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Topics: Carcinogenesis in congenital malformatious of the biliary ductal system

Bile duct cancer developed after cyst excision for choledochal cyst

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Abstract: Oncogenesis after cyst excision for choledochal cyst and suitable surgical procedures for this operation are discussed. The clinical data of 23 patients with cancer of the biliary tree after excision of choledochal cyst reported in the English-language and Japanese literature were reviewed, and data for 1353 Japanese patients with choledochal cyst and/or pancreaticobiliary malunion were analyzed. In the 23 patients reported in the literature, age at cyst excision ranged from 1 to 55 years (average, 23.0 ± 13.7 years), and cancers were detected at age 18–60 years (average, 32.1 ± 12.2 years), with intervals between cyst excision and cancer detection of 1–19 years (average, 9.0 ± 5.5 years). Sites of cancer development were: intrahepatic, six; anastomotic, eight; hepatic side residual cyst, three; and the intrapancreatic duct, six. In the Japanese patients with choledochal cyst and/or pancreaticobiliary malunion, the incidence of cancer associated with primary choledochal cyst and/or pancreaticobiliary malunion was 16.2% (219/1353). The incidence of cancer development after cyst excision in this population, of whom 1291/1353 underwent surgery, was assumed to be 0.7%. Nearly half of the 23 patients in the literature had undergone inadequate cyst excision. Oncogenesis of cancers after cyst excision is possibly different from that of choledochal cysts.

Key words: choledochal cyst, postoperative complications, bile duct neoplasms

Introduction

Choledochal cyst is frequently associated with bile duct carcinoma. Total cyst excision has been recommended as the best surgery to prevent malignant changes, and is now the worldwide standard procedure for the treatment of choledochal cyst. However, reports of bile duct cancer after cyst excision are gradually increasing. If cancers develop frequently in the remnant biliary tree after cyst excision, the reconstruction technique should be revised. The aim of this study was to investigate oncogenesis after cyst excision by analyzing reported late malignant complications after cyst excision. Suitable surgical procedures for this troublesome disorder are also discussed.

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Patients

Twenty-eight patients have been reported in the English-language and Japanese literature as having cancer of the biliary tree after excision of a choledochal cyst. Five of these patients were excluded from this analysis because of inadequate clinical data, pancreatic cancer, or because of improper surgery for choledochal cyst. The clinical data from 23 patients[1–21] was the subject of this analysis.

We also analyzed data from 1353 patient with choledochal cyst and/or pancreaticobiliary malunion in Japan, collected over 8 years between 1990 and 1997, offered by courtesy of the Committee of the Japanese Study Group on Pancreaticobiliary Maljunction (JSPBM).

Results

Cancer after cyst excision

The clinical data of 23 patients with bile duct cancer which developed after cyst excision for choledochal cyst are summarized in Table 1. Nineteen patients were from Japan and 4 were from other countries. Ages at cyst excision ranged from 1 to 55 years, with an average of 23.0 ± 13.7 years. Bile duct cancers were detected at age 18–60 years (average, 32.1 ± 12.2 years) with intervals of 1 to 19 years (average, 9.0 ± 5.5 years) after cyst

Table 1. Bile duct carcinomas that developed after cyst excision

Patient number	Sex	Type	Age at internal drainage (years)	Age at cyst excision (years)	Procedures of the operation	Complications after cyst excision	Age at cancer detection (years)	Interval between cyst excision and cancer detection (years)	Year reported
Carcinomas developed in the intrahepatic bile duct									
1	F	?	—	19	Ex, HD jejunal interposition		20	1	1987[1]
2	M	I	—	26	Ex, HJ		29	3	1990[2]
3	F	I	—	47	Ex, HJ	Cholangitis, gallstone	54	7	1984[3]
4	F	IV-A	36	51	Partial Ex, CJ	None (cholangitis before excision)	58	7	1972[4]
5	M	?	11	32	Ex, HJ	Cholangitis	42	10	1994[5]
6	F	IV-A	—	21	Ex, HJ	Cholangitis, gallstone	38	17	1982[6]
Carcinomas developed in the hepatic duct at or near anastomosis									
7	M	I	—	21	Ex, HJ with Brown	None	25	4	1967[7]
8	M	?	—	18	Ex, HJ		23	5	1990[8]
9	F	I	—	55	Ex, HJ	None	60	5	1996[9]
10	F	IV-A	—	40	Ex, HJ	None	45	5	1997[10]
11	F	IV-A	—	27	Ex, HJ	Gallstone	33	6	1987[11]
12	M	IV-A	—	10		Cholangitis, anastomotic stricture	25	15	1978[12]
13	M	IV-A	—	20	Ex, HJ	Cholangitis	35	15	1988[13]
14	F	IV-A	—	1	Ex, HD	None	19	18	1998[14]
Carcinomas developed in the remnant choledochal cyst (hepatic side)									
15	F	?	—	16	Ex		18	2	1998[15]
16	F	?	—	15	Ex		24	9	1998[15]
17	F	?	—	16	Ex		35	19	1998[15]
Carcinomas developed in the intrapancreatic remnant bile duct or choledochal cyst									
18	F	?	—	24	Ex, HJ		28	4	1982[16]
19	F	I	—	17	Partial Ex		23	6	1985[17]
20		I	—	20	Partial Ex	Cholangitis	29	9	1984[18]
21	F	IV-A	—	11	Partial Ex, CJ		23	12	1988[19]
22	F	IV-A	—	14	Ex, HJ	None	27	12	1986[20]
23	M	?	—	8	Ex, HJ	None	25	17	1996[21]

Ex, Cyst excision; HJ, hepaticojejunostomy; CJ, choledochojejunostomy; HD, hepaticoduodenostomy

Table 2. Age distribution of patients with choledochal cyst and/or pancreaticobiliary malunion and cancer (registered in Japan, 1990–1997) and patients with cancer developed after cyst excision (present review of literature)

Age at operation (years)	Number of patients with choledochal cyst and/or pancreaticobiliary malunion	Number of patients with bile duct cancer	Incidence of cancer (%)	Number of patients with cancer after cyst excision
0–9	461	0	0.0	
10–19	88	0	0.0	2
20–29	130	3	2.3	12
30–39	106	6	5.7	4
40–49	135	34	25.2	2
50–59	156	62	39.7	2
60–69	123	53	43.1	1
70–79	63	31	49.2	
80–89	8	6	75.0	
Unknown	21	5	23.8	
Subtotal of operated patients	1291	200	15.5	
Not operated or treatment unknown	62	19	30.7	
Total	1353	219	16.2	23

excision. Of the 23 cancers, 5 developed within a 4-year interval after cyst excision, and 18 were detected at an interval of more than 5 years.

Cancers developed in all portions of the residual biliary tree: in the intrahepatic bile duct in six patients, at the hilar bile duct or the anastomosis in eight, in the hepatic side remnant cyst in three, and in the intrapancreatic bile duct or pancreatic side remnant cyst in six. Intrahepatic cancer developed in six patients with type I or type IV cysts. In this group, cholangitis and/or intrahepatic gallstone were reported in three patients in the period between cyst excision and cancer detection, and only one patient showed an uneventful postoperative course. Two of these patients had undergone internal drainage before the cyst excision. Of the eight patients with hilar or anastomotic site cancers, six patients had undergone hepaticojejunostomy and one had undergone hepaticoduodenostomy.

Cancer in choledochal cyst in Japan

In the 1353 patients registered at the JSPBM (1990–1997), primary cancers were found in 219 (16.2% of all patients; Table 2). The peak age distribution for cancer was in the 50s age group, and the rate of malignancies apparently increased with age from 2.3% in patients in their 20s to 75.0% in patients in their 80s. The age distribution of patients with cancer after cyst excision (age at cancer detection) is also tabulated in the Table 2. Cancers in these patients were most frequently detected in their 20s (12/23).

From 1990 to 1997, 1291 patients with choledochal cyst and/or pancreaticobiliary malunion underwent surgery in Japan, and during this period, 9 patients who developed cancer after cyst excision were reported. If this group of 1291 patients is postulated as the population for post-excision malignancies, the rate of cancer after cyst excision is 0.70% (9/1291).

Discussion

Although carcinogenesis associated with choledochal cyst is still unresolved, various oncogenous factors have been proposed by numerous investigators. Stagnant bile in the dilated biliary tract is easily infected or denaturalized, and generates unconjugated secondary bile acids, which act as mutagens, resulting in metaplasia and carcinoma of the cyst wall.[22] Choledochal cysts are frequently associated with pancreaticobiliary malunion, especially in almost all types I and IV-A.[23] Pancreatic juice mixes with infected or denaturalized bile in the choledochal cyst, and pancreatic enzymes (trypsin, elastase I, and phospholipase A_2) are activated by the presence of enterokinase, which is produced by the metaplastic epithelial cells on the cyst wall.[24,25] The presence of a low-molecular-weight mutagen in the biliary tract in this situation has recently been reported.[26] These harmful substances possibly initiate malignant change and promote cancer development on the cyst wall.[23]

Cyst excision[27,28] or total resection of the extrahepatic bile duct[29] have been recommended as the best procedure for treatment of choledochal cyst. This procedure provides two advantages in preventing subsequent cancer development in the bile duct; removing the portion

most frequently affected by cancer,[23] and separating bile and pancreatic juice flow to avoid extraintestinal mixture of the fluids. If bile and pancreatic juice flow into the intestine separately, the hazardous mixture in the bile duct can be eliminated. However, cancers arising from the residual biliary tree have occasionally been reported.

Cancer in the intrahepatic bile duct

Six of the 23 patients in the literature were reported as having cancer in the intrahepatic bile duct. In 2 of these patients, the intervals between cyst excision and cancer detection were short; 1 and 3 years, respectively. Cancers in these 2 patients had possibly already developed at the time of cyst excision.

The remaining 4 patients underwent hepatico- or choledochojejunostomy. Pancreatic juice and bile could mix at the bifurcation of the Roux-en-Y loop, far from the site of cancer development. Three of the remaining 4 patients showed evidence of bile stasis; cholangitis and/or intrahepatic gallstones, caused by an anastomotic stricture. Activated pancreatic enzymes could not be regurgitated into the intrahepatic duct. Oncogenesis in this situation would be different from that of choledochal cyst. Infected bile stasis and gallstones are possibly responsible for the malignant change in this group,[30] as in ordinary cholangiocarcinoma without malunion. An operative technique to prevent the anastomotic structure is the choice of treatment, and creating a wide stoma at the hepatic hilum is recommended.[31,32] Release or excision of the stenosis at the bifurcation of the bilateral hepatic duct to prevent subsequent stone formation should be emphasized.[33,34]

Two patients in this group had undergone internal drainage, 15 and 21 years before the cyst excision, respectively, and cancer developed 22 and 31 years after the internal drainage (7 and 10 years after the cyst excision). Internal drainage deals with a precancerous situation.[35] Initiation of cancer probably occurred before the cyst excision, and the cyst excision may have prolonged the interval before development by eliminating the promoter.

Cancer at the hepatic hilum or anastomotic site

Cancers at the hepatic hilum or at the anastomotic site were found in 8 of the 23 patients in the literature. The bile duct epithelia are exposed to the intestinal contents, a mixture of bile and intestinal fluid. Pancreatic juice is assumed to be absent when a reconstruction is performed by Roux-en-Y jejunostomy. However, when the hepatic duct is anastomosed to the duodenum, the biliary epithelia will be immersed in the mixture of food, bile, pancreatic juice, and intestinal fluid. This situation is identical that seen after internal drainage. The present series revealed that 6 patients with hepaticojejunostomy and 1 patient with hepaticoduodenostomy developed cancer at the anastomotic site or at the hepatic hilum. According to the registered data from the JSPBM in 1996, the jejunum was used for the biliary reconstruction in 76 patients and the duodenum was used in 9 (ratio, 8.4:1).[36] The difference was not statistically significant (Fisher's exact probability test; $P = 0.566$). Although no difference between these two reconstructive methods was shown at this time, further follow-up study is mandatory, because a long-term follow-up is necessary to evaluate the results of the operation. In patient 14, cancer developed 18 years after cyst excision and hepaticoduodenostomy.

Cancer in the residual cyst or bile duct

Cancer developed in the hepatic side residual choledochal cyst in 3 of the 23 patients in the literature. Although details of the reconstruction were not provided, the cyst excision was obviously inadequate. Complete removal of the cyst most frequently affected by cancer is mandatory.

Cancer developed in the pancreatic side residual cyst or the intrapancreatic bile duct in 6 of the 23 patients. In patient 18 (aged 28 years of cancer detection), a retrospective study revealed mucosal cancer of the specimen obtained from the initial surgery 4 years previously. A short interval, of less than 5 years, is likely to be inadequate to eliminate the possibility of the existence of cancer at cyst excision.

In this group, the major cause of cancer development was the leaving of the distal choledochal cyst or bile duct. The intrapancreatic portion of the distal choledochus is sometimes transected at the pancreatic margin to avoid injury to the pancreatic parenchyma.[37] This technique is obviously inadequate to prevent subsequent cancer development in this part. The distal choledochus must be completely removed at the level of confluence with the pancreatic duct.[29,33] In patients with cystic dilatation, complete removal of the distal choledochus is easy; however, in those with fusiform or cylindrical dilatation (type Ic), complete removal is sometimes difficult, especially when the common channel with the pancreatic duct is dilated. Utilization of endoscopy or hemostatic clips to mark the transection level, with repeat intraoperative cholangiography of this area, is helpful for complete removal of the distal bile duct without pancreatic duct injury.[33,38]

Carcinogenesis in this situation still remains obscure. Only pancreatic juice, not a bile mixture, refluxes into the remnant distal bile duct. The carcinogenesis may be different from that of primary choledochal cyst.

Incidence of cancer development after cyst excision

Reported incidences of cancer associated with primary choledochal cyst have increased from 2.5% in 1977[39] to 15.6% in 1984[40] and 14.5% in 1985.[41] Recent registered data from the JSPBM, collected between 1990 and 1997 in Japan, revealed that the incidence of cancer in association with choledochal cyst and/or pancreaticobiliary malunion was 16.2% (219/1353). This incidence was calculated from a population of patients with pancreaticobiliary malunion with or without choledochal cyst. Therefore, the incidence is higher than the incidence based on patients with choledochal cyst only, because the incidence of cancer in patients with pancreaticobiliary malunion without choledochal cyst is much higher than that in patients with cyst.[41] The incidence of cancer associated with primary choledochal cyst based on large series by several authors, including this report, was stable at around 15% in these 15 years, and this is likely to be the actual incidence of cancer associated with choledochal cyst in Japan.

We assumed the incidence of cancer development after cyst excision to be 0.7%. Although this incidence was still markedly higher (approximately 200 times) than the incidence of biliary cancer in the general population in Japan,[23] the incidence was far less (about 1/20) than that of primary choledochal cyst. Therefore, complete cyst excision was effective in reducing malignant transformation in the biliary tree. We believe that nearly half of the cancer cases after cyst excision could be prevented, or at least could be decreased, if cyst excision was carried out correctly or adequately, as described above.

In summary, carcinogenesis after cyst excision may be different from that of choledochal cyst. However, the hazardous effect of the bile and pancreatic juice mixture is likely to be maintained for a long period even after the bile and pancreatic flow line is separated by cyst excision and biliary reconstruction.

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