52 cases confirmed intrahepatic cholangiocarcinoma, the diagnosis rate of the CT scans was 92.9% (52/56), 52cases examination liver with MRI and MRCP, all found intrahepatic biliary calculi, 48cases confirmed intrahepatic cholangiocarcinoma, the diagnosis rate of MRI and MRCP was 88.5% (48/52).

Operative procedure

Of the 66 patients, 60 patients underent surgical resection, inciluding 38 cases (63.3%) underwent radical resection, and 14 cases(23.3%) underwent palliative resection, Amonge the 38 patients receiving radical resection, 8 patients underwent skeletoniztion resection (SR), 12 SR in combination with partial hepatectomy, 6 SR in comination with portal vein resection and reconstruction and 12 SR in combination with pancreaticoduodenectomy, radical resection is still the optimal. 8 patients abdominal exploration including simple laparotomy and biopsy in 6 patients (8.2%), simple laparoscopic and biopsy in 2 patients (3.3%), other 6 cases with IHHCC underwent endoscopic retrograde biliary internal drainage and stent implantation (Table 2).

Classification and pathology

The pathological diagnosis in patients whom underwent surgical operation are 12 cases of well-differentiated adenocarcinoma (Figure 1A), 22 cases of moderately differentiated adenocarcinoma (Figure 1B), 24 cases of poorly differentiated adenocarcinoma (Figure 1C) and 2 cases of papillary adenocarcinoma (Figure 1D). (The segment on right bottom of each pic is the HP image for them [original magnification ×20]). According to the morphologic classification system proposed by the Liver Cancer Study Group of Japan, intrahepatic cholangiocarcinoma is classified into mass-forming, periductal infiltrating, and intraductal growth types (Figure 2), mass-forming 32 cases, periductal infiltrating 17 cases, intraductal growth types 11cases, TNM staging: stage I 7 cases, stage II 12 cases, stage III 28 cases, stage IV 13 cases (Table 3).

Survival

All the IHHCC patients undergoing surgical treatment

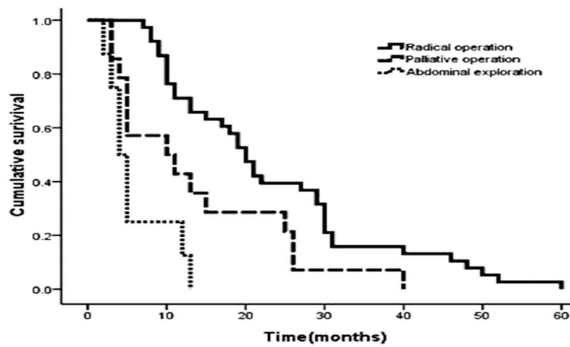


Figure 2. The Survival Curve of the whole Surgical Treatment Group

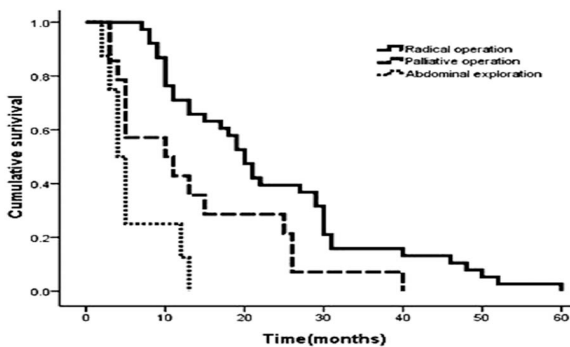


Figure 3. The Survival Curve of IHHCC Patients Undergoing Radical Resection, Palliative Resection or Abdominal Exploration

Table 3. The Relation Between Tumor Types and TNM Staging

Tumor types	cases	stage I	stage II	stage III	stage IV
mass-forming	32	4	6	17	5
periductal infiltrating	17	1	3	8	5
intraductal growth	11	2	3	3	3
total	60	7	12	28	13

received regular postoperative follow-up until death or the study deadline. No patients failed to follow-up. The overall 1-, 3-, and 5-year survival rates for patients with IHHCC were 58.3%, 31.7% and 11.7%, respectively, with a median survival of were 13 months (95%CI: 7.6-18.4 months) (Figure 2), In the radical resection group (n=38), the 1, 3 and 5 year survival rates were 71.1%, 39.4% and 15.8%, respectively, in the palliative resection group (n=14), the 1, 3 and 5 year survival rates were 42.9%, 28.6% and 7.1%, respectively, in the group of abdominal exploration (n=8), the 1, 3 and 5 year survival rates were 25%, 0%, and 0%, respectively, there was significant difference in the survival rates among these 3 groups ($P < 0.001$), median survival time of radical resection group was 20 months, 10 months for the palliative resection group and 4 months for abdominal exploration, There were significant difference in the Median survival time among these 3 groups ($P < 0.001$) (Figure 3).

Discussion

Hepatolithiasis is more frequently seen in East Asian countries than in Western countries, and it is well known

to represent a high-risk state for IHCC (Yeh et al., 2005). IHCC is an aggressive tumour that shows a dismal outcome even after resection (Lazaridis et al., 2005). Chen et al. (2000) reported that 5-6.5% of patients with hepatolithiasis were associated with IHCC. Conversely, they reported that 66% of patients with IHCC had concomitant hepatolithiasis. The pathogenetic relationship between hepatolithiasis and IHCC is still not clear, most people think calculous mechanical stimuli and it is a cause of bacteria infection, cholestasis deposition can cause mucosa glandular epithelium hyperplasia and proliferative cholangitis. Proliferative cholangitis can cause atypical epithelial hyperplasia, thus conversion into bile duct carcinoma. Long-term calculous biliary stimulation, damage and bile duct epithelium repeated the repair will cause epithelial atypical and bile duct carcinoma (Zhou Met al., 2008). They have also found that hepatolithiasis does not provide the sole carcinogenic stimulus leading to malignancy. cholangiocarcinoma arising in association with hepatolithiasis is probably the cumulative result of several etiologic agents, which may include nutritional, genetic, environmental, and immunologic factors (Kuroki et al., 2005), recent efforts in stem cell biology suggest the possibility of the involvement of hepatic progenitor cell (HPC), corresponding to oval cell in rodent model, in the development of HCC, ICC, and combined hepatocellular cholangiocarcinoma (Tanaka et al., 2005).

Patients with IHHCC present with non-specific symptoms including abdominal pain, diminished appetite, weight loss, malaise and night sweats, and incidental abdominal mass which may be detected during either aphysical examination or imaging study (Lazaridis et al., 2005; Kinjo et al., 2005). The disease clinical symptoms nonspecific, it is easy to be masking with intrahepatic bile ducts residue, calculi recurrence cover, imaging and laboratory tests sensitivity low, early diagnosis rate low, clinicians usual tend to lack of attach importance to these diseases. The diagnosis rates of IHHCC by ultrasonography, CT scan and MRCP were 82.6%, 95.7%, and 91.7% in available literature (Han et al., 2009).

Our data indicated that the diagnosis rate of ultrasonography was 78.3% (47/60), the rate obtained by CT scan was 92.9% (52/56), and by MRCP was 88.5% (49/56). IHHCC with typical imaging features can easily be diagnosed; however, not all the tumors show typical imaging findings, and the tumors may mimic a variety of tumorous and nontumorous lesions. We think that the causes of misdiagnosis were: (1) clinical physicians were not aware of this disease and the lack of vigilance; (2) the disease incidence were low, and clinical symptoms lack specificity; (3) ultrasound shows high-density calculi shadow covered intrahepatic space-occupying lesions; (4) tumors often cause Stenosis of pathological change, so that shadow agent can't reach biliary distal intahepatic bile ducts; (5) merger hepatolithiasis are easy to cause misdiagnosis, when the tumor with less than 1cm is not easy to find. Therefore we thinks high-risk patients are those who have stubborn symptoms, repeated attack, especially above 10 years history. Type-B ultrasonic is the first selection of noninvasive imaging examination. If intrahepatic organization with low appears echoes and

hyperechoic and disorderly echo should remain vigilant, it can be followed up with further CT examination. In our study, 46 patients shows the typical features of CT and 42 patients shows the typical features of MRI were: (1) the dynamic nature of the enhanced feature of progressive nature of concentric enhancement, internal lesions was flaky, grid-like or linear strengthening; (2) intrahepatic duct dilatation; (3) capsular retraction; (4) satellite nodule is also seen. With the recent advances of imaging techniques, 3D MR cholangiopancreatography (3D-MRCP) is emerging as a promising technique due to its high image quality and ability to clarify anatomic relationships (Sodickson et al 2006; Glockner et al., 2007; Choi et al., 2008; Palmucci et al., 2010). The diagnostic procedures of IHHCC can be summarized as follows: clinical features → B-ultrasound → CT or MRI → surgical resection (radical resection or palliative resection or abdominal exploration) or stent implantation.

Laboratory tests usually show increased tumour markers, such as CA 19-9, CEA, may be increased sometimes. Elevated concentration of serum CA19-9 (>37 KUL-1) in cholangiocarcinoma has been frequently reported. Multiple studies have suggested that elevated serum concentration of CA19-9 was significantly related the prognosis in patients with ICC (intrahepatic cholangiocarcinoma), others also demonstrated that both serum CA19-9 and CEA levels could be independent prognostic factors (Jan et al., 2005). Minato et al. (Li et al., 2009) reported that when the serum level of CA19-9 is greater than 129U/ML, its diagnostic sensitivity and specificity for ICC is 78.6 per cent and 98.5 percent, respectively and that when the serum level of CA19-9 is greater than 632U/ML, its sensitivity is 90.0 per cent and specificity is 98.0 percent. Since detection of AFP in the serum of HCC (hepatocellular carcinoma) patients in 1963, AFP has been widely used for screen examination and clinical diagnosis as an HCC tumor marker, and positive AFP is rarely seen in ICC patients (Zhou et al., 2008). Carcinoembryonic antigen (CEA), which is mainly used for colorectal cancers, is of scarce utility being increased only in approximately 30% of patients with Cholangiocarcinoma (Patel et al., 2007; Morris-Stiff et al., 2008; Schulick et al., 2008). In our study, 9.1% (6/66) patients had elevated serum AFP, 15.2% (10/66) patients had elevated serum CEA, and 80.3% patients (53/66) with IHHCC had elevated serum CA 19-9. These results indicated that a combination measurement of AFP, a representative tumour marker for HCC, and CA19-9 is considered to be one of the most important serological indicators in ICC.

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. Jan et al analysed the surgical treatment of 373 patients with peripheral cholangiocarcinoma (PCC), they found the survival rates at 1, 3, and 5 years were 32.5%, 9.2%, and 4.1%, respectively (Jan et al., 2005). Our result indicated that the median survival of patients undergoing radical resection were 20 months (95%CI: 16.9-23.0 months), whereas the mean survival rate for patients with

palliative resection was only 10 mo, indicating that radical resection is the most important factor in prolonging survival rate. For those patients who received a radical resection the survival rates were 71.1%, 39.4%, and 15.8%, which was significantly longer than the patients who underwent palliative resection 42.9%, 28.6%, and 7.1%. Furthermore, the median survival time of patients undergoing palliative resection was significantly better than abdominal exploration (10 months vs 4.0 months, $P < 0.001$, Figure 3). Lang et al. (2006) studies showed that the 1-year survival rate of patients receiving radical resection was between 83%, and the 5-year survival rate was between 48%, indicating that their survival rates were much higher than those of our patients. 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.

The median survival of unresectable IHCC was dismal. patients with advanced unresectable cholangiocarcinoma were reported to have a wide range of survival time from 57 days to 8.7 months (Witzigmann et al., 2006; Connor et al., 2007; Shaib et al., 2007; Paik et al., 2009). In this study, 6 patients non resection underwent internal or external drainage, median overall survival in inoperable patients was only 6 months, which might be related to the fact that most of these patients have already developed intrahepatic or extrahepatic metastasis when diagnosed. The aims of internal or external drainage are to relieve jaundice and pruritus, prevent cholangitis, avoid liver failure due to progressive biliary obstruction, and to enhance quality of life. For patients with unresectable ICC, therapeutic options are chemotherapy or chemoradiation or stent implantation, there are not so much evidences for the evidence-based evaluation of the chemotherapeutic efficacy for ICC patients. Previous studies were mainly retrospective analysis on small number of case including extrahepatic, hilar and intrahepatic cholangiocarcinoma. By and large, chemotherapy had low response rate and failed to show survival benefit (Patt et al., 2001). In recent years, study revealed that radiotherapy could be used to treat unresectable ICC to relieve symptoms such as jaundice and improve survival. Patients with central ICC appear to benefit more from radiation compared with patients with peripheral ICC (Chen et al., 2010).

In patients with IHHCC, unresectable disease is often found at the time of exploration despite extensive preoperative evaluation, thus resulting in unnecessary laparotomy. In the 60 patients undergoing surgical exploration, 8 patients were found to have unresectable disease. Therefore, the overall accuracy for detecting unresectable disease was 13.3% (8/60), including simple laparotomy in 6 patients (10.0%) and simple laparoscopic in 2 patients (3.3%). Among them the positive rate of CA199 was 100% (8/8), and the positive rate of CEA was 87.6% (7/8), and incidence rate of ascites was 100% (8/8), and short-term significant weight loss was 100% (8/8), median overall survival in the 8 patients was only 4 months (95%CI: 2.6-5.4 months), and no one of the patients survived for over 1 years. In our experience, patients with suspected IHHCC have significant higher CA199

and significant higher CEA and short-term significant weight loss and ascites should be considered with advanced stage of IHHCC and unnecessary laparotomies should be avoided. Patients with potentially unresectable IHHCC metastases are incorrectly deemed resectable on standard pre-operative evaluation, including contrast-enhanced CT and MRI, Laparoscopy can identify unresectability in a majority of patients at highest risk of being incorrectly deemed resectable, sparing them an unnecessary laparotomy. Laparoscopy is associated with decreased postoperative pain, a shorter hospital stay and a higher likelihood of receiving systemic therapy compared to laparotomy without significantly increasing the operative time (Sebastien et al., 2010). In this study, laparoscopic and biopsy in 2 patients (3.3%), laparoscopy correctly identified unresectable IHHCC and prevented unnecessary laparotomy, the utility of laparoscopic assessment in the preoperative staging of suspected IHHCC is feasible and effective.

In conclusion, radical resection is mandatory for IHHCC patient to achieve long-term survival, the CT and MR imaging features of IHHCC are concentric enhancement, patients with suspected IHHCC have significant higher CA199 and significant higher CEA and short-term significant weight loss and ascites should be considered with advanced stage of intrahepatic cholangiocarcinoma and unnecessary laparotomies should be avoided, laparoscopy correctly identified unresectable IHHCC and prevented unnecessary non-therapeutic laparotomy.

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