The Malignant Potential in Adult Choledochal Cysts; an Awareness Issue

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ABSTRACT

Objective: Although still uncommon, choledochal cysts (CCs) are more frequently found in Asians than Caucasians. The incidence of malignancy associated with these cysts and the surgical outcomes have not been reported in Thailand.

Methods: A retrospective review was performed of 48 adult CC patients who underwent surgery January 2005–December 2015. Their clinical data and outcomes were analyzed.

Results: There were 31 (64.6%) female patients, with a female-to-male ratio of 1.8:1. The mean age ± SD at diagnosis was 40.5 ± 17.4 years. Using the modified Todani classification, 32 patients (66.7%) had a type I CC, one (2.1%) had type II, twelve (25.0%) had type IV, and three (6.3%) had type V. Twelve patients (25%) had a malignant tumor: eleven had synchronous cancer at surgery, while one with CC type I developed metachronous intrahepatic cholangiocarcinoma during the follow-up. The cholangiocarcinoma was inside the CC in 6 cases, intrahepatic in three, perihilar in two, and distal in one. The 5-year overall survival of the cohort was 68%. The factor affecting the overall survival was the coexisting cancer ($p < 0.001$). The 1-year and 5-year overall survival rates were 58.3% and 20%, respectively, for patients with cancer, but 96.7% and 88.4% for patients without cancer.

Conclusion: The adult choledochal cysts had a high incidence of associated malignancy. Factors predicting coexisting malignancy were an age above 40 years and a significant weight loss. If cancer occurred, the overall survival was significantly poor. Even after definitive surgery, patients still need life-long surveillance for cancer.

Keywords: Cholangiocarcinoma; choledochal cyst; malignancy; prognosis factors; risk factors (Siriraj Med J 2019; 71: 466-471)

INTRODUCTION

Choledochal cysts (CCs) are an uncommon congenital anomaly of the bile duct that present as an abnormal cystic dilatation of the intra and/or extra hepatic bile ducts. In 1959, Alonso-Lej et al. first described and proposed a classification of CCs into 3 types.[1] This was modified in 1977 by Todani et al. by adding types IV and V.[2] The Todani system is currently the most widely used classification scheme for CCs. The incidence of CCs is approximately 1 in 100,000 to 150,000 live births in the Western population, but it has been reported to be as high as 1 in 13,500 live births in the United States and 1 in 15,000 in Australia.[3] In Asia, CCs are more commonly reported, especially in Japan, with an incidence of up to 1 in 1,000 live births.[4]

CCs are usually diagnosed in childhood; however about 20% of patients present in adulthood.[5] In adult patients, CCs commonly present with abdominal pain, jaundice, and a palpable mass. The patients may also present with severe complications, such as cholangitis,

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pancreatitis, secondary biliary cirrhosis, and cancer. Cancer associated with CC is one of the dire complications of CC and drastically affects the outcome. Carcinoma arising in CC can be found within the cyst or any part of the biliary system. The incidence of cholangiocarcinoma arising with CCs varies and depends on the CC subtype and the patient's age.[6-11] Moreover, the risk of malignancy is not reduced in patients with inadequate treatment, such as a cystoenterostomy and/or incomplete cyst excision.[10,11]

In Thailand, little data regarding CCs[12-16] have been reported as case reports or small case series. Therefore, this study aimed to analyze the clinical data, operative procedures, surgical outcomes, and risk factors associated with cancer in a large series of CC patients.

MATERIALS AND METHODS

A total of 48 consecutive patients diagnosed with CCs who underwent surgery between January 2005 and December 2015 at the Hepatopancreatobiliary and Transplant Surgery Unit, Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, were enrolled. We obtained the demographic data, medical comorbidities, laboratory information, operative outcomes, and long-term survival of the patients from a retrospective chart review. All of the patients were above 18 years of age at the time of definitive surgery. The type and extent of the surgery were based on a clinical assessment by a consultant surgeon. This study was approved by the Institutional Review Board of the Faculty of Medicine Siriraj Hospital, Mahidol University (Si 089/2016).

Statistical analysis

Continuous variables are expressed as mean and standard deviation (± SD), and comparisons were made using Student's t-test. Categorical variables were compared using a chi-squared or Fisher's exact test, as appropriate. A logistic regression model was used to identify factors predicting a coexisting malignancy. The overall survival rates were analyzed with the Kaplan–Meier method and log-rank tests. All statistical analyses were performed using Stata for Macintosh, version 15.0 (StataCorp, College Station, TX, USA). The level of statistical significance was set at a p-value of ≤ 0.05.

RESULTS

Forty-eight consecutive patients diagnosed with CCs underwent operations in the Hepatopancreatobiliary and Transplant Surgery Unit at Siriraj Hospital between January 1, 2005 and December 31, 2015. There were 31 (64.6%) female and 17 (35.4%) male patients, with a female-to-male ratio of 1.8:1. The mean age (± SD) of the patients at diagnosis was 40.5 (± 17.4) years. Most of the patients had at least one symptom. The most common presentation was abdominal pain (93.8%), followed by obstructive jaundice (45.8%) and cholangitis (45.8%). Choledocholithiasis and hepatolithiasis were also observed in 52.1% and 14.6% of patients, respectively. As to the treatments, preoperative endoscopic retrograde cholangiopancreatography and percutaneous transhepatic biliary drainage were performed in 15 (31.3%) and 5 (10.4%) patients, respectively. Fourteen patients (29.2%) had previously undergone a cholecystectomy before definitive surgery. The mean time between the first presenting symptoms and definite surgery was 49.7 months. The demographic data of the cohort are detailed in Table 1.

Based on the modified Todani classification[2], 32 patients (66.7%) had a type I cyst, one (2.1%) had type II, twelve (25.0%) had type IV, and three (6.3%) had type V. Of note, there was no CC type III in this cohort. CC type IV was significantly associated with hepatolithiasis (33% ; p = 0.02). A CC excision with a hepaticojejunostomy was the most frequently performed operation (24 patients; 50%). The detail of the operations and the CC types are presented in Table 2.

In this series, there were 12 patients (25%) with a malignant tumor. Eleven patients had cancer at the time of the surgery. Of the eleven, five underwent curative surgery, while six only had a palliative bypass or a biopsy. Thirty-six patients had no cancer at the beginning. Thirty-one patients had no symptoms after surgery, with a mean follow-up time of 31.4 months. However, 2 patients died from liver abscess and massive upper gastrointestinal bleeding, and another 3 patients had to undergo reoperation. Moreover, one patient with CC type I developed intrahepatic cholangiocarcinoma 18 months after the cyst excision and hepaticojejunostomy.

The malignancy most often associated with the CCs was cholangiocarcinoma. Patients with CC type V had the highest incidence of malignancy (66.7%), following by types I and IV at 25% and 16.7%, respectively. One patient with CC type II had no cancer at the beginning or during the follow-up. The cholangiocarcinoma was inside the CC in 6 cases, intrahepatic in three, perihilar in two, and distal in one. The other cancer types that occurred in our patients were pancreatic adenocarcinoma in the pancreatic head and the body of the pancreas, and adenocarcinoma in the sigmoid colon.

Three patients had 2 concomitant cancers, but they were different types. The first patient had distal cholangiocarcinoma and pancreatic adenocarcinoma in the body of the pancreas. The second had perihilar

TABLE 1. Patient characteristics and clinical manifestations of patients with and without malignancy.

Characteristics	Total	%	Non-CA	%	CA	%	*P*
Number	48	100.0	36	75.00	12	25.00	
Sex							0.60
Male	17	35.4	12	70.6	5	29.4	
Female	31	64.6	24	77.4	7	22.6	
Age (mean ± SD; years)	40.5 ± 17.4		35.8 ± 15.7		54.9 ± 14.2		0.001
Clinical manifestation							
RUQ pain, epigastric pain	45	93.8	33	91.7	12	100.0	0.40
Jaundice	22	45.8	17	47.2	5	41.7	0.74
Cholangitis	22	45.8	15	41.7	7	58.3	0.31
Significant weight loss	6	12.5	2	5.6	4	33.3	0.01
Palpable mass	6	12.5	3	8.3	3	25.0	0.13
Pancreatitis	4	8.3	4	11.1	0	0.0	0.22
Cholecystitis	3	6.3	2	5.6	1	8.3	0.73
Liver abscess	1	2.1	1	2.8	0	0.0	0.56
Asymptomatic	2	4.2	2	5.6	0	0.0	0.40
Concurrent CBD stone	25	52.1	18	50.0	7	58.3	0.62
Concurrent IHD stone	7	14.6	5	13.9	2	16.7	0.81
Prior cholecystectomy	14	29.2	9	25.0	5	41.7	0.08
CA 19-9 (mean ± SD; ng/ml)	422.8 ± 1,573.9		47.1 ± 70.1		736.0 ± 2,119.0		0.32
CEA (mean ± SD; U/ml)	4.00 ± 5.3		2.3 ± 3.6		5.9 ± 6.3		0.13
Time to surgery (mean ± SD; months)	49.7 ± 71.1		48.0 ± 76.3		54.6 ± 54.7		0.80

Abbreviations: Non-CA: no malignancy; CA: malignancy; RUQ: right upper quadrant; CBD: common bile duct; IHD: intrahepatic duct

TABLE 2. Choledochal cyst type and operative procedure.

Operation	Choledochal cyst type			
	I	II	IV	V
CE + HJ	24		7	
CE		1		
CE + HJ + LR	1		3	
CE + HJ + PD	2		1	
LR				2
Palliative	4		1	1
Other	1			
Total	32	1	12	3

Abbreviations: CE: cyst excision; HJ: hepaticojejunostomy; LR: liver resection; PD: pancreaticoduodenectomy; Palliative: palliative surgical bypass

cholangiocarcinoma and sigmoid colon cancer. The last patient had intrahepatic cholangiocarcinoma and cholangiocarcinoma arising in the CC (type I).

Despite undergoing curative surgery, the patients with cancer had a poor overall survival. Four patients (80%) died at 2, 20, 35, and 40 months after surgery due to disease recurrence. Only one patient survived without evidence of disease after 67 months of follow-up. Furthermore, all patients who had an unresectable disease died within a year of surgery. In the case of the patient who developed intrahepatic cholangiocarcinoma during surveillance, she had not experienced any disease recurrence as at 12 months after a right hepatectomy.

The patients with cancer were significantly older than those without cancer (mean age ± SD: 54.9 ± 14.2 vs 35.8 ± 15.7 years; $p < 0.001$). The levels of CA 19-9 and CEA in the patients with cancer were also higher than in those without cancer, but the differences were not statistically significant. A univariable analysis identified that the two risk factors associated with cancer in these patients was an age above 40 years and a significant weight loss before surgery.

The operations were mostly performed in an elective setting. However, six patients (12.5%) had urgent surgery after improvement of acute cholangitis in the same admission. These patients had significantly more blood loss (1,064 ml vs 465 ml; $p = 0.034$) and usually required more blood transfusion (1.2 units vs 0.2 units; $p = 0.013$). On the other hand, the urgent operations did not affect the patients' post-operative morbidity or long-term survival.

The overall post-operative complication rate was around 54%, with half of the complications being minor (such as surgical site infection, at 23%). A comparison of the patients with and without cancer revealed that the overall complications were quite similar, except that there was a significantly higher rate of intrabdominal collection in the cancer group (33% vs 8%; $p = 0.03$). The complication rates and surgical outcomes of the patients with and without cancer are presented in Table 3.

The 5-year overall survival rate of the cohort was 68%. The factor affecting the overall survival was the coexisting cancer ($p < 0.001$). In the case of the patients with cancer, the 1-year and 5-year overall survival rates were 58.3% and 20%, respectively, whereas for the patients without cancer, the corresponding rates were 96.7% and 88.4% (Fig 1).

TABLE 3. Surgical outcomes and post-operative complications of patients with and without malignancy.

Parameters	Total	%	Non-CA	%	CA	%	P
Operation type							0.94
Elective	42	87.5	31	86.1	11	91.7	
Urgent	6	12.5	5	13.9	1	8.3	
Cyst size (mean ± SD; cm)	4.6 ± 3.6		4.8 ± 4.1		4.1 ± 2.2		0.55
Operative time (mean ± SD; min)	235 ± 14		235 ± 13		234 ± 44		0.96
EBL (mean ± SD; ml)	541 ± 95		575 ± 118		431 ± 125		0.52
PRC transfusion (mean ± SD; units)	0.36 ± 0.87		0.42 ± 0.94		0.18 ± 0.60		0.44
Length of stay (mean ± SD; days)	11.5 ± 9.0		10.5 ± 6.4		14.7 ± 14.5		0.18
Complications	26	54.2	6	50	8	66.7	
Anastomosis stricture	4	8.3	4	11.1	0	0.0	0.23
Bile leakage	5	10.4	5	13.9	0	0.0	0.17
Vascular injury	4	8.3	3	8.3	1	8.3	1.0
Wound infection	11	22.9	8	22.2	3	25.0	0.84
Intra-abdominal collection/abscess	7	14.6	3	8.3	4	33.3	0.03
Cholangitis	6	12.5	4	11.1	2	16.7	0.61
Pancreatitis	2	4.2	2	5.6	0	0.0	0.40
Pseudoaneurysm	1	2.1	0	0.0	1	8.3	0.08
Pancreatic fistula	4	8.3	2	5.6	2	16.7	0.23

Abbreviations: Non-CA: no malignancy; CA: malignancy; EBL: estimated blood loss; PRC: packed red blood cells

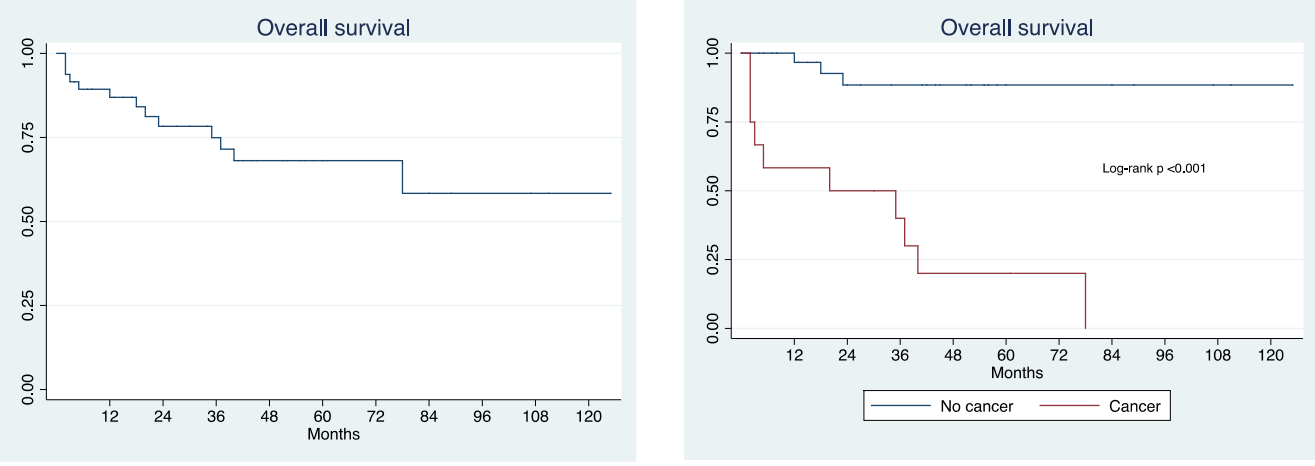

Fig 1. Overall survival estimates of all patients (A), and a comparison between patients with and without cancer (B).

DISCUSSION

In this single-center study, we describe a series of CCs, which is not a common disease, especially in adults. Patients usually present with recurrent, self-limited, abdominal discomfort at the beginning without any other symptoms. Therefore, they are often misdiagnosed with dyspepsia until they develop more obvious clinical symptoms related to, for example, obstructive jaundice or cholangitis. As abdominal ultrasonography sometimes misses the identification of a cystic dilatation of bile duct, there were some patients in our series who had undergone a cholecystectomy before definitive surgery (29.2%). Moreover, the average time to definite surgery was quite long at about 49.7 months. Due to the late diagnosis, the patients in the current study had a high incidence of CBD and IHD stones; this was in concordance with many previous studies comparing CCs in adults and children.[8,9,18]

Many previous studies have reported that the malignancies occurring in CC patients are cholangiocarcinoma and gallbladder cancer.[10,11,17-23] The reported incidence rate of synchronous biliary tract malignancy ranges from 7% to 23.5%.[6,10,11,17-23] Our series saw a similar high incidence of concomitant cancer (25%), especially in patients aged more than 40 years, which may result from late diagnosis. Our results support previous studies that found a higher age is associated with a higher cancer incidence.[7,23] It is noteworthy that our series found no coexisting gallbladder cancer, which may be due to the high incidence of prior cholecystectomy.

Cholangiocarcinoma can subsequently develop in about 0.6%-5.4% of cases, even after curative surgery, as described in numerous other reports.[6,10,11,17,18,20] This is consistent with our finding that one patient (2%) with a type I CC developed intrahepatic cholangiocarcinoma 18 months after cyst excision and hepaticojejunostomy. Therefore, continued surveillance is advocated in every patient after definitive surgery. Interestingly, we also found some CC patients presented with pancreatic adenocarcinoma and colonic carcinoma. CCs may increase the risk for other types of cancer without a clear pathogenesis. This issue warrants further investigation.

The management of a CC type IVa is more complex and still controversial. At our institution, it is managed in two ways: cyst excision and hepaticojejunostomy, with or without a hepatectomy. The indications for hepatectomy in unilobar disease are hepatolithiasis, atrophy, or suspected malignancy. A unilobar cystic dilation only is not an indication for hepatectomy. As to bilobar involvement, hepatectomy is performed only on liver segments that have hepatolithiasis, lobar atrophy, or a suspected malignancy. During surveillance, three patients with additional liver resection were symptom-free after a mean follow-up of 63 months. Seven patients without an indication for hepatectomy also had no symptoms after a mean follow-up of 15.6 months. Nevertheless, it was difficult to compare the outcomes of the two groups because of the markedly different mean follow-up times. This study has some limitations due to its retrospective nature and the small patient population. The follow-up duration was not long enough to enable conclusions to be drawn on the cumulative risk of cancer and hepatolithiasis developing after surgery. A larger series with a long-term follow-up, such as a multi-center study or a national registry, is therefore still needed.

CONCLUSION

The adult CCs had a high incidence of associated malignancy. The factors predicting a coexisting malignancy were an age above 40 years and a significant weight loss. If cancer occurred, the overall survival was significantly poor. Even after definitive surgery, patients still need life-long surveillance for cancer.

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