

## Incidence of Cholangiocarcinoma with or without Previous Resection of Liver for Hepatolithiasis

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**Background/Aims:** To investigate the incidence of cholangiocarcinoma in patients with hepatolithiasis with or without previous resection of liver. **Methods:** From 2002 to 2009, we retrospectively reviewed 117 patients who were diagnosed and treated for hepatolithiasis in Korea University Guro Hospital. Among the 117 patients, 55 patients who were lost during follow-up were excluded, and 62 patients were eligible for analysis. The hepatic resection group (n=25) included patients who underwent left hemihepatectomy (n=2); left lateral segmentectomy (n=10); left lobectomy (n=9); right lobectomy (n=3); or wedge resection (n=1). The nonhepatic resection group (n=37) included transhepatic cholangiographic lithotomy and endoscopic retrograde cholangiopancreatography-treated patients. The mean follow-up period was 47 months. **Results:** The incidence of cholangiocarcinoma while patients were followed for hepatolithiasis was 12.9% (8/62) (hepatic resection group, three cases [12%] vs nonhepatic resection group, five cases [13.5%];  $p=1.000$ ). The mean follow-up period was 53 months ( $47 \pm 11$  months) until the diagnosis of cholangiocarcinoma. **Conclusions:** There was no difference in the incidence of cholangiocarcinoma according to previous liver resections. Patients with hepatolithiasis should be carefully followed up for detection of cholangiocarcinoma even after a previous liver resection. (*Gut Liver* 2013;7:475-479)

**Key Words:** Hepatolithiasis; Cholangiocarcinoma; Liver resection

### INTRODUCTION

Hepatolithiasis is common in East Asian countries where the incidence has been reported to be 20% to 30% of all patients undergoing surgery for gallstone disease.<sup>1,2</sup> Even though hepatolithiasis is considered benign in nature, it frequently recurs and may lead to cirrhosis and liver failure.<sup>3-5</sup> In 1942, Sane and Maccallum<sup>6</sup> first reported an association between hepatolithiasis and cholangiocarcinoma, which was then confirmed by many investigators that the development rate of intrahepatic cholangiocarcinoma while patients were being treated and followed for intrahepatic ductal stones was 4% to 11%.<sup>6-9</sup>

However, accurate diagnosis of cholangiocarcinoma associated with hepatolithiasis is very difficult in preoperative imaging studies and even during operation, since the affected liver segment is often fibrotic and scarred. Furthermore, it was reported that cholangiocarcinoma with stones is associated with significantly poorer survival than cholangiocarcinoma alone.<sup>10</sup>

The exact mechanism of cholangiocarcinoma arising from hepatolithiasis is not definitely clear. However bile stasis, chronic bacterial infection, and mechanical irritation of bile duct resulting in the atypical epithelium may play a role in the development of cancerous lesions.<sup>11-13</sup> Hepatic resection is an established treatment and is recommended for its ability to resolve recurrent stone formation, cholangitis and also biliary strictures.<sup>14-16</sup> However, there is no definite evidence and data rather hepatic resection for intrahepatic stones may reduce the development of cholangiocarcinoma.

The aim of this study is to investigate the incidence and clinical characteristics of cholangiocarcinoma during the follow-up of hepatolithiasis with or without previous resection of liver segment or lobe.

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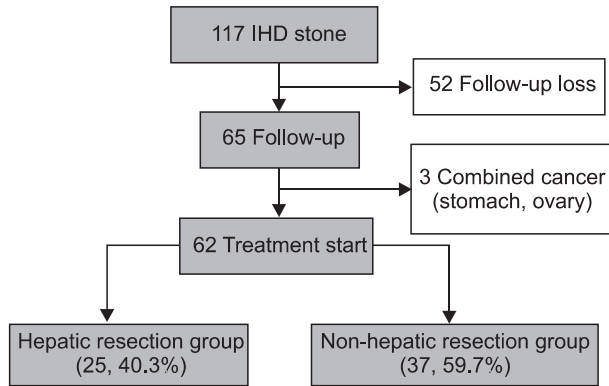
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**Fig. 1.** Study population. IHD, intrahepatic duct.

## MATERIALS AND METHODS

From January 2002 to May 2009, we retrospectively reviewed 117 patients who were diagnosed and treated for hepatolithiasis in Korea University Guro Hospital, Korea University College of Medicine, Seoul, Korea. Among 117 patients, 52 patients who were lost during follow-up and three patients who had malignancy elsewhere including stomach and ovary were excluded. Sixty-two patients were eligible for analysis with a mean follow-up of  $47 \pm 11$  months (Fig. 1).

Of the 62 patients with hepatolithiasis, 25 underwent hepatic resection (hepatic resection group) and 37 were treated without hepatic resection (nonhepatic resection group). Among the hepatic resection group, 10 patients underwent left lateral segmentectomy, nine by left lobectomy, three by right lobectomy, two by left hemihepatectomy, and one by wedge resection. Among the nonhepatic resection group, 14 patients were treated by percutaneous transhepatic cholangioscopic lithotomy (PTCLS), 10 by endoscopic retrograde cholangiopancreatography (ERCP), three by cholecystectomy with common bile duct exploration, two by choledochojunostomy, and eight patients underwent observation due to old age or patients request (Table 1).

We compared the two groups (hepatic resection group and nonhepatic resection group) with regard to clinical features such as: gender, age, location of the intrahepatic ductal stone, and tumor markers (carcinoembryonic antigen [CEA] and carbohydrate antigen [CA] 19-9). We retrospectively investigated the incidence and the location of cholangiocarcinoma in both groups during the follow-up period.

Statistical significance was tested by two sample t-test for continuous variables. Fisher's exact test was used for categorical variables. Comparison of the cholangiocarcinoma development between the two groups was analyzed with Mann-Whitney U test. A value of  $p < 0.05$  was considered to be significant.

**Table 1.** Methods of Treatment in the Liver Resection Group and the Non-Liver Resection Group

Methods of treatment	No.
Liver resection group (n=25)	
Lt. hemihepatectomy	2
Lt. lateral segmentectomy	10
Lt. lobectomy	9
Rt. lobectomy	3
Wedge resection	1
Non-liver resection group (n=37)	
Cholecystectomy with CBD explore	3
Choledochojunostomy	2
Transhepatic-cholangiographic lithotomy	14
Endoscopic retrograde cholangiopancreatography	10
Observation*	8

Lt., left; Rt., right; CBD, common bile duct.

\*Observation due to old age and patient requests.

## RESULTS

### 1. Patient characteristics

We compared the two groups with regard to the clinical characteristics. The results are summarized in Table 2. Mean age in hepatic resection group was significantly younger than the nonhepatic resection group but no significant difference in the gender and duration of follow-up period between the two groups. Aspartate aminotransferase, alanine aminotransferase, total bilirubin, and gamma-glutamyl transferase level was higher in the hepatic resection group but no significant difference in tumor markers (CEA and CA 19-9).

### 2. Incidence of cholangiocarcinoma in regard to the hepatic resection

During the follow-up period of 62 patients with hepatolithiasis, eight patients (12.9%) developed cholangiocarcinoma. Of the 25 patients in hepatic resection group, three (12.0%) developed cholangiocarcinoma and of 37 patients in nonhepatic resection group, five (13.5%) developed cholangiocarcinoma. There were no significant difference in developing cholangiocarcinoma between the two groups ( $p=1.000$ ) (Fig. 2).

### 3. Clinical characteristics of the patients who developed cholangiocarcinoma

The mean follow-up period was 53 months ( $47 \pm 11$  months) for eight patients who had developed cholangiocarcinoma until the diagnosis of hepatolithiasis. Three cases (case 1 to 3) developed cholangiocarcinoma in hepatic resection group. Case 1 underwent left lateral segmentectomy due to a left lobar ductal stone. After 109 months of follow-up duration, ductal stone had recurred and underwent left lobectomy. The final pathol-

ogy was cholangiocarcinoma. Case 2 had cholangiocarcinoma at right lobe 82 months after left lateral segmentectomy for bilateral ductal stones. Case 3 had cholangiocarcinoma arising from caudate lobe 8 months after left lobectomy suggesting a hidden malignancy at the time of operation (Table 3).

Five cases developed cholangiocarcinoma in nonhepatic resection group. Intrahepatic ductal stones were treated mainly through PTCLS and ERCP. As for five cases of nonhepatic resection group, cholangiocarcinoma occurred from the same place

**Table 2.** Comparisons of the Characteristics of the Liver Resection and Non-Liver Resection Groups

Characteristic	Liver resection group (n=25)	Non-liver resection group (n=37)	p-value
Age, yr	54±16	61±23	0.008*
Duration, mo	63±21	36±18	0.081*
Sex, male:female	16:21	5:20	0.058 <sup>†</sup>
AST	41±22	146±65	0.000*
ALT	51±27	133±53	0.021*
Total bilirubin	1.74±1.19	2.71±2.29	0.060*
ALP	136±67	184±82	0.231*
GGT	138±72	343±172	0.004*
CEA	1.27±0.87	1.86±1.21	0.260*
CA 19-9	99.21±69.30	45.93±24.31	0.401*

Data are presented as mean±SD.

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; CEA, carcinoembryonic antigen; CA, carbohydrate antigen.

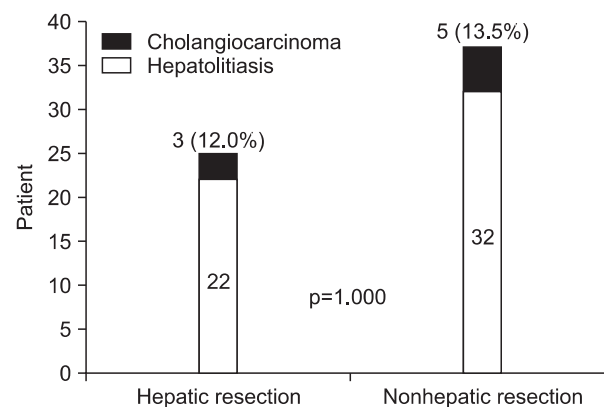
\*Statistical significance was tested by the two sample t-test for continuous variables; <sup>†</sup>Fisher exact test for categorical variables.

as the stone existed (Table 4). In cases 2, 3, and 5, the growth pattern of tumor was an intraductal type so the diagnosis was made through biopsy from choledochoscopy.

**DISCUSSION**

Risk factors for intrahepatic cholangiocarcinoma include intrahepatic ductal stones, cystic liver disease, Clonorchis sinensis, primary biliary cirrhosis, ulcerative colitis, and Carolis disease.<sup>17-21</sup> Especially in Asia, intrahepatic ductal stone is one of the factors that have been highly associated with cholangiocarcinoma.<sup>22,23</sup>

Since cholangiocarcinoma associated with stones has poorer prognosis than cholangiocarcinoma alone, early diagnosis is crucial. Current diagnostic modalities including tumor markers



**Fig. 2.** The incidence of cholangiocarcinoma while patients are being followed for hepatolithiasis.

**Table 3.** Clinical Characteristics of Cholangiocarcinoma with Previous Liver Resection

Case	Age/Sex	Stone location	Cancer location	Liver resection for IHD stone	Follow-up before cancer diagnosis, mo	Morphology
1	51/F	Left	Left	Left lateral segmentectomy	109	Intraductal
2	56/F	Both	Right	Left lateral segmentectomy	82	Mass-forming
3	47/F	Left	Caudate lobe	Left lobectomy	8	Mass-forming

IHD, intrahepatic duct; F, female.

**Table 4.** Clinical Characteristics of Cholangiocarcinoma without Previous Liver Resection

Case	Age/Sex	Stone location	Cancer location	Previous surgical procedure	Treatment of IHD stone	F/U before diagnosis, mo*	Morphology
1	56/F	Right	Right	Cholecystectomy	THCL	110	Mass-forming
2	71/F	Left	Left	Cholecystectomy	THCL	68	Intraductal
3	65/M	Left	Left	Cholecystectomy	ERCP	13	Intraductal
4	51/M	Both	Left	-	ERCP	13	Mass-forming
5	66/M	Left	Left	-	THCL	21	Intraductal

IHD, intrahepatic duct; F/U, follow-up; F, female; THCL, transhepatic cholangiographic lithotomy; M, male; ERCP, endoscopic retrograde cholangiopancreatography.

\*Mean follow-up periods before the diagnosis of cholangiocarcinoma.

(CA 19-9 and CEA) and advanced imaging studies such as helical computed tomography (CT), magnetic resonance cholangiogram are widely used for early detection. Recent study reported a "helical CT criteria" which include the periductal soft tissue density, ductal wall thickening, ductal enhancement on portal venous phase being useful for the diagnosis.<sup>24</sup> However, the accurate preoperative diagnosis of cholangiocarcinoma in association with hepatolithiasis remains difficult. Furthermore, unlike the mass forming type, intraductal type of cholangiocarcinoma is especially difficult to predict through conventional diagnostic tools whether an accompanying malignancy exists in patients with hepatolithiasis. Of the eight patients with coexisting cholangiocarcinoma in this study, four patients showed intraductal type of growth pattern with two patient diagnosed by choledochoscopy and one case diagnosed only through surgical resection.

Nonsurgical procedures such as percutaneous transhepatic cholangioscopic lithotripsy and peroral choangioscopic lithotripsy have been used to treat hepatolithiasis. Although these procedures markedly increase the stone clearance rate, the high rates of residual stones and of recurrence of stones have been serious problems, especially in patients with biliary strictures. Hepatic resection is the most definitive approach to treating hepatolithiasis and can remove both intrahepatic stones and the strictured bile duct responsible for stone formation. Thus, recent report suggests hepatic resection may offer another advantage in eliminating the risk of new development of cholangiocarcinoma in patients with hepatolithiasis.<sup>25</sup> But in contrast, incidence of cholangiocarcinoma showed no significant difference among patients with hepatolithiasis with or without previous hepatic resection.<sup>26</sup>

In this study, during the 53 months of mean follow-up period in patients with hepatolithiasis, eight patients (12.9%) developed cholangiocarcinoma. No significant difference was found in the development of cholangiocarcinoma among hepatic resection group and nonhepatic resection group (12.0% vs 13.5%,  $p=1.000$ ). Furthermore, there were no difference between the two groups in clinical manifestation and laboratory data to predict the development of malignancy. Limitation of the study is that the study design is retrospective, cross sectional, and the number of patients enrolled was too small. However it is difficult to conclude rather hepatic resection definitely prevents the development of cholangiocarcinoma in patients with hepatolithiasis.

In conclusion, patients with hepatolithiasis should be carefully followed up for detection of cholangiocarcinoma even after previous resection of liver segment or lobe.

#### CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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