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The risk of carcinogenesis in congenital choledochal cyst patients: an analysis of 214 cases

Xiao-dong He,*,◆ Lei Wang,*,**,◆ Wei Liu,* Qi Liu,* Qiang Qu,* Bing-lu Li,* Tao Hong*

* Department of General Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China.** Peking University Wu-Jieping Urology Center, Peking University Shougang Hospital, Peking University Health Science Center, Beijing, 100144, China. ◆Xiao-dong He and Lei Wang are the first authors who contributed equally to the article.

ABSTRACT

Background. Choledochal cysts are most common in Asian populations. In addition, the incidence of biliary tract malignancies from choledochal cysts is increasing, but the risk of carcinogenesis is still unclear. **Material and methods.** Clinical data from 214 congenital choledochal cyst cases from 1968 to 2013 were retrospectively analyzed. **Results.** Todani type I was more common (139, 65.0%) than type IVa (53, 24.8%) or type V (17, 7.9%) in these choledochal cyst patients. Biliary tract malignant tumors occurred in the gallbladder (2, 13.3%), common bile duct (10, 66.7%), and intrahepatic bile duct (3, 20%) in 15 patients (7.0%), including one patient in whom malignant transformation occurred in the intrahepatic bile duct in a type IVa patient 15 years after extrahepatic cyst resection. An age at symptom onset ≥ 60 years was a risk factor ($p < 0.001$), while an initial complete surgery was a protective factor for carcinogenesis ($p = 0.001$). **Conclusions.** Choledochal cysts should be removed once diagnosed because of an increased risk of malignant transformation with increasing age. Complete cyst removal is necessary for the first surgical treatment. Additional hepatectomy should be considered for type IVa choledochal cysts because cholangiocarcinoma can arise from the intrahepatic bile duct years after the extrahepatic cyst excision.

Key words. Age of onset. Bile ducts. Cholangiocarcinoma. Risk factors. Surgical procedures.

INTRODUCTION

Congenital choledochal cysts (CCCs) are characterized by single or multiple congenital dilations of the extrahepatic and/or intrahepatic biliary tree.[1] CCCs are rare in Western countries, with an incidence of 1:100,000 to 1:150,000, and account for approximately 1% of all benign biliary diseases, but they are relatively common in Asian countries. In the United States, they account for one in 13,000 hospital admissions, compared with one in 1,000 in Japan.[2] CCCs are usually confirmed during infancy or childhood; however, approximately 20% of cases are not diagnosed until adulthood[3,4] because CCCs usually coexist with cholecystolithiasis, cholelithiasis, or pancreatitis and manifest with atypical clinical symptoms of epigastric pain, jaundice, and fever, which increases the difficulty of diagnosis and treatment.[5,6] Once the disease is confirmed, complete cyst removal is necessary because the incidence of biliary tract malignancy arising from CCCs ranges from 2.5 to 26%.[7-10] However, few studies on the risk of carcinogenesis from CCCs have been conducted. Therefore, we analyzed the clinical data from 214 CCC patients and focused on the risk of malignant tumors arising from CCCs.

MATERIAL AND METHODS

The study was designed to investigate a specialized group of biliary duct diseases in Peking Union Medical College Hospital (PUMCH) in China. The study design and questionnaire were approved by a panel that consisted of general surgeons, digestive physicians, pediatricians, and members of the ethics committee of the hospital on July 8, 2013. This ret-

Correspondence and reprint request: Lei Wang, M.D., Ph.D.
Department of General Surgery, Peking Union Medical College Hospital, 1# Shuai Fuyuan, Dong Cheng district, Beijing, 100730, China.
Ph./Fax number: + 86 10 69152610
E-mail: wanglei_09243633@163.com

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rospective study complied with the ethical guidelines of the Declaration of Helsinki and was approved by the ethics committee of PUMCH.

Inpatients who were diagnosed with choledochal cysts at PUMCH between September 1968 and July 2013 were recruited into the study. The clinical data, including gender, age, clinical features, radiological images, surgical approaches, complications, pathological data, and follow-up outcomes, were collected and analyzed. In addition, radiological images and operation logs were reviewed to reclassify the cases according to the Todani 2003 classification.[11] Follow-up was performed by a standardized telephone interview.

Continuous data are expressed as the mean (SD) and were analyzed using the t test. Categorical variables were analyzed using the Pearson χ^2 test or Fisher's exact test where appropriate. Statistical analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

General data

A total of 214 CCC patients were included in the study. Among them, 59 (27.6%) patients were admitted before 2000 and 47 (21.7%) patients were male; the mean (SD) age at diagnosis was 36.2 (16.4) years (range 1-78 years). Abdominal pain was the most common symptom (167, 78.0%), followed by jaundice (54, 25.2%), fever (40, 18.7%), and an abdominal mass (9, 4.2%). Thirteen patients (6.1%) were asymptomatic. B ultrasonography (156, 72.9%), computed tomography (93, 43.5%), endoscopic retrograde cholangiopancreatography (ERCP) (53, 24.8%), magnetic resonance cholangiopancreatography (MRCP) (94, 43.9%), and percutaneous transhepatic cholangiography (24, 11.2%) were performed as part of the diagnostic work-up. Coexisting diseases included cholecystitis (60, 28.0%), cholecystolithiasis (48, 22.4%), pancreatitis (27, 12.6%), choledocholithiasis (63, 29.4%), calculus of the intrahepatic duct (24, 11.2%), portal hypertension (10/17 Todani type V patients, 58.8%), and polycystic kidney (5/17 Todani type V patients, 29.4%).

Classification of choledochal cysts and abnormal pancreatic biliary duct (APBD)

According to the Todani classification of choledochal cysts in 2003,[11] 139 (65.0%) patients were type I, 3 (1.4%) patients were type II, 1 (0.5%) patient was type III, 53 (24.8%) patients were type IVa, 1 (0.5%) patient was type IVb, and 17 (7.9%) patients were type V. Among the Todani type I patients, 74 (56.9%) patients were Ia, 9 (6.9%) patients were Ib, 47 (36.2%) patients were Ic, and 9 patients were classified with indefinite subtypes (lack of medical records). A total of 137 patients underwent ERCP and/or MRCP examinations, and the pancreaticobiliary ductal junctions of 101 (73.7%) patients were visible. Eighty-two patients (81.2%) exhibited an APBD, 54 patients (65.9%) exhibited a BP type (common bile duct joining the pancreatic duct), 9 patients (11.0%) exhibited a PB type (pancreatic duct joining the choledochus), and 19 patients (23.2%) exhibited a complex type (complicated union of the pancreaticobiliary ductal system).

Treatments

Of the 214 patients, 197 (92.1%) underwent surgical procedures. Among them, 182 (92.4%) underwent definitive surgery, including cyst excision and hepaticojejunostomy (163, 82.7%); additional hepatectomy, cyst excision, and hepaticojejunostomy (11, 5.6%); hepatectomy (3, 1.5%); Whipple procedure (4, 2.0%); and cystectomy (1, 0.5%). The other 15 (7.6%) patients underwent incomplete or palliative surgeries, including calculus removal from the biliary tract (7, 3.6%), internal drainage (3, 1.5%), external drainage (1, 0.5%), exploratory surgery (2, 1.0%), and partial cyst excision (2, 1.0%). Among the 182 patients who underwent definitive surgery, 57 (31.3%) had undergone previous incomplete surgeries, including internal drainage (31, 54.4%), external drainage (2, 3.5%), extrahepatic cyst excision and choledochojejunostomy (1, 1.8%), calculus removal (18, 31.6%), and partial cyst excision (5, 8.8%).

Follow-up and complications

A total of 187 (87.4%) patients were followed up for a mean (SD) time of 110.7 (96.8) months. Cyst excision and hepaticojejunostomy were the most common surgical approaches employed (164 patients), either as initial surgery (118, 72.0%) or remedial treatment for previous incomplete operations (46, 28.0%). For this surgical approach, cholangitis (39, 33.1%), pancreatic leakage (13, 11.0%), and bile leakage (8, 6.8%) were the most common three early postoperative complications (data from the 118 patients as initial surgery); biliary duct stones (21, 14.2%), recurrent cholangitis (9, 6.1%), and biliary-

Table 1. Clinical data of 15 patients with choledochal cysts and malignant transformation.

N	Gender /Age	Type	Initial treatment	Definitive treatment	Time interval[a]	Pathological diagnosis	TNM Stage[b]	Follow-up (mo.)	Outcome
1	F/64	Ic	-	External drainage and cholecystectomy; radiotherapy postoperatively[c]	-	Adenocarcinoma of GB	T2NxM0	28	Died
2	M/46	IVa	-	Radical cholecystectomy	-	Mucinous adenocarcinoma of GB	T3N0M0	12	Died
3	F/49	Ia	-	Cyst excision and choledochojejunostomy	-	Moderately differentiated adenocarcinoma of CBD	T3N1M1	4	Died
4	F/63	Ia	-	Cyst excision and choledochojejunostomy	-	Mucinous adenocarcinoma of CBD	T4NxMx	7	Died
5	M/38	Ia	Internal drainage	Palliative gastroenterostomy and resected biopsy	37 yrs	Poorly differentiated adenocarcinoma of CBD	T3NxM1	5	Died
6	M/63	Ic	-	External drainage and resected biopsy (emergency surgery)	-	Mucinous adenocarcinoma of CBD	T3NxM1	3	Died
7	M/37	I	Internal drainage	Needle biopsy and chemotherapy	36 yrs	Adenocarcinoma of CBD	T4NxMx	1	Died
8	F/75	I	-	Needle biopsy and chemotherapy	-	Adenocarcinoma of CBD	T4NxMx	3	Died
9	F/69	IVa	-	Exploratory laparotomy and biopsy	-	Adenocarcinoma of CBD	T3N2Mx	2	Died
10	F/40	IVa	External drainage	Whipple	6 yrs	Poorly differentiated adenocarcinoma of CBD	T3N1M0	8	Died
11	F/28	IVa	-	Whipple	-	Moderately differentiated adenocarcinoma of CBD	T3N0M0	7	Died
12	F/69	IVa	Cholecystectomy	Left hepatectomy, cyst excision and choledochojejunostomy	6 yrs	Papillary cystadenocarcinoma of IHD	T1N0M0	29	Disease-free Survived
13	F/45	IVa	Extrahepatic cyst excision and choledochojejunostomy	Needle biopsy and chemotherapy	15 yrs	Poorly differentiated adenocarcinoma of IHD	T3NxMx	12	Died
14	M/67	V	-	Left hepatectomy	-	Cystadenocarcinoma of IHD	T1N0M0	71	Disease-free Survived
15	M/34	Ia	Extrahepatic cyst excision and choledochojejunostomy	Whipple	2 yrs	Moderately differentiated adenocarcinoma of CBD (initial surgery); poorly differentiated adenocarcinoma of head of pancreas (definitive surgery)	T2N0M0	69	Disease-free Survived

[a] Time interval between initial and definite treatments. [b] According to NCCN 2010 TNM classification. [c] The patient gave up radical surgery. CBD: common bile duct. IHD: intrahepatic bile duct. GB: gallbladder.

enteric anastomosis stricture (8, 5.4%) were the three most common late postoperative complications (data from all the 164 patients as initial or remedial surgery). Internal drainage was a common surgical approach for early cases. Of the 35 patients who underwent internal drainage as the primary treatment, 32 (91.4%) eventually underwent reoperations due to biliary-enteric anastomosis stricture (9, 25.7%), cholangitis (28, 80%), and/or biliary and intrahepatic stones (16, 45.7%) after a mean (SD) time of 191.8 (101.4) months.

Biliary malignant tumors

A total of 15 patients were found to have malignant tumors arising from the biliary tree. Clinical data from these patients are presented in table 1. Ten patients were confirmed on their first admission, and malignant transformation occurred in the other 5 patients 20.0 ± 15.5 (range 6-37) years after the primary surgeries. Thirteen (87%) of the 15 patients exhibited cholangiocarcinoma, and the number of stage I, II, III, and IV tumors was 2, 1, 2,

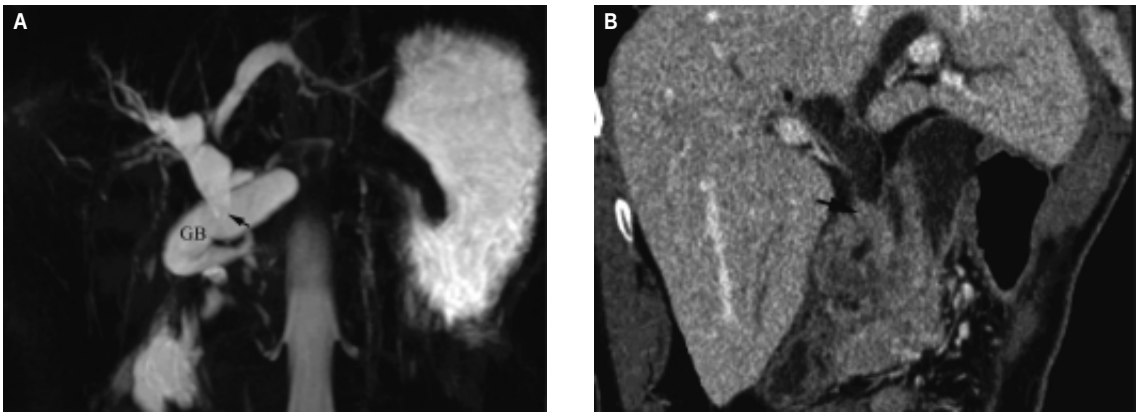

Figure 1. No. 5 patient, M/38, who had undergone an internal drainage with cystoduodenostomy 37 years ago, presented to our institution with vomiting after meal. A. MRCP showed extrahepatic bile duct disrupted (arrow). B. CT manifested a mass (arrow) deriving from bilioenteric anastomotic stoma. An exploratory surgery and biopsy revealed low-differentiated adenocarcinoma of distal bile duct.

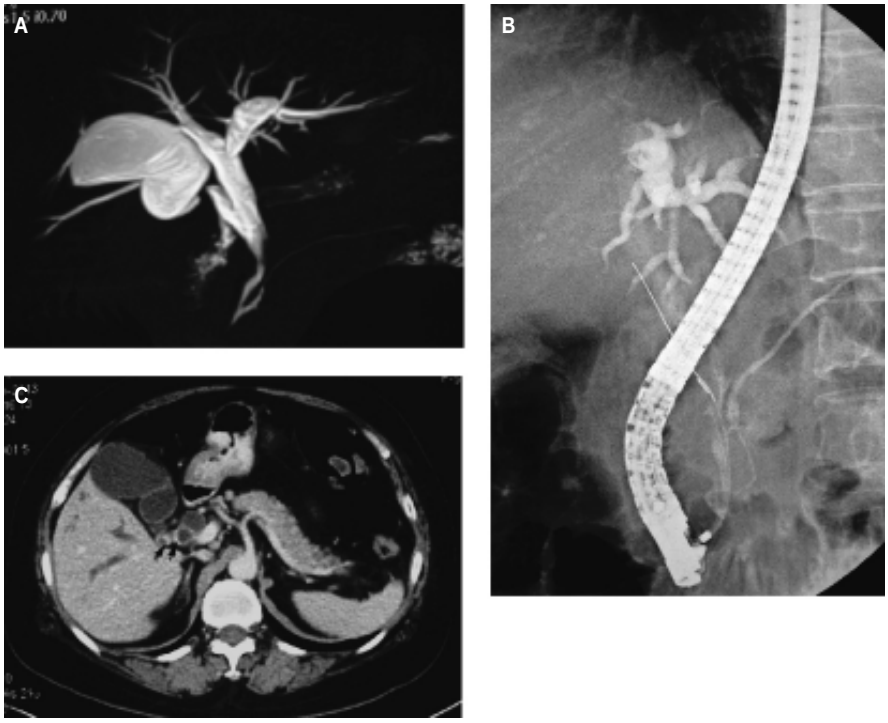

Figure 2. No. 9 patient, F/69, diagnosed as type IVa congenital choledochal cyst with abnormal pancreatic biliary duct two years ago, as shown in MRCP image (A). The patient was admitted to our institution due to fever and jaundice. ERCP (B) showed an obvious dilation of intrahepatic bile duct; (C) CT manifested thick, abnormally enhanced wall of extrahepatic bile duct as well as cystic duct (arrow). An exploratory surgery and biopsy revealed adenocarcinoma of distal bile duct.

and 8, respectively. Nine of the 10 stage III/IV patients died within 8 months after diagnosis. Three patients with stage I/II survived to the end of follow-up, which was 29, 71, and 69 months after surgery. Images of two typical cases (No. 5 and No. 9) are shown in figures 1 and 2. Precancerous lesions were found in 4 other patients, including gallbladder adenoma, extrahepatic biliary epithelial squamous metaplasia, intrahepatic adenomatous hyperplasia, and intrahepatic biliary cystadenoma.

Twenty-five (47%) of the 53 type IVa patients underwent extrahepatic cyst excision and choledochojejunostomy as the initial surgery. Among them, malignant transformation within the intrahepatic bile duct (IHD) occurred in one case (No. 13) after 15 years of follow-up. Eleven (21%) type IVa patients underwent an additional hepatectomy as definitive surgery, including 3 patients who were confirmed, based on pathological findings, to have cancerous (one patient, No. 12) or precancerous lesions (two patients) in the IHD.

The potential risk factors for carcinogenesis of CCCs were analyzed (Table 2). Older age at admission ($p < 0.001$) or at symptom onset ($p = 0.016$) was found to be a risk factor for carcinogenesis. Then, the correlation between age at symptom onset and malignant transformation was stratified and analyzed, and age ≥ 60 years was found to be associated with a high risk of carcinogenesis (Table 3). The malignant rate increased dramatically with age and reached 50% for patients older than 60 years. The incidence of carcinoma of type I and IVa CCCs after the initial operations was analyzed to determine the correlation between initial surgery and carcinogenesis (Table 4). Complete excision of the cyst at the time of initial treatment ($p = 0.001$) was a protective factor against carcinogenesis.

DISCUSSION

The incidence of malignant biliary tumors arising from choledochal cysts is relatively high (2.5-26%).[7-10] An abnormal pancreaticobiliary junction, which leads to a reflux of pancreatic juice into the biliary tract, and bile stagnation, which is induced by cystic dilation and leads to long-term inflammatory stimulation, are considered to play important roles in the carcinogenesis of the biliary tract.[10] Repeated damage and restoration of the biliary epithelium may stimulate the process of carcinogenesis.[12,13] However, the mechanism has not been fully elucidated. In our study, we focused on biliary malignant tumors arising from choledochal cysts and its risk factors.

Cholangiocarcinoma was revealed as the most common malignant tumor arising from choledochal cysts in previous reports.[14] The prognosis for patients with cholangiocarcinoma arising from choledochal cysts is grim, with a reported median survival of 6 to 21 months.[5,15,16] The poor prognosis

Table 2. Statistical analysis of the correlation between choledochal cyst carcinogenesis and the potential risk factors.

Factors	Unit	Carcinogenesis (-)	Carcinogenesis (+)	P
Age at admission	Year	34.9 ± 15.7	52.5 ± 15.3	< 0.001
Age at symptom onset	Year	25.1 ± 16.9	43.6 ± 24.8	0.016
Gender	Male	42/199	6/15	0.11
CCC type				
I		131	8	0.64
IVa		47	6	0.32
V		16	1	0.86
Total		199	15	
Symptoms				
Stomachache (%)	+	156/199 (78.4%)	11/15 (73.3%)	0.66
Jaundice (%)	+	47/199 (23.6%)	7/15 (46.7%)	0.09
Fever (%)	+	37/199 (18.6%)	3/15 (20.0%)	0.89
Bile duct stone	+	91/199 (45.7%)	8/15 (53.3%)	0.57
APBJ (%)	+	75/94 (79.8%)	7/7 (100%)	0.41
Tumor marker	+	9/156 (5.8%)	2/13 (15.4%)	0.44
Early cases (before 2000)	+	56/199 (28.1%)	3/15 (20.0%)	0.70

APBJ: abnormal pancreatic biliary junction.

of cholangiocarcinoma patients in our study was mainly attributed to the late stage of the tumors at diagnosis (Table 1). Comparatively, in a report by Lee, *et al.*,[17] 40 cholangiocarcinoma patients were diagnosed at much earlier stages and, thus, had better prognoses; specifically, the 5-year survival rates of patients with stage Ia, Ib, and IIa cholangiocarcinoma reached 90.4, 40.0, and 25.1%, respectively.

Among all of the possible risk factors of carcinogenesis in choledochal cysts, age was widely mentioned in previous reports.[18,19] Malignancy was rarely observed in patients with cysts removed in infancy, but the risk of carcinogenesis increases with age. Voyles, *et al.*[18] concluded that the risk of malignant transformation was less than 1% if the choledochal cyst appeared before 10 years of age but increased to 14% above 20 years of age. Nicholl, *et al.*[19] revealed a direct correlation between patient age and cancer risk: 0 year to 30 years (0%), 31 years to 50 years (19%), and 51 years to 70 years (50%). We analyzed the correlation between age of onset and malignant rates with stratification and found similar trends (Table 3); specifically, the malignant rate increased dramatically with age and reached 50% for patients older than 60 years. Considering such a high malignant rate in older patients, a complete surgery with cyst excision should be performed once a choledochal cyst is confirmed.

Many patients (31.3%) in our study underwent incomplete surgeries during the initial treatment, such as cholecystectomy, calculus removal, and internal or external drainage, for a few reasons. First, subtle fusiform dilation of the common bile duct was difficult to identify compared with large cysts, and these dilations were easily missed or misdiagnosed as cholecystitis or biliary calculi. Second, some patients were primarily treated at small hospitals with a lack of experience. Third, internal drainage was widely used before the 1990s in China, especially in emergency cases. As type II, III, and IVb cases were rare and most type V cases only underwent conservative treatment in our series, the correlation of initial surgical treatment with malignant transformation was analyzed based on type I and IVa cases (Table 4). As a result, complete surgeries with intact excision of the cyst at initial treatment was found to be a protective factor against carcinogenesis, whereas incomplete surgeries carried a risk of malignancy similar to that of the total patients. These conclusions were consistent with previous reports.[20-22] Incomplete surgical procedures, in which the cyst could not be drained fully or pancreatic juice could not be prevented from refluxing into the

Table 3. Stratified analysis of age at symptom onset as a risk factor for carcinogenesis.

Age	Number (total)	Number (Ca)	P
0-9	45	2* (4.4%)	0.51
10-19	34	1 (2.9%)	0.33
20-39	83	4 (4.8%)	0.49
40-59	40	2 (5%)	0.63
≥ 60	12	6 (50%)	< 0.001
Total	214	15 (7.0%)	

Ca: carcinogenesis. *The two patients accepted internal drainage as the initial treatment.

Table 4. Correlation of initial surgical treatment with malignant transformation in type I and IVa CCC.

Todani type	Initial surgery[a]	Total, n[b]	Ca (Ca + preCa), n	P
I	Complete	85	0 (0)	
	Incomplete	45	2 (3)	
IVa	Complete	3	0 (0)	
	Relatively incomplete	25	1 (1)	
	Incomplete	20	2 (4)	
I + IVa	Complete	88	0 (0)	
	Incomplete	65	4 (7)	0.031 (0.002) [d]
I + IVa (all)[c]		192	14 (18)	0.001 (< 0.001) [d]
				0.98 (0.74) [e]

Ca: carcinogenesis after initial surgery. preCa: precancerous lesion after initial surgery. [a] Complete surgeries include cyst excision and choledochojejunostomy for type I; hepatectomy, cyst excision, and choledochojejunostomy for type IVa. Relatively incomplete surgery for type IVa indicates excision of the extrahepatic part of the cyst and choledochojejunostomy without management of intrahepatic cyst, such as hepatectomy; Incomplete surgeries include all surgeries without a complete cyst excision, such as internal and external drainage, choledochalcystectomy, and calculus removal from the biliary duct. [b] Patients who were diagnosed with carcinoma or a precancerous lesion during the first treatment were excluded (7 Ca and 1 preCa for type I, 2 Ca for type IVa). [c] All of the type I+ Iva patients, including those who did not undergo surgery at the initial treatment and those who were diagnosed with carcinoma at the first treatment. [d] *vs.* Complete surgery. [e] *vs.* incomplete surgery.

bile duct, were unable to eradicate stimulation of bile stagnation or pancreatic juice reflux and, thus, did not minimize the risk of carcinogenesis.

For type I choledochal cysts, the ideal treatment is excision of the entire dilated extrahepatic biliary tree, which could minimize the continuing risk of malignant transformation.[23] However, in cases of type IVa choledochal cysts, cholangiocarcinoma can also develop from cysts of the IHD years after the operation despite total resection of the extrahepatic duct.[24-31] Whether an additional hepatectomy surgery is essential for type IVa choledochal cysts remains controversial.[24-26] Zheng, *et al*.[25] reported 4 (11.4%) cases of malignant transformation in a group of 35 type IVa patients several years after extrahepatic cyst resection. However, among 29 patients who underwent additional liver resection, malignant transformation was observed in only 1 (3.4%) case. Kobayashi, *et al*.[27] concluded that the relative risk of carcinogenesis in the post-surgery group was still higher than that in the general population, although it was decreased by approximately 50% after excision of the extrahepatic cyst. In our study, we also found 1 case of malignant transformation in the IHD in a total of 25 type IVa patients who underwent extrahepatic cyst resection as the initial treatment. Bile stasis due to stenosis of the intrahepatic bile duct and repeated cholangitis with multiple stones may be a high-risk factor.[32] Another reasonable explanation is that the epithelium of the remnant bile duct wall may have already progressed to a precancerous stage by the time of the operation and that genetic changes may have occurred or continued during the postoperative period.[33]

One interesting phenomenon in our study was that a substantial percentage of type IVa patients were confirmed to have cancerous or precancerous lesions based on pathological findings after an additional hepatectomy (3/11, 27.3%). The rate of carcinogenesis seemed to be higher compared with the rate for the patients who did not undergo an additional hepatectomy. One potential explanation for this result is that we tended to perform additional hepatectomy surgeries under relatively negative clinical scenarios and strict indications for type IVa cases, such as serious intrahepatic cholelithiasis with recurrent symptoms or atrophy of the liver lobes. This delay and the dilatation of IHD prolonged bile stasis and related genetic changes and, thus, increased the risk of carcinogenesis. We suggested that a more aggressive surgery with additional hepatectomy should be performed actively and in a timely manner for some selected type IVa patients,[26] which may decrease the risk of carcinogenesis in the IHD for type IVa choledochal cysts. However, this conclusion requires support from further studies and much stronger evidence.

In conclusion, age at symptom onset > 60 years was found to be a high risk factor for malignant tumors arising from choledochal cysts, and complete surgery with intact excision of the cyst at initial treatment was considered to be a protective factor against carcinogenesis. Congenital choledochal cysts should be removed once diagnosed, and complete cyst removal is necessary. Additional hepatectomy should be considered for selected type IVa choledochal cysts because cholangiocarcinomas can also arise in the intrahepatic bile duct years after the extrahepatic cyst excision.

ABBREVIATIONS

- **APBD:** abnormal pancreatic biliary duct.
- **CCC:** congenital choledochal cyst.
- **ERCP:** endoscopic retrograde cholangiopancreatography.
- **IHD:** intrahepatic bile duct.
- **MRCP:** magnetic resonance cholangiopancreatography.

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