



Hepatolithiasis and intrahepatic cholangiocarcinoma: A review

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Abstract

Although the incidence of hepatolithiasis is decreasing as the pattern of gallstone disease changes in Asia, the prevalence of hepatolithiasis is persistently high, especially in Far Eastern countries. Hepatolithiasis is an established risk factor for cholangiocarcinoma (CCA), and chronic proliferative inflammation may be involved in biliary carcinogenesis and in inducing the upregulation of cell-proliferating factors. With the use of advanced imaging modalities, there has been much improvement in the management of hepatolithiasis and the diagnosis of hepatolithiasis-associated CCA (HL-CCA). However, there are many problems in managing the strictures in hepatolithiasis and differentiating them from infiltrating types of CCA. Surgical resection is recommended in cases of single lobe hepatolithiasis with atrophy, uncontrolled stricture, symptom duration of more than 10 years, and long history of biliary-enteric anastomosis. Even after resection, patients should be followed with caution for development of HL-CCA, because HL-CCA is an independent prognostic factor for survival. It is not yet clear whether hepatic resection can reduce the occurrence of subsequent HL-CCA. Furthermore, there are no consistent findings regarding prediction of subsequent HL-CCA in patients with hepatolithiasis. In the management of hepatolithiasis, important factors are the reduction of recurrence of cholangitis and suspicion of unrecognized HL-CCA.

Key words: Cholangiocarcinoma; Hepatolithiasis; Intra-hepatic; Management

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Core tip: In this study, we review recent studies on hepatolithiasis and discuss hepatolithiasis-associated cholangiocarcinoma (HL-CCA). Management of hepatolithiasis requires proper treatment to reduce recurrence and achieve early detection of HL-CCA. It is not clear whether hepatic resection can reduce the occurrence of HL-CCA, and there is no surveillance tool to predict subsequent occurrence. Patients should be followed after treatment because there are no effective measures to prevent HL-CCA and premalignant lesions.

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INTRODUCTION

Gallstone disease is common in Western and Asian countries. One type of gallstone disease, hepatolithiasis, is characterized by the presence of stones within the intrahepatic bile ducts proximal to the right and left hepatic ducts. Hepatolithiasis is rare in Western countries, and the incidence in East Asian, such as Taiwan, China, Hong Kong, South Korea, and Japan, is higher^[1-4].

Hepatolithiasis is benign in nature, but the prognosis is poor due to an association with recurrent cholangitis, biliary strictures, liver abscesses, and atrophy or cirrhosis of the affected liver; however, there have been advances in the management of the stones associated with hepatolithiasis^[5-7]. Hepatolithiasis is also a known risk factor for intrahepatic cholangiocarcinoma (CCA)^[8,9]. Although mortality due to cholangitis from hepatolithiasis is very low, the occurrence of hepatolithiasis-associated CCA (HL-CCA) is a prognostic factor for poor outcome^[10-12]. Early diagnosis of HL-CCA is still challenging even though there have been advances in diagnostic modalities and various efforts to identify it in early stages^[13].

Here, we review the epidemiology, pathogenesis, diagnosis, and management of hepatolithiasis and HL-CCA. This review also summarizes the predictive factors for HL-CCA.

EPIDEMIOLOGY

Hepatolithiasis

The incidence of hepatolithiasis varies, but it is fairly common in Asian, such as China, Taiwan, Hong Kong, Korea, and Japan, with incidence rates ranging from 2% to 25%^[1-4]. In Western countries hepatolithiasis is rare, with incidences reported between 0.6% and 1.3%^[4,14].

The mechanism of intrahepatic stone formation is

not well understood, but malnutrition and low socio-economic status have been suggested to be causatively related to hepatolithiasis. According to epidemiologic surveys, the pattern of gallstone disease is changing, and the incidence of hepatolithiasis is decreasing as people in Eastern countries adopt a Westernized diet. A national survey conducted in Japan reported that the relative proportion of hepatolithiasis was 4.1% in the years from 1970-1977, 3.0% in the years from 1975-1984, 2.3% in the years from 1985-1988, 2.2% in the years from 1989-1992, and 1.7% in the years from 1993-1995^[15]. The apparent decrease in the incidence of hepatolithiasis has contributed to this chronological shift, but it may be partly caused by the increase in gallbladder stones due to westernized diet^[16]. In Taiwan, the relative proportion of hepatolithiasis slightly decreased from 21.3% in 1981 to 18.7% in 1989^[1]. In South Korea, the pattern of gallstone disease has become similar to that seen in Western countries, except for a high prevalence of hepatolithiasis. The proportion of gallbladder stones has gradually increased from 80% to 85% and that of common bile duct stones has decreased from 34% to 19%; however, that of hepatolithiasis remains unchanged, at 11%-15% over a 20 year period from 1980 to 2000^[2,3].

Parasitic infestation has often been thought to be a major cause of hepatolithiasis and infestation, as parasites have been detected in up to 30% of patients with hepatolithiasis^[17]. In Eastern countries, the persistent prevalence of hepatolithiasis in Korea and the relatively high prevalence in Taiwan may be due to cultural trends of ingesting raw freshwater fish infected with *Clonorchis sinensis* (*C. sinensis*). Clonorchiasis is endemic in the Far East, but heavily endemic areas within individual countries are geographically distributed in parallel with the population of the snail that is an intermediate host for this parasite^[18]. Nationwide surveys in Korea of intestinal parasitic infections revealed no drop in the average prevalence of *C. sinensis* infection over time (*i.e.*, 2.6% in 1981 and 2.4% in 2004)^[19], and *C. sinensis* infection remains common in Korea. In 1984, the prevalence was reported to be 1.5% in Taiwan^[20]. In Japan, the clonorchiasis rate has markedly decreased in parallel with the decreased number of host snails, which is due to various causes, including water pollution^[18].

Hepatolithiasis-associated cholangiocarcinoma

Hepatolithiasis is an established risk factor for CCA, similar to clonorchiasis, especially in Asian countries^[8,9,21-24]. The association between hepatolithiasis and CCA has been well-documented, and many studies on HL-CCA have been published^[25-31]. Cases of HL-CCA are not rare, especially in areas with a high prevalence of hepatolithiasis. The overall incidence of HL-CCA was reported to be 5%-13%^[12,32,33]. HL-CCA can be

Table 1 Concomitant cholangiocarcinoma in hepatic resection for hepatolithiasis *n* (%)

Ref.	Year	Nation/region	Case (<i>n</i>)	Incidence
Zhu <i>et al</i> ^[34]	2014	China	2056	107 (5.2)
Lin <i>et al</i> ^[32]	2013	Taiwan	211	10 (4.7)
Tabrizian <i>et al</i> ^[35]	2012	Italy	30	7 (23.3)
Cheon <i>et al</i> ^[30]	2009	South Korea	90	8 (9.0)
Uenishi <i>et al</i> ^[12]	2009	Japan	86	10 (11.6)
Lee <i>et al</i> ^[36]	2007	Taiwan	123	4 (3.3)
Catena <i>et al</i> ^[37]	2006	Italy	17	2 (11.7)
Chen <i>et al</i> ^[38]	2004	Hong Kong	103	10 (9.7)

detected at any stage, during evaluation, treatment, or follow up of hepatolithiasis. Detection of concomitant HL-CCA during treatment of hepatolithiasis was reported in 12% of patients in Japan, 5% in Taiwan, 9% in South Korea, and 10% in Hong Kong^[12,30,32,34-38] (Table 1). HL-CCA can also develop during follow up for hepatolithiasis. Subsequent HL-CCA following hepatolithiasis has been reported to be 1.6%-9.9% in several studies^[6,12,30,32,33,36,38-40]. These studies are summarized in Table 2.

PATHOGENESIS

Hepatolithiasis

The mechanism of intrahepatic stone formation has not yet been fully described; but the presence of brown pigment stones as well as cholesterol stones suggests a complex pathogenesis^[41-44]. Factors that may contribute to development of these stones include the precipitation of calcium bilirubinate, the solubility of cholesterol in hepatic bile, gene mutations, and ethnic differences^[45-51].

A low fat and low protein diet may increase bile stasis and bacterial infection through relaxation of the sphincter of Oddi and decreased release of cholecystokinin^[52,53]. Association with bacterial infection has been implicated in stone formation. Bacteria, such as *Escherichia coli*, and those belonging to the *Clostridium* and *Bacteroides* genera are frequently isolated from the bile of patients with hepatolithiasis. The possible route is ascending infection through the sphincter of Oddi, bacteriobilia through the portal venous system, or transient infection with bile stasis^[54,55].

Recent experiments suggest that enhanced inflammatory cytokine-induced phospholipase A₂, cyclooxygenase-2 (COX-2) and COX-2-derived prostaglandin E₂ (PGE₂) synthesis in the bile ducts are related to the initiation and propagation of inflammatory changes in hepatolithiasis^[56,57].

In terms of the biliary mucin molecules, an increase in acidic mucins, such as sulfomucins and sialomucins, in hepatolithiasis reduces pH in the bile and leads to precipitation of calcium bilirubinate in the bile ducts^[56]. The abundance of secretory-type mucins (MUC2, MUC3, MUC5AC, MUC5B, and MUC6) was

shown to be significantly higher in the bile ducts of hepatolithiasis patients compared to controls, and gel-forming mucins of MUC2 and 5AC were thought to be more important for the pathogenesis^[58,59]. Excessive amounts of mucin secreted into the ducts may provide a microenvironment that initiates a nidus for stones by trapping calcium salts and lipids, which may also cause stones to expand by altering biliary flow in the bile ducts^[60,61].

HL-CCA

Known risk factors for CCA are primary sclerosing cholangitis, Caroli's disease, congenital choledochal cysts, parasite infections (*C. sinensis*, *Opisthorchis viverrini*), hepatolithiasis, and toxins^[8,9,19]. Considerable progress has been made in understanding the pathogenesis of CCA^[23,62]. It has been proposed to be a multi-step process, involving hyperplasia, dysplasia, and adenocarcinoma *in situ* to invasive adenocarcinoma^[63]. Although the process of carcinogenesis from hepatolithiasis is not fully understood, chronic proliferative cholangitis plays a role in biliary carcinogenesis^[27]. Recurrent cholangitis, biliary stricture, bile stasis, and chronic bacterial infection are common problems in hepatolithiasis patients, even after multimodal treatment. These recurrent or chronic inflammatory events cause prolonged inflammation of the bile duct epithelium and can lead to the development of CCA^[27,62].

The main morphologic feature of stone-containing bile ducts in hepatolithiasis is chronic proliferative cholangitis and peribiliary glands proliferation, in which the epithelial lining becomes hyperplastic^[43]. Chronic inflammation can cause epithelial cell proliferation, and this may increase the rate of cellular DNA synthesis and the subsequent production of mutagens coupled with a compromised cellular repair function^[64-66]. If these processes are sustained for a long period of time, they may cause the multiple molecular changes necessary to trigger the development of CCA. During histologic exam by choledochoscopy using percutaneous transhepatic cholangioscopic lithotripsy (PTCSL), atypical epithelial hyperplasia and dysplasia are frequently recognized^[27]. Chen *et al*^[67] reported that intraductal papillary neoplasia was found in 30% of patients with hepatolithiasis and displayed a histologic spectrum from papillary growth with dysplasia to carcinoma. Biliary carcinogenesis associated with hepatolithiasis is thought to be present as precancerous lesions. Intraductal papillary neoplasm of the bile duct (IPNB) and biliary intraepithelial neoplasia (BilIN) are known as precancerous lesions of biliary tract carcinomas^[68].

Similar to hepatolithiasis and clonorchiasis, IPNB has mainly been reported in Far Eastern countries. IPNB, including carcinoma and precursor lesions, is known to transform from low-grade dysplasia to invasive carcinoma^[69]. BilIN is a flat or micropapillary

Table 2 Subsequent cholangiocarcinoma after initial management for hepatolithiasis

Ref.	Year	Nation/region	Cases (n)	Incidence of cholangiocarcinoma		
				Total	Stone removal	
					Complete	Residual
Kim <i>et al</i> ^[33]	2015	South Korea	236	6.8%	3.3%	10.4%
Tsuyuguchi <i>et al</i> ^[39]	2014	Japan	121	9.9%	9.1%	10.4%
Lin <i>et al</i> ^[32]	2013	Taiwan	197	6.1%	4.9%	11.8%
Park <i>et al</i> ^[6]	2013	South Korea	85	2.4%		
Cheon <i>et al</i> ^[30]	2009	South Korea	225	4.9%	4.0%	8.0%
Uenishi <i>et al</i> ^[12]	2009	Japan	76	2.6%		
Lee <i>et al</i> ^[36]	2007	Taiwan	123	1.6%		
Chen <i>et al</i> ^[38]	2004	Hong Kong	91	3.3%		
Huang <i>et al</i> ^[42]	2003	Taiwan	209	2.4%	0.7%	6.6%

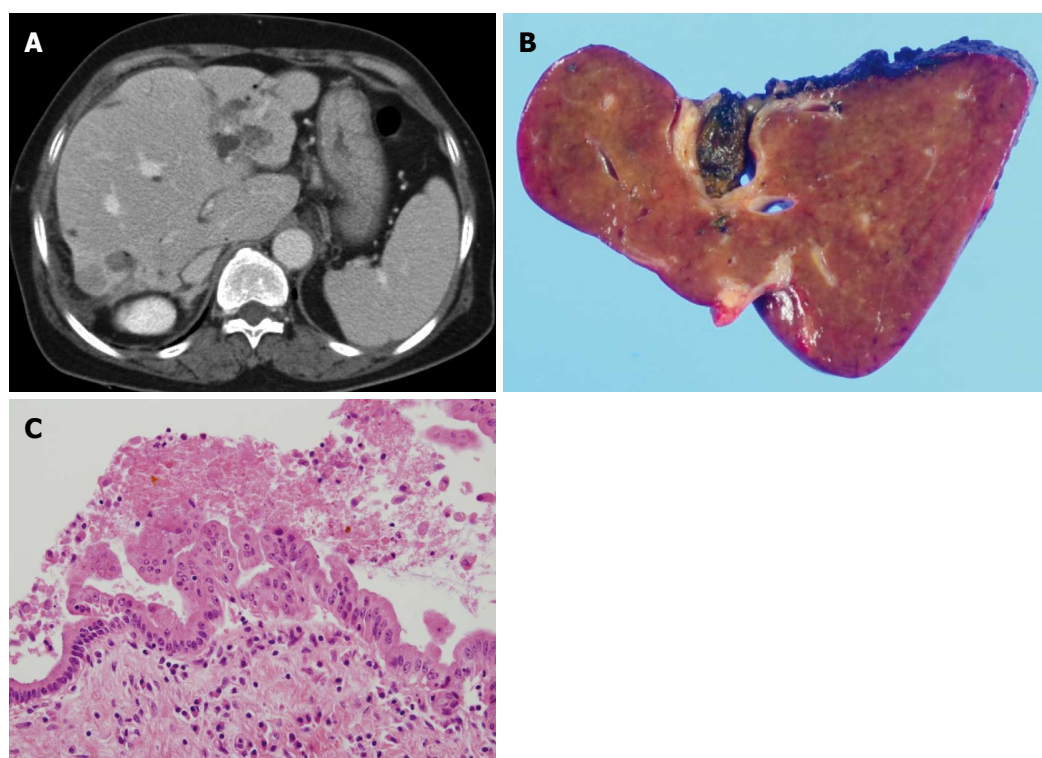


Figure 1 Sixty-seven years old, female was admitted for cholangitis and treated with hepatic resection. She was followed and underwent second resection 1 year later. A: Abdominal computed tomography demonstrated that B2 IHD dilatation with stones and 2 cm sized low density lesion in liver S7; B: Liver, left, lateral, segmentectomy was done; C: BilIN1 and two were shown on dilated duct with glandular proliferation.

dysplastic epithelium in the bile duct and classified as BilIN-1, BilIN-2, and BilIN-3^[70]. It is frequently found in the surgical margin of resection specimens of CCA and is also reported in patients with hepatolithiasis^[71,72]. Both BilIN and IPNB can be seen at the same time in patients with hepatolithiasis, unlike primary sclerosing cholangitis and parasitic infections, which are only associated with BilIN^[70,72] (Figures 1 and 2). A study of BilIN reported that metaplastic changes were more frequently observed in BilIN-2/3 than BilIN-1, and gastric type foveolar metaplasia was the most frequently observed change^[70]. In immunohistochemical studies of IPNB, aberrant expression of cytokeratin 20, MUC2, and MUC5AC was frequently shown^[73,74]. Another immunohistochemical

study showed that decreased expression of β -catenin and E-cadherin occurred early in the carcinogenesis of both BilIN and IPNB^[75].

Recent studies have elucidated the molecular mechanism of HL-CCA, which involves epidermal growth factor receptor (EGFR), nuclear factor kappa-B (NF- κ B), COX-2, PGE₂, p16, c-met, and deleted in pancreatic cancer 4 (DPC4)/signaling effectors mothers against decapentaplegic protein 4 (Smad4)^[76,77]. Increased expression of c-erbB2 and EGFR in both hepatolithiasis and intrahepatic CCA has been reported^[78,79]. Zhou *et al*^[80] reported that NF- κ B and EGFR were more highly expressed in HL-CCA than in patients with hepatolithiasis. These findings demonstrate that prolonged inflammation due to the

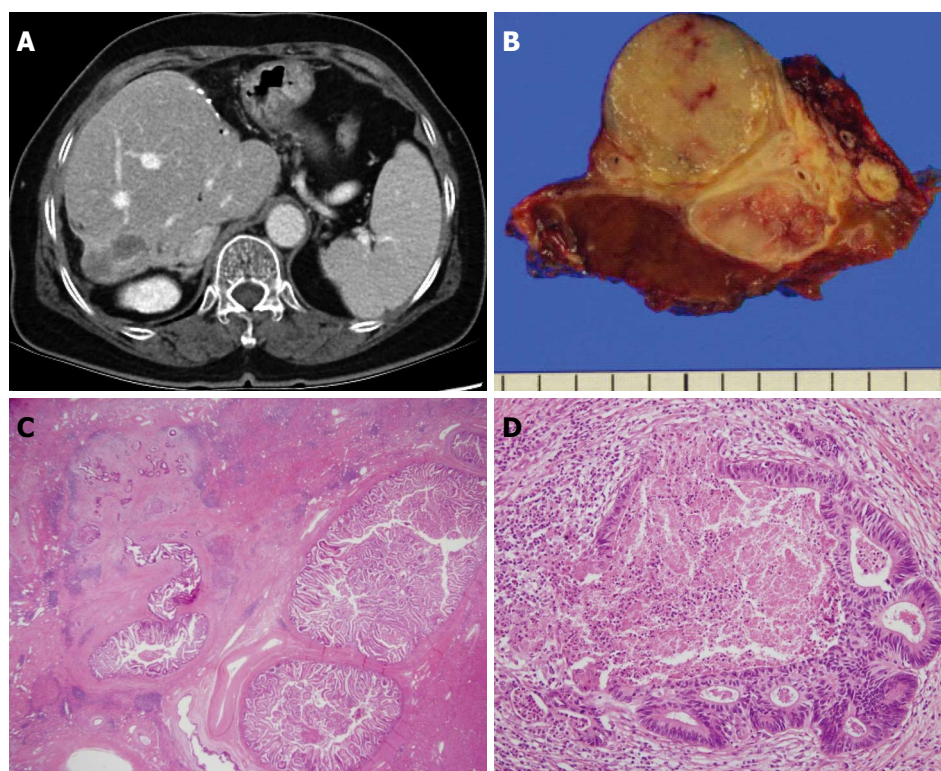


Figure 2 Sixty-seven years old, female was admitted for cholangitis and treated with hepatic resection. She was followed and underwent second resection 1 year later. A: Follow-up abdominal computed tomography. Exophytic hypodense mass in S7 of the liver was more enlarged with peripheral enhancement; B: Liver, S7, segmentectomy was done; C and D: Hematoxylin and eosin (HE) stain (C: $\times 12.5$; D: $\times 200$). Intraductal papillary neoplasm with an associated invasive carcinoma. 6 cm \times 3 cm \times 3 cm sized intraductal papillary neoplasm including 0.6 cm \times 0.5 cm sized invasive tumor.

presence of stones could induce upregulation of these cell-proliferating factors.

COX-2 overexpression correlated with the carcinogenesis of intrahepatic CCA, and it occurred during the early stages of cholangiocarcinogenesis^[81,82]. Endo *et al*^[83] reported that ErbB2 and COX-2 were overexpressed in the hyperplastic bile ducts of patients with hepatolithiasis.

PGE₂ is known to be increased by upregulated COX activity in inflammatory sites. Shoda *et al*^[57] reported that the synthesis of PGE₂ is significantly higher in affected bile ducts with hepatolithiasis, and it can mediate morphologic changes of the intrahepatic bile duct, such as dilatation, stricture, and periductal fibrosis.

It is well known that c-met plays a role in the carcinogenesis of CCA. The *c-met* gene, a proto-oncogene, encodes the membranous tyrosine kinase receptor for hepatocyte growth factor^[84]. Terada *et al*^[85] reported that c-met protein was overexpressed in proliferated biliary cells of hepatolithiasis and in neoplastic biliary epithelium of intrahepatic CCA.

The cyclin-dependent kinase inhibitor p16 is known as a tumor suppressor gene, and p16 promoter hypermethylation is known to occur in various cancers, including CCA^[86]. Ishikawa *et al*^[87] reported that inactivation of p16 occurred frequently and at an early stage of IPNB with hepatolithiasis. Sasaki *et al*^[88] reported that p16 expression was decreased from

BilIN-2,3 to cholangiocarcinogenesis in patients with hepatolithiasis.

In a study of the *DPC4/Smad4* gene, another tumor suppressor gene, Lee *et al*^[89] reported that inactivation of *DPC4/Smad4* occurred in both CCA and stone-containing bile ducts, and it was especially pronounced in the dysplastic epithelium of stone-containing bile ducts.

DIAGNOSIS

Hepatolithiasis

Diagnosis of hepatolithiasis is performed mainly through radiologic examinations, and often incidentally without symptoms or laboratory abnormalities. If symptoms occur, they may include fever, fatigue, abdominal pain, and jaundice. Laboratory tests can show leukocytosis, neutrophilia, and abnormal liver biochemistry of an obstructive pattern with raised serum alkaline phosphate and bilirubin.

A hepatolithiasis research group in Japan classified the severity of hepatolithiasis: grade 1 as no symptoms, grade 2 as having abdominal pain, grade 3 as transient jaundice or cholangitis, and grade 4 as continuous jaundice, sepsis, or concurrent CCA. They reported that more than half of 473 new hepatolithiasis cases were classified as grade 3 or 4^[90]. Another recent study of 68 hepatolithiasis patients used a new clinical classification system: type 1 primary type (no

previous biliary tract surgery), type 2 inflammatory type (previous biliary tract surgery and cholangitis), type 3 mass-forming type (complicated by hepatic mass-forming lesion), and type 4 terminal type (with secondary biliary cirrhosis and resultant portal hypertension). The authors reported that the incidence of new cases of types 1-4 was 50.1%, 36.8%, 10.3%, and 2.8%, respectively^[91].

Abdominal ultrasound (US) and computed tomography (CT) are the primary imaging modalities for hepatolithiasis. The advantages of US are that it is non-invasive, safe, and easily available (even bedside), and can detect dilatations of the biliary tract and stones, as shown by echogenic spots with an acoustic shadow. However, the detectability of stones is dependent on the stone size, shadowing characteristics, echogenicity, and the location in the hepatic lobe^[7,90]. Multidetector CT (MDCT) has advanced the diagnosis of hepatolithiasis. MD-CT is very useful for detecting dilated bile ducts, stricture of the bile duct, and calcification stones in the bile duct^[7,92]. Therefore, recently, US and CT have become the first choice for examining patients suspected of having hepatolithiasis.

Magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) can provide realistic bile duct images and can detect stones without exposing patients to radiation^[93,94]. The T1-weighted (T1-W) sequence is helpful for depicting stones and demonstrating parenchymal complications, such as an abscess^[95]. However, the cost is high, and its spatial resolution is not perfect. MRI and MRCP are usually performed as ancillary investigations to US and CT.

CCA and HL-CCA

The clinical manifestations of intrahepatic CCA are nonspecific, although there may be abdominal pain, cachexia, fatigue, and night sweats^[96]. Serum CA 19-9 is known as a tumor biomarker for CCA, but it may be normal or increased in benign diseases, such as bacterial cholangitis or choledocholithiasis^[96,97].

Macroscopically, intrahepatic CCA is classified as a mass-forming, periductal-infiltrating, or intraductal-growing carcinoma, where the mass-forming type is most common^[98]. MDCT is used to evaluate the location of the tumor and its relationship with adjacent vascularity^[99]. Pre-contrast and multiphase CT is useful for the detection and differentiation of an intraductal stone from an intraductal tumor because hypovascular tumors with abundant fibrous stroma show progressive uptake of contrast during the venous phase^[100]. Park *et al.*^[101] suggested the following as specific CT findings for HL-CCA: the presence of periductal soft-tissue density, higher enhancement of the duct than the adjacent bile duct on portal venous phase images, ductal wall thickening or enhancement, portal vein obliteration, and lymph node enlargement.

On MRI, CCA is visible as a hypointense mass on T1-W images and a central hypointensity with irregular hyperintense areas on T2-weighted (T2-W) images^[102]. MR imaging with MR cholangiography is superior to CT for the assessment of intraductal lesions, intrahepatic metastasis, and presence of satellite lesions^[103]. However, CT may be better for the assessment of vascular encasement, identification of extrahepatic metastasis, and determination of resectability^[104].

Positron emission tomography (PET) scan is another useful imaging modality, but the accuracy varies depending on morphologic type^[105]. The sensitivity of PET for detection is reported to be 85% for the mass-forming type but 18% for the infiltrating type^[105]. Mass forming type intrahepatic CCA shows ring-shaped fluorodeoxyglucose uptake (due to desmoplastic lesions within the tumor) and neovascularity at the periphery, but this finding can be shown in any lesion with central necrosis^[103]. Thus, PET scanning is more helpful for detection of distant metastases^[106,107].

Difficulty in diagnosis of concomitant CCA in hepatolithiasis

In cases of HL-CCA, there are no specific symptoms other than the clinical manifestation of hepatolithiasis. Laboratory tests can show increased alkaline phosphatase, bilirubin, and CA 19-9^[108].

Therefore, detection of CCA in hepatolithiasis is dependent on imaging modalities, such as US, CT, and MRI. However, there are many limitations in differentiating CCA from fibrosis in hepatolithiasis. It is difficult to differentiate strictures, infiltrating types of CCA, mass-forming CCA, and inflammatory pseudotumor because prolonged affected liver segments often become fibrotic and scarred^[90,109].

MANAGEMENT STRATEGY FOR HEPATOLITHIASIS

The primary goals of treatment for hepatolithiasis are complete stone removal and the prevention of recurrent cholangitis. Current treatment methods are non-surgical treatments, such as percutaneous transhepatic cholangioscopic lithotripsy (PTCSL), and surgical treatment, such as hepatic resection. PTCSL has been frequently used with a fair success rate^[110-113]. The rate of complete stone removal was reported to be similarly high in both treatments, but recurrent cholangitis is quite common in PTCSL^[6,11,111]. Generally, hepatic resection has been considered the definite treatment for hepatolithiasis, because it could effectively reduce recurrent cholangitis or stone formation^[114-116]. The reported overall success rate of hepatic resection is 95%-98%, and the rates of residual stone and stone recurrence are 15.6% and 7.8%-13.9%, respectively, upon long-term follow-up^[5,12,115,116].

However, the incidence of post-hepatectomy

infection was 23.8% higher in hepatolithiasis than in other hepatic malignancies^[117]. Additionally, operative intervention is sometimes not acceptable for patients with risky co-morbidities or stones distributed in multiple segments of both hepatic lobes^[118,119]. Thus, a tailored multidisciplinary approach combining both approaches is more reasonable.

Meanwhile there are many hepatolithiasis cases with strictures that make it difficult to manage and differentiate CCA. Thus, patients should be screened for concomitant HL-CCA, even though the incidence is low. Choledochoscopy may be indicated in these cases.

Detection and predictive factors of concomitant HL-CCA

Known risk factors for concomitant HL-CCA are older age, bile duct stenosis (stricture), liver atrophy, elevated CA 19-9, left side stone location, residual stone, recurrence of stone, and choledochenterostomy^[120-124]. Neither symptoms (abdominal pain, fever, jaundice, and nausea) nor the location of stones (intrahepatic duct only, both intra- and extra-hepatic ducts, right lobe, left lobe, or both lobes) is a significant risk factor^[122,125].

In a comparative study of concomitant HL-CCA and hepatolithiasis only, Kim *et al.*^[120] reported that concomitant HL-CCA should be suspected in patients with a longstanding duration of hepatolithiasis accompanied by weight loss, high levels of serum alkaline phosphatase, low levels of serum albumin, high levels of serum CEA, hepatolithiasis located in either the right or both lobes of the liver, and age > 40 years. Liu *et al.*^[121] reported that symptom duration of more than 10 years is the most powerful risk factor for ICC in patients with hepatolithiasis, and Lee *et al.*^[126] reported an association between localized stricture and long-term history (over 10 years) of hepatolithiasis. Additionally, it is suggested that HL-CCA may occur in cases of atypical clinical manifestation of liver abscess, biliary tract infection that is difficult to control, relapsing infection, and abscesses in a more consolidated area^[34].

In a Japanese multicenter study, Suzuki *et al.*^[122] reported that the predictive risk factors were a history of choledochenterostomy (OR = 3.718) and liver atrophy (OR = 4.424). Association of CCA occurrence with previous surgical biliary-enteric anastomosis may be due to chronic inflammation caused by reflux of bowel contents late after choledochenterostomy^[123,124].

When is hepatic resection advisable for improving prognosis?

Hepatic resection can eliminate both stones and surrounding ductal changes, such as strictures, fibrosis, and micro abscesses. In a long-term follow-up study, operative treatment was reported to reduce recurrence^[30,36].

In patients with hepatolithiasis, treatment-related difficulties include the high rates of residual stones and a high recurrence rate even after complete

stone removal, especially in patients with biliary strictures^[111,112]. Biliary strictures often lead to bile stasis, cholangitis, and stone formation, thus causing stone recurrence. A multivariate logistic regression analysis study reported that risk factors for incomplete stone removal are intrahepatic strictures, nonoperative treatment, and bilateral stones^[113]. Thus, hepatectomy is recommended in cases of single lobe hepatolithiasis, atrophy of the affected liver, and stricture^[37,118,119].

Furthermore, resection is considered when differential diagnosis is difficult, because detection of HL-CCA is very difficult even during surgical operations, and accurate diagnosis can be proven only through resection. Catena *et al.*^[37] reported that the rate of unrecognized CCA was quite high at 11.7% and that it might be underestimated.

Can hepatic resection prevent subsequent HL-CCA?

Although mortality due to cholangitis is low, the development of HL-CCA is known to be an independent prognostic factor for survival^[34,127]. Hepatolithiasis is a significant risk factor for CCA, and the OR was 40 in a Korean report^[128].

Theoretically, hepatectomy for treatment of hepatolithiasis has another advantage for eliminating the risk of developing HL-CCA besides complete removal of stones. In general, hepatectomy seems to reduce the risk of developing of CCA. A cohort study in Japan reported that hepatectomy significantly reduced the risk of developing CCA^[15]. A Western study by Tabrizian *et al.*^[35] reported a high rate (23.3%) of concomitant HL-CCA and excellent long-term results with hepatectomy.

It is not clear whether hepatic resection can reduce the occurrence of HL-CCA. During the follow-up period, the incidence of HL-CCA showed no significant difference between patients with hepatolithiasis with or without previous hepatic resection^[30,33]. It is difficult to conclude that hepatic resection definitely prevents the development of HL-CCA in patients with hepatolithiasis.

Meanwhile, incomplete resection is also a problem. Survival outcomes are good only in cases with safe surgical margins, even in incidental HL-CCA found in post-operative pathology^[32]. In addition, HL-CCA could develop in the hepatic lobe adjacent to the resection margin (Figures 3 and 4). It is possible that the undetected CCA was present in the remnant liver^[32,33]. Therefore, aggressive resection, including neighboring segments, is crucial to achieve sufficient hepatic volume.

MANAGEMENT STRATEGY FOR HEPATOLITHIASIS-ASSOCIATED INTRAHEPATIC CCA

The secondary goal of treatment for hepatolithiasis is to prevent the progression of the disease to cirrhosis or

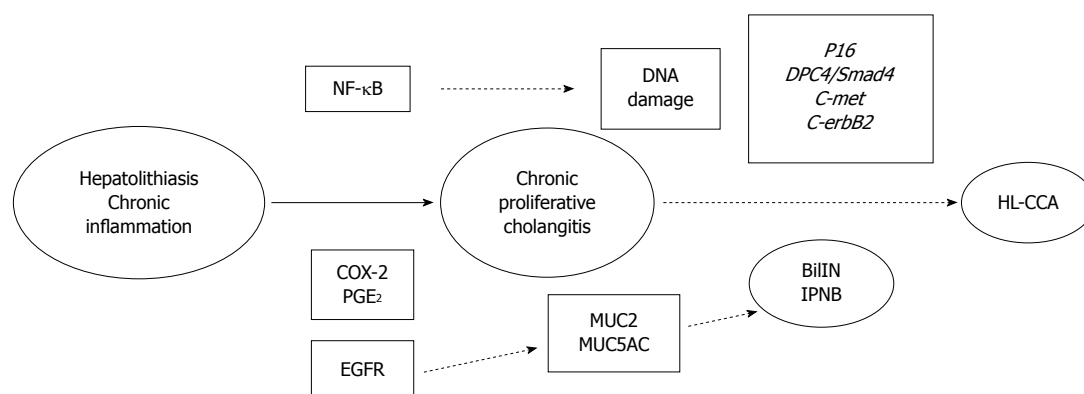


Figure 3 Molecular mechanism of hepatolithiasis-associated cholangiocarcinoma. HL-CCA: hepatolithiasis-associated cholangiocarcinoma; NF-κB: Nuclear factor kappa-B; EGFR: Epidermal growth factor receptor; PGE₂: Prostaglandin E₂; COX-2: Cyclooxygenase-2; IPNB: Intraductal papillary neoplasm of the bile duct; BiliIN: Biliary intraepithelial neoplasia.

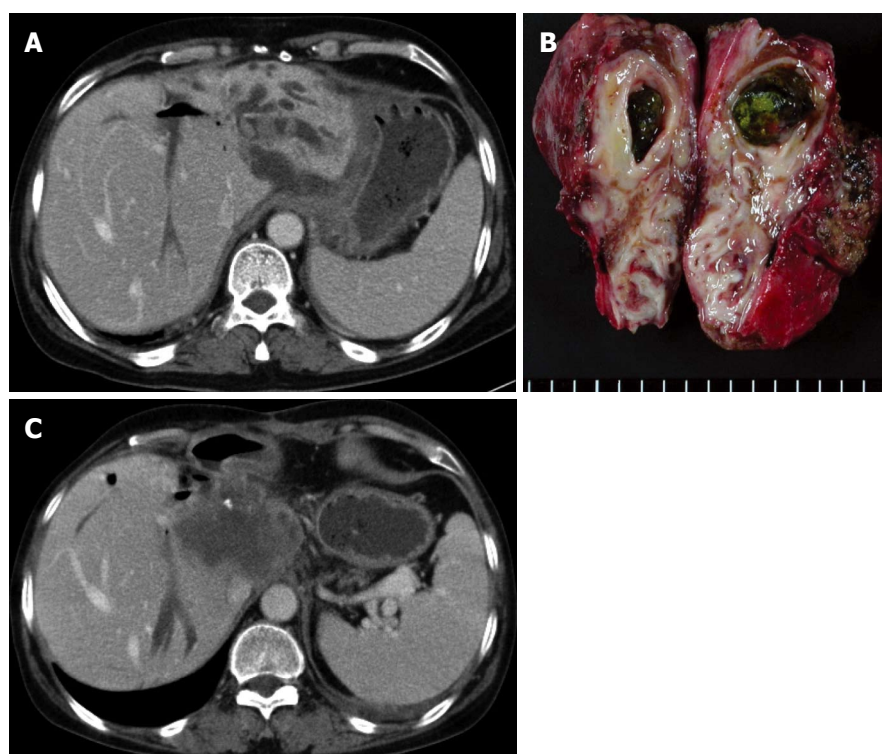


Figure 4 Forty-six years old, female was admitted for cholangitis. A: Abdominal CT demonstrated that multiple calcified stones are present in the lateral segment of the left lobe; B: Liver, left lobectomy was performed, and there was no cancerous lesion; C: Abdominal computed tomography taken 14 mo after resection demonstrated development of cholangiocarcinoma in the caudate lobe of the liver.

cancer. HL-CCA can develop even after complete stone removal through PTCSL or initial hepatectomy^[33,129]. Development of HL-CCA is an independent predictor for survival in patients who have undergone hepatic resection with hepatolithiasis^[12,38]. Early detection of HL-CCA is very important in follow-up after treatment of hepatolithiasis. However, to date, there is no effective measure to predict subsequent HL-CCA in patients with hepatolithiasis.

Follow-up for early detection of subsequent HL-CCA

Known predictive factors for subsequent HL-CCA after treatment are old age, bile duct stricture, bilioenteric

anastomosis, stone recurrence, stones in both hepatic lobes, and no hepatic resection^[33,42,122].

Kim *et al.*^[33] reported that age, gender, CA 19-9, stone location, bile duct stenosis, liver atrophy, stone recurrence, residual stone, and hepatic resection were not significant predictive factors by multivariate analysis. Cheon *et al.*^[30] reported that there was no significant risk factor for CCA during the follow-up period.

Huang *et al.*^[42] and Lin *et al.*^[32] reported that the subsequent HL-CCA incidence was significantly lower after complete stone removal than in cases of residual stones (0.7% vs 6.6% and 4.9% vs 11.8%,

Table 3 Clinical characteristics of subsequent cholangiocarcinoma patients^[33]

Case	Sex/age	Location of stone	Treatment method	Residual stone	Time of CC (mo)	Location of CC	Stage
1	M/65	Lt	ERCP	Yes	14	Lt	IVA
2	M/69	Lt	PTCSL	Yes	15	Lt	III
3	M/72	Lt	PTCSL	Yes	17	Lt	IVA
4	M/66	Lt	ERCP	Yes	21	Lt	III
5	M/51	Lt	PTCSL	Yes	13	Lt	IVA
6	M/63	Lt	PTCSL	No	53	Lt	IVA
7	F/71	Rt	ERCP	Yes	79	Both	III
8	F/54	Both	PTCSL	Yes	10	Lt	IVA
9	F/56	Rt	PTCSL	No	111	Rt	IVA
10	F/65	Both	PTCSL	Yes	72	Lt	IVA
11	M/60	Both	Lt. hemi-hepatectomy	Yes	102	Rt	III
12	F/67	Both	Lt. lobectomy	Yes	55	Rt	IVA
13	F/51	Lt	Lt. hemi- hepatectomy	No	109	Lt	II
14	M/52	Both	Lt. lobectomy	Yes	28	Rt	IVA
15 ¹	F/47	Lt	Lt. hemi-hepatectomy	No	14	Caudate	III
16	F/56	Both	Lt. lobectomy	Yes	81	Rt	IVB

¹Described in Figure 3. M: Male; F: Female; CC: Cholangiocarcinoma; Lt: Left; Rt: Right; ERCP: Endoscopic cholangiopancreatography; PTCSL: Percutaneous transhepatic choledochoscopic lithotomy.

respectively). Jo *et al*^[108] reported that incomplete removal of stones was a risk factor for subsequent HL-CCA, but complete stone removal was not significant as a good prognostic factor. Furthermore, there are reports that the incidence of subsequent HL-CCA is not significantly different between groups: Kim *et al*^[33] reported 3.3% vs 10.4% ($P = 0.263$), Tsuyuguchi *et al*^[39] reported 9.1% vs 10.4% ($P = 0.554$), and Cheon *et al*^[30] reported 4% vs 8% ($P = 0.06$).

The risk of subsequent HL-CCA was increased in bilateral hepatolithiasis^[118,119]. Lin *et al*^[32] reported that the incidence of concomitant HL-CCA and subsequent HL-CCA was similar in patients with unilateral hepatolithiasis (4.8% and 4.5%, respectively), but the incidence of subsequent HL-CCA (12.2%) was higher than concomitant HL-CCA (4.7%) in patients with bilateral hepatolithiasis.

Most subsequent HL-CCA has been reported to occur within the same hepatic lobe where treatment was performed^[130]. However, Cheon *et al*^[30] reported the tumor occurrence in the contralateral hepatic lobe in six out of 11 cases, and Kim *et al*^[33] reported it in three out of 12 cases. It is possible that chronic inflammatory conditions play a role in the development of CCA arising from the bile duct without stones^[77].

Suzuki *et al*^[122] reported that risk factors for HL-CCA were choledochoenterostomy (OR = 3.718), biliary stricture (HR = 4.615), and stone recurrence (HR = 6.264)^[122]. Bettschart *et al*^[123] reported that patients who underwent bilioenteric anastomosis due to hepatolithiasis should be followed.

Is the prognosis of HL-CCA worse than CCC alone?

Su *et al*^[11] reported that the survival of patients with HL-CCA is worse than that of patients with only CCA. In a study of 66 patients with HL-CCA, radical resection was possible in only 38 patients^[131].

In contrast, there are studies that HL-CCA is not

inferior in resectability and survival. Chen *et al*^[132] showed a higher rate of resectability for HL-CCA than for CCC without HL (31.1% vs 26.8%). Lee *et al*^[133] showed a resectability rate of 52.6% in HL-CCA and 39.2% in CCC only, and Guglielmi *et al*^[134] also reported a higher rate of resectability in HL-CCA than CCC alone (91.3% vs 68.8%). A possible explanation is that the presence of symptoms due to hepatolithiasis could lead to an earlier diagnosis of CCA^[132].

However, despite a higher rate of resectability, there were no differences in overall survival between patients with HL-CCA and patients with CCC alone^[133,134]. In 23 patients who underwent resection for HL-CCC, Han *et al*^[135] reported that the overall cumulative survival rates were 43.8%, 13.0%, and 4.3% at 1, 3, and 5 years, respectively, even though they were higher at 88.9%, 33.3%, and 11.1%, respectively, in patients with curative resection.

A recent interesting study showed that palliative surgery resulted in a gain in survival. Li *et al*^[131] reported that the overall survival rates were 58.3%, 31.7%, and 11.7% at 1, 3, and 5 years, respectively. In the radical resection group, survival rates were 71.1%, 39.4% and 15.8%, respectively, 42.9%, 28.6% and 7.1%, respectively, in the palliative resection group, and 25%, 0%, and 0%, respectively, in the group of abdominal exploration ($P < 0.001$). Zhang *et al*^[136] suggested three reasons for performing palliative resection even in patients classified as Stage IV. First, the indication for operation was not only due to the tumor, but also due to hepatolithiasis, which frequently causes biliary tract infections. Second, significant differences in the median overall survival were found between R1, R2, and non-resection-treated patients (18.2, 14.2, and 9.1 mo, respectively). Third, adjuvant therapy did not significantly prolong the survival. Considering these results, aggressive resection should be performed in practice to prolong

survival even when curative treatment cannot be accomplished for patients with advanced HL-CCA.

Subsequent HL-CCA leads to worse survival than concomitant HL-CCA

Subsequent HL-CCA diagnosed after treatment of hepatolithiasis has a worse prognosis than concomitant HL-CCA. Lin *et al.*^[32] reported that most patients who developed subsequent HL-CCA after hepatectomy were not eligible for a second hepatectomy due to its locally advanced state, peritoneal seeding, distant metastasis, or insufficient remnant liver volume. Overall, mortality and disease-related mortality of subsequent HL-CCA is significantly higher than that for concomitant HL-CCA. Recently, Tsuyuguchi *et al.*^[39] and Kim *et al.*^[33] reported similar poor results (Table 3).

CONCLUSION

Although there have been many advances in the management of hepatolithiasis, there are no consistent results regarding HL-CCA until now. Important factors to consider are the proper treatment to reduce recurrence and early detection of HL-CCA. Patients should be followed after treatment because there is no effective prevention of HL-CCA or premalignant lesions.

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