Diagnosis and Surgical Treatment of Intrahepatic Hepatolithiasis Associated Cholangiocarcinoma

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Liver malignancy is known to be associated with hepatolithiasis. The present report summarises the results and our experience for management of 23 patients with intrahepatic hepatolithiasis associated cholangiocarcinoma (IHHCC). The correct diagnosis rates of US (ultrasonography), CT (computed tomography), and MRCP (magnetic resonance cholangiopancreatography) were 82.6% (19/23), 95.7% (22/23), and 91.7% (11/12), respectively. Carbohydrate antigen 19-9 (CA 19-9) was helpful in the diagnosis of IHHCC. All 23 patients with IHHCC underwent laparotomy. The surgical procedure consisted hepa-tectomy with a bile duct exploration in 16 patients (69.6%), a hepatectomy and drainage procedure such as sphincteroplasty and choledo-jejunostomy in three patients (13.0%), a bile duct exploration with biopsy in two patients (8.7%), and simple laparotomy and biopsy in two patients (8.7%). All the IHHCC patients who underwent a palliative procedure or laparotomy died within 1 year, and the overall cumulative survival rates at 1, 3, and 5 years were 43.8% (10/23), 13.0% (3/23), and 4.3% (1/23), respectively, and those patients who underwent curative resection were 88.9% (8/9), 33.3% (3/9), and 11.1% (1/9), respectively, which significantly longer than those (20.0%, 2/10; 0.0%, 0/10; and 0.0%, 0/10) patients who underwent palliative resection, respectively (p < 0.05). A suspicion of malignancy is necessary when managing patients with long-term hepatolithiasis. Hepatic resection with postoperative treatment is the treatment of choice for cholangiocarcinoma when it is resectable. [Asian J Surg 2009;32(1):1–6]

Key Words: cholelithiasis, explosive decompression, intrahepatic cholangiocellular carcinoma, liver neoplasm

Introduction

Intrahepatic cholangiocarcinoma (IHCC) is a malignant tumour occurring in the liver or arising from the second or more distal branches of the intrahepatic bile ducts.1 The incidence of IHCC exhibits wide geographical variation, and generally accounts for between 5% and 30% of primary liver cancers.1 According to the Japan Liver Cancer Society, histologically proven IHCC represented 3.58% of all primary liver cancers.6 Early detection of cholangiocarcinoma has been difficult and the overall survival after resection remains poor compared with that of hepatocellular carcinoma (HCC). The clinical features and the population at high risk of IHCC are not well clarified, in order to the well-defined high-risk group in HCC. Although no specific aetiological factor has been identified for IHCC, various well-recognised predisposing conditions involving chronic inflammation of the bile ducts exist.3–9 These conditions include hepatolithiasis, primary sclerosing cholangitis,7 choledochal cysts,7,8 and Caroli’s disease.9 Clinically, IHCC remains challenging because it is difficult to diagnose in its early stages, and patients
typically do not present until the disease is quite advanced because of the vague symptoms. 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.\textsuperscript{10–13}

Hepatolithiasis is a common disease in China and 5% to 10% of hepatolithiasis is known to be associated with cholangiocarcinoma.\textsuperscript{14,15} However, it is difficult to detect early cholangiocarcinoma that occurs as a complication of hepatolithiasis. The clinicopathologic features of hepatocellular carcinoma patients have been well described in literature.\textsuperscript{2,16} On the other hand the biological behaviour of primary hepatic cholangiocarcinoma, especially intrahepatic hepatolithiasis associated cholangiocarcinoma (IHHCC) has not been fully clarified. To investigate the clinicopathologic features of IHHCC, we retrospectively analysed the clinical and pathologic data of resected IHHCC at our hospital.

**Patients and methods**

From July 1982 to January 2006, 23 consecutive patients with histologically proven IHHCC, underwent surgical treatment at the Department of General Surgery, the First Hospital of Wenzhou Medical College, Wenzhou, China. IHHCC was defined as carcinoma arising from second order or more distal branches of the intrahepatic ducts. Meanwhile, a curative resection was defined as negative resection margin observed during histopathological examination, that is, R0 resection.

**General data**

The general data of patients with IHHCC is presented in Table 1. IHHCC occurred predominantly in men in this study. There were 14 males and 9 females with a male to female ratio of 1.56:1; the mean age was 57.6 years with patients ages ranging from 40 to 74 years. The mean duration from the onset of the disease to diagnosis was 8.3 months, ranging from 1 month to 38 months.

**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 73.9% (17/23). This was, followed by 56.5% (13/23) of patients with fever and chills, 47.8% (11/23) of patients with a loss of appetite, 65.2% (15/23) of patients with liver enlargement, 34.8% (8/23) of patients with jaundice and 8.7% (2/23) of patients with ascites. Twenty-one patients had a history of stone disease, four patients had a history of hepatitis B, three patients were positive with hepatitis B surface antigen (HBsAg) and slightly elevated alpha-fetoprotein (AFP) (normal limits of 0.0–20.0 ug/L) was present in two patients. The mean history of hepatolithiasis was 7.2 years, ranging from 5 years to 36 years.

**Follow-up study**

Follow-up evaluation included clinical physical examinations and blood chemistry tests at each visit. Additionally, serum carbohydrate antigen (CA19-9) (a glycoprotein tumour marker, with normal limits of 0.0–37.0 U/mL) and carcinoembryonic antigen (CEA; normal limits of 0.0–5.0 ug/L) were both measured, and the remnant liver was examined with US every 3 months. When US detected a new lesion or elevated CA 19-9 or when CEA were noted, abdominal CT or MRCP was performed for confirmation. Moreover, when patients complained of bone pain, bone scans were performed to detect possible metastasis. If any of the above procedures indicated recurrence, the patient was readmitted for more compressive assessment, including angiographic evaluation or magnetic resonance imaging (MRI). Treatment for tumour recurrence include surgery, systemic chemotherapy, external beam radiotherapy, intraluminal radiotherapy, interventional radiological therapy, and conservative treatment.

**Statistical analysis**

SPSS for Windows statistics software (SPSS version 13.0, Chicago, IL, USA) was used for the statistical analysis. The cumulative survival rates were calculated with the Kaplan-Meier method and a value of $p < 0.05$ was considered statistically significant.

<table>
<thead>
<tr>
<th>Table 1. Clinical presentation of IHHCC patients</th>
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<tr>
<td><strong>Finding</strong></td>
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<tr>
<td>Right upper abdominal pain</td>
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<tr>
<td>Liver enlargement</td>
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<tr>
<td>Fever and chill</td>
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<tr>
<td>Loss of appetite</td>
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<tr>
<td>Jaundice</td>
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<td>Ascites</td>
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IHHCC = intrahepatic hepatolithiasis associated cholangiocarcinoma.
Results

Laboratory and imagine examination
Laboratory tests were conducted the day before surgery. Serum CA 19-9 was elevated in 18 patients (78.3%), and CEA was slightly elevated only in two patients (8.7%). The tumours were preoperatively evaluated by abdominal US, CT, and MRCP. All patients with IHHCC were scanned by US and the correct diagnosis obtained was 82.6% (19/23). The diagnosis rate of the CT scans was 95.7% (22/23), and the diagnosis rate of MRCP was 91.7% (11/12, only the latest twelve patients received the MRI scan).

The tumour stage was defined according to the pathological tumour node metastasis (pTNM system) classification proposed by the UICC. Stages II and I were assigned as early-stage and Stages III and IV as advanced-stage disease (Table 2). There was no early stage disease in this study; all diseases were at an advanced stage, comprising of 17 patients with Stage III disease and six patients with Stage IV. Adjuvant chemotherapy was unsystematically performed with a 5-flurouracil-based regimen due to either a positive section margin or local recurrence.

Operative and histopathological findings
All tumours were near or at the sites of the stone located including tumours located at the left lobe in 16 patients, the right lobe in four patients, the bilateral lobes in two patients, and caudate lobe in one patient. The tumour presented as a massive type in 16 patients, nodular type in five patients and a diffused type through the whole liver in two patients. The mean size of IHHCC was 6.7 cm in diameter, varying from 4 cm to 12 cm. The tumour did involve the capsule in 15 patients, but did not in 8 patients.

The cut surface showed marked fibrosis around the diluted bile duct, with atrophy of the liver parenchyma. Microscopic examination of the resected liver specimen revealed no evidence of malignancy. The epithelium of the dilated bile duct distant from the tumour often showed papillomatous and adenomatous hyperplasia with moderate atypia. There was also proliferation of many glands. A chronic inflammatory infiltrate was present in the periductal fibrous stroma.

The bile duct wall was markedly thickened due to the presence of cholangitis. Unilobular bile duct obstruction usually results in atrophy of the affected hepatic lobe followed by hypertrophy of the unaffected lobe, forming a so-called phenomenon known as the atrophy-hypertrophy complex. Additionally, atrophy and fibrosis of the lobe, abscess formation or a cholangitic appearance in the surrounding liver parenchyma, and recurrent or retained stones that had not be removed by other methods are suitable for hepatic resection. Bacteriology of the choledochal bile taken during the operation revealed Escherichia coli and Klebsiella. Chemical analysis of the intrahepatic stones showed they were composed predominantly of bilirubin.

Operative procedure
All 23 patients with IHHCC underwent laparotomy. The surgical procedure included irregular hepatectomy with bile duct exploration in 16 patients (69.6%), hepatectomy and drainage procedure (sphincteroplasty and choledojejunostomy) in three patients (13.0%), bile duct exploration with biopsy in two patients (8.7%), and simple laparotomy and biopsy in two patients (8.7%). The only postoperative complications were incisional infections in three patients, but there were no operative deaths in this group.

Survival
All the IHHCC patients undergoing surgical treatment received regular postoperative follow-up until death or the study deadline. No patients failed to follow-up. All the IHHCC patients who underwent palliative procedure or laparotomy died within 1 year. Among the 19 patients with IHHCC, nine patients had a curative resection (curative resectability rate; 39.1%), 10 patients had a palliative resection and four had a laparotomy and biopsy. Only one patient who had a so-called small liver cancer (< 3 cm in

Table 2. TNM pathologic classification of intrahepatic cholangiocellular carcinoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumour</th>
<th>Node</th>
<th>Metastasis</th>
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<tbody>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
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<tr>
<td>IIIA</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
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<tr>
<td>IIIB</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
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<tr>
<td>IIIC</td>
<td>Any T</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
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T1 = solitary tumour without vascular invasion; T2 = solitary tumour with vascular invasion or multiple tumours, none > 5 cm; T3 = multiple tumours > 5 cm or tumour involving a major branch of the portal or hepatic vein(s); T4 = tumours with direct invasion of adjacent organs other than gallbladder or with perforation of visceral peritoneum; N0 = no regional lymph node metastasis; N1 = regional lymph node metastasis; M0 = no distant metastasis; M1 = distant metastasis.
diameter) survived than 5 years in this group. The overall cumulative survival rates at 1, 3, and 5 years were 43.8% (10/23), 13.0% (3/23), and 4.3% (1/23), respectively. For those patients who received a curative resection the survival rates were 88.9% (8/9), 33.3% (3/9), and 11.1% (1/9), at the same intervals respectively, which was significantly longer than the patients who underwent palliative resection (20.0%, 2/10; 0.0%, 0/10; and 0.0%, 0/10), respectively ($p < 0.05$) (Figure). Moreover, the disease-free survival rates at 1, 3, and 5 years were 30.4% (7/23), 8.7% (2/23), and 4.3% (1/23) respectively.

**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. IHCC is an aggressive tumour that shows a dismal outcome even after resection. Cancer results from multistep carcinogenesis; however, the precise molecular mechanism involved in the genetic alteration in cancer remains unknown. The accumulation of alterations in cancer-related genes leads to disruptions in cell-cycle regulation and also to continuous cell proliferation.

Chen et al 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 not well established. Most authors have suggested that repeated chronic infection and the bile stasis of hepatolithiasis can lead to the development of mucosal adenomatous epithelial hyperplasia and bile duct carcinoma. They have also found that hepatolithiasis does not provide the sole carcinogenic stimulus leading to malignancy. Bile duct carcinoma arising in association with hepatolithiasis is probably the cumulative result of several etiologic agents, which may include nutritional, genetic, environmental, and immunologic factors.

Kim et al reported the expression of epidermal growth factor receptor (EGFR) was increased in hepatolithiasis group (79%, 11/14) compared with the cholangiocarcinoma group (25%, 5/20) ($p < 0.05$), and the expression of erbB2 (erythroblastic leukaemia viral oncogene homolog 2) was detected only in cholangiocarcinoma (25%, 5/20).

**Clinical presentation and diagnosis of IHHCC**

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 a physical examination or imaging study. The clinical manifestations of patients with IHHCC in this study, were right upper abdominal pain, fever and chill, loss of appetite, liver enlargement, jaundice and ascites.

Laboratory tests usually show increased tumour markers, such as CA 19-9, may be increased sometimes. Several investigators have reported that CA 19-9 and CEA determinations are useful for diagnosing peripheral cholangiocarcinoma in primary sclerosing cholangitis. These investigators also demonstrated that serum CA 19-9 values are related to tumour burden, and suggested that values were elevated in patients with PCC related to the unresectable disease. A previous Japanese study has also demonstrated that serum CA 19-9 values were predictors of dismal prognosis. Although the reason for this is unclear, our study also demonstrated that elevated CEA and CA 19-9 were predictors of a dismal prognosis. Our results demonstrated that serum CA 19-9 was elevated in 78.3% patients, and CEA was slightly elevated only in two patients (8.7%), differing from the reports in the literature.

Kawarada Y et al reported that serum CA 19-9 was elevated in 42.7% of patients and CEA in 60.0% patients, both of whom suffered from pancreatico-biliary system carcinoma. In addition, Ohtsuka et al reported that serum
CA 19-9 concentration was not only helpful in differentiation diagnosis, but also a determining factor influencing survival. In our study, 25.5% patients had elevated serum AFP, 6.4% patients had elevated serum CEA, and 75.0% patients (35/47) with IHHCC had elevated serum CA 19-9. These results indicated that a combination measurement of AFP, a representative tumour marker for HCC, and CA 19-9, a specific tumour marker for pancreaticobiliary system carcinoma, was helpful in the differentiation diagnosis of peripheral intrahepatic carcinoma.

The diagnosis rates of IHHCC by ultrasonography, CT scan and selective angiography were 94%, 94%, and 83% in available literature. However, it is difficult to differentiate it from HCC, metastatic tumour and liver abscess. Our data indicated that the diagnosis rate of ultrasonography was 82.6% (19/23) the rate obtained by CT scan was 95.7% (22/23) and by MRCP was 91.7% (11/12). IHHCC had no characteristic sonographic features, and it demonstrated on ultrasonography as having low or isodensity, irregular margins and it lacked vessel images and its features varied greatly. Colour Doppler flow imaging usually revealed a shortage of arterial blood flow. The typical features of CT were as follows: (1) a localised hypecho lesion at the marginal liver; (2) the margin between the tumour and the non-tumour are unclear; (3) the bile duct ectasies distal to tumour. On MRI scanning, T₁-weighted magnetic resonance imaging revealed a hypointense mass, and T₂-weighted imaging revealed that a central hypointensity with irregular hyperintense. An important secondary sign of PHCC was the dilation of the small bile duct distal to the tumour.

Treatment and survival
Surgery is the best option for effective and potentially curative therapy for IHHCC. When diagnosed IHHCC are large tumours that necessitate major liver resection. The prognosis of cholangiocarcinoma is generally poor with the presence of lymph node metastases and perineural infiltration preventing curative surgical resection in most patients. Several studies demonstrated that lymph node metastasis of IHHCC was high as 25%, and the lymphatic drainage was from the hepatoduodenal ligament, hepatic artery and the back of the head of the pancreas, towards to the para-aortic lymph nodes. Also in some cases, and the lymph node metastasis to the greater curvature via lesser omentum and lymph node along the gastric curvature and para-aortic region.

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. According to a report by Harrison et al the mean survival period for PHCC was 59 months, the 5-year survival was 42%, and the prognosis for the patients with vessel invasion and intrahepatic metastatic nodules was poor. Also the 1, 3, and 5-year survival rates were only 41%, 14%, and 14%, respectively, according to Yalcin’s report. Our result indicated that the overall cumulative survival rates at 1, 3, and 5 years were 43.8% (10/23), 13.0% (3/23), and 4.3% (1/23) respectively, and for patients that underwent curative resection were 88.9% (8/9), 33.3% (3/9), and 11.1% (1/9), respectively, which is significantly longer than those (20.0%, 2/10; 0.0%, 0/10; and 0.0%, 0/10) patients who underwent palliative resection, respectively (p < 0.05). This agrees with the results reported by Ohtsuka et al, where the 1, 3, and 5-year survival rates were 62%, 38%, and 23% respectively.

Literature reports and our experience suggest that cholangiocarcinoma should be suspected in patients with any of the following; hepatolithiasis combined with weight loss, higher levels of serum alkaline phosphatase, a low level of serum albumin, a serum carcinoembryonic antigen level exceeding 5.0 ng/mL, detection of a hyperechoic mass in the liver parenchyma during abdominal ultrasonography, a nodular tumour mass or an atrophic and fibrotic liver found during surgery, or hepatolithiasis that is located either in the right or both lobes of the liver.

Conclusions
In conclusion, a suspicion of malignancy is necessary in managing patients with hepatolithiasis. Hepatic resection with postoperative chemotherapy is the treatment of choice for cholangiocarcinoma when it is resectable.

References


