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Can Endoscopic Sphincterotomy and Bilio-Enteric procedures promote late cholangiocarcinoma occurrence?

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ABSTRACT

Background & Aim

The ablation of the sphincter of Oddi causes bilioenteric reflux that could promote development of bile duct cancer. Aim of this review is to present the currently published reports on late cholangiocarcinoma development after endoscopic sphincterotomy and trans-duodenal sphincteroplasty/bilioenteric procedures.

Methods

An extensive search was performed in Pubmed, Google scholar databases, for publications including the title phrases “late cholangiocarcinoma (or bile duct cancer) +/- after endoscopic sphincterotomy +/- after bilioenteric procedures”. Furthermore, we reviewed the currently published studies examining the changes on biliary/choledochal epithelium after performing endoscopic or surgical sphincterotomy and bilioenteric procedures.

Results

Eighteen case reports, 2 retrospective human trials and several experimental animal trials address the issue of late cholangiocarcinoma after surgical sphincteroplasty/bilioenteric procedures. Three population-based studies examine the risk of late bile duct cancer after endoscopic sphincterotomy. Several other publications studying the sphincter function and bilioenteric reflux complications were also reviewed.

Conclusions

The available evidence demonstrates a clear correlation of cholangiocarcinoma and bilio-enteric procedures. On the contrary, large population-based studies failed to show a relation between ES and late bile duct malignancy.

KEYWORDS: Cholangiocarcinoma, Biliary Reflux, Bilio-Enteric Anastomosis, Surgical Sphincteroplasty, Endoscopic Sphincterotomy

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy (ES) of the Oddi sphincter was first introduced in 1974 in Germany and Japan [1, 2]. ES represented an alternative way to remove common bile duct stones (CBDS) compared to open surgery and offered the advantage of reducing the associated morbidity of the surgical procedures [3]. During the first years it was mainly used in elderly patients or patients with severe comorbidity, but with

the introduction of laparoscopic cholecystectomy, ERCP with ES became the most common procedure in the treatment of CBDS [4]. Today, a wide variety of biliary and pancreatic disorders can be treated with ERCP and ES [5]. As a result of that, an increasing number of young patients with a long life expectancy will undergo ES, and this raises concern about the long-term complications of the procedure and especially about the late development of cholangiocarcinoma [6]. Furthermore, the ablation of sphincter function seems to promote the late development of cholangiocarcinoma after open bilio-enteric procedures (BEP) such as choledochoduodenostomy and hepaticojejunostomy, and transduodenal sphincteroplasty (TS) [18,19]. Aim of this review is to present the currently published reports on the late development of cholangiocarcinoma after ES and TS/BEP.

METHODS

In this review we considered the disruption or by-pass of the Oddi sphincter a common primary incident among endoscopic and surgical procedures and for that reason both surgical and endoscopic trials involving late bile duct cancer are included and discussed in this review. An extensive search was performed in Pubmed, Google Scholar databases, for publications including the title phrases "late cholangiocarcinoma (or bile duct cancer) +/- after endoscopic sphincterotomy +/- after bilioenteric procedures". Furthermore, in order to have a complete picture on biliary carcinogenesis process we reviewed the currently published studies that examine the changes on biliary/choledochal epithelium after performing TS/BEP and ES. Statistics performed with Minitab version 16.

RESULTS

Published case reports. The risk of malignant transformation of the biliary tract as a result of sphincteroplasty or by-pass of the sphincter of Oddi was first introduced by several reports that described the occurrence of cholangiocarcinoma after open bilio-enteric drainage procedures (Table 1). A total cohort of 18 cases has been published, 3 men and 11 women with median age 65, 5 years (SD 8, 5).

Author/year	Sex	Age	Type of prior biliary-enteric operation	Tumor location	Time interval from biliary-enteric operation to malignancy presentation
Shields HM (1977)	Male	49	Pancreatoduodenectomy	Adenocarcinoma (Biliary or pancreatic origin unknown)	14
Haratake et al (1983)	Female	54	Choledocho-jejunostomy	Adenocarcinoma of the intrapancreatic common bile duct remnant	9
Leborgne et al (1984)	?*	?*	Choledocho-duodenostomy	Cholangiocarcinoma above the anastomosis	?*
	?*	?*	Choledocho-duodenostomy	Cholangiocarcinoma above the anastomosis	?*
Herba et al (1986)	Male	64	Choledocho-enteric anastomosis	Cholangiocarcinoma at the anastomosis with upwards extension	17
	Female	52	Choledocho-duodenostomy	Cholangiocarcinoma at the anastomosis	10
Perez et al (1994)	?*	?*	Cholecysto-jejunostomy	Adenocarcinoma at the gallbladder	11
	?*	?*	Cholecystectomy-choledochoduodenostomy	Cholangiocarcinoma	3
Schumacher et al (1997)	Female	71	Cholecystectomy-choledochoduodenostomy	Cholangiocarcinoma at the anastomosis	38
Strong et al (1999)	Female	71	Roux-en-Y jejunal loop	Cholangiocarcinoma at the left hepatic duct and dysplasia at the right hepatic duct	40

	Female	66	Roux-en-Y jejunal loop	Cholangiocarcinoma at the confluence of hepatic ducts	25
	Female	57	Choledocho-duodenostomy	Cholangiocarcinoma at the confluence of hepatic ducts	27
Bettschart et al (2002)	Female	51	Choledocho-duodenostomy	Cholangiocarcinoma at the anastomosis	26
	Female	73	Choledocho-enteric anastomosis	Multifocal cholangiocarcinoma	39
	Male	72	Choledocho-duodenostomy	Cholangiocarcinoma at the confluence of hepatic ducts	15
Maeda et al (2003)	Female	67	Choledocho-duodenostomy	Cholangiocarcinoma at the anastomosis	21
Padilla et al (2004)	Female	65	Pancreatoduodenectomy (malignant ampullary carcinoma)	Cholangiocarcinoma at the anastomosis with upwards extension	8
Lee et al (2004)	Female	68	Cholecystectomy-choledochoduodenostomy	Cholangiocarcinoma at the anastomosis	12

?*: insufficient data in English language

Table 1: Case reports of late cholangiocarcinoma occurrence after bilio-enteric operations.

A prior biliary-enteric operation for benign disease had been performed in 17 cases. There was only one case with prior pancreatoduodenectomy for ampullary carcinoma. Sixteen patients had undergone choledocho-enteric anastomoses and two patient's pancreatoduodenectomy. Adenocarcinoma of the bile ducts and the gallbladder has occurred after a mean period of 19, 7 years (SD: 11). In seven cases cholangiocarcinoma arose exactly at the site of the biliary-enteric anastomosis. In all the reported cases a positive histological confirmation was obtained. In most of the cases a poor clinical outcome has been reported.

Human trials after surgical bilio-enteric procedures

There are only two published retrospective trials that specifically examine the late development of bile duct cancer after surgical bilio-enteric procedures.

Hakamada et al in 1997 published the first retrospective trial that examined the late development of cholangiocarcinoma after TS [18]. A total cohort of 108 patients, 52 men and 56 women with a median age of 57 years (30-78) that underwent TS was followed for a median period of 18 years. Indications

For the procedure were benign biliary and pancreatic disorders. At the time of operation the absence of bile duct cancer was confirmed in all cases by means of operative exploration, preoperative or intra-operative direct cholangiography, postoperative T-tube cholangiography or cholangioscopy. Patency of the TS was confirmed with upper gastrointestinal series in 75 patients at 5 to 7 years after the operation.

During follow-up 8 cases (7, 4%) of primary bile duct cancer, six men and two women with a median age of 60 years were diagnosed in a period of 15 months to 20 years after sphincteroplasty. Patency of the TS was confirmed in all cases and only two out of eight patients had intrahepatic gallstones. Pathologic specimens were evaluated in seven cases and all of them had fibrous thickening of the ductal wall, inflammatory cells infiltration, proliferation of glandular elements and atypical hyperplastic lesions. Although three patients underwent curative resection for the tumors, all eight patients died of cancer or cancer recurrence within 8 months after the diagnosis.

Tocchi et al in 2001 presented the largest published trial about the late development of bile duct cancer after BEP and TS [19]. A total number of 1003 of patients, 374 men and 629 women that underwent TS and BEP (choledochoduodenostomy and hepaticojejunostomy) for benign disease were retrospectively examined for the late development of bile duct cancer. Indications for the procedure were stratified in three categories: choledocholithiasis, sphincter of Oddi stenosis and postoperative benign strictures. Follow-up was obtained from medical records and patient interviews or telephone communications. Mean follow-up period was 10.8 years. The presence and frequency of postoperative cholangitis was also recorded.The results demonstrated the development of late bile duct cancer in 55 patients (5, 5%) between 11 and 19 years after the biliary operation. The incidence of cholangiocarcinoma was higher (7, 6%) in choledochoduodenostomy patients

and lower (1, 9%) in hepaticojejunostomy patients. Multivariate analysis confirmed cholangitis as the only independent factor affecting the incidence of cholangiocarcinoma. Only 12 out of 55 patients underwent curative resection and all of them died because of tumor recurrence within 9 months.

Animal trials after surgical bilio-enteric procedures

There are several animal trials that examine the development of cholangiocarcinoma after bilio-enteric procedures.

Experimental animal trials

Since 1950 many investigators have attempted to produce carcinomas in the biliary tree of animals in order to explore and clarify the mechanisms of carcinogenesis [20]. Several laboratory animals have been used including hamsters [21-23] mice [24], dogs [25,26] and cats [26], but the results were less than satisfactory in inducing extrahepatic cholangiocarcinoma.

Chemically induced cancer in animal models

Tajima et al in 1994 were the first to publish a well-described method of inducing extrahepatic biliary carcinoma [27]. Female Syrian golden hamsters were first subjected to cholecystoduodenostomy with dissection of the extrahepatic bile duct at the distal end of the common duct (CDDB) and were, 4 weeks later, treated with weekly subcutaneous injections of N-nitrosobis (2-oxopropyl) amine (BOP), a carcinogen synthesized for the study purpose. A control group was also present were the hamsters underwent simple laparotomy (SL). The results showed a statistically higher incidence of cholangiocarcinoma and gallbladder carcinoma in the CDDB group than in the sham-operated controls. *Immunohistochemical staining demonstrated that the CDDB procedure greatly accelerated the cell kinetic activity of the biliary epithelium and this was considered a major factor promoting carcinogenesis.*

The same research group studied weather the bilioenterostomy type influenced the cholangiocarcinoma incidence in hamsters given BOP [28]. In a comparison of cholecystoduodenostomy (CD) versus cholecystoileostomy (CI) with dissection of the extrahepatic bile duct, the CD group favored extrahepatic cholangiocarcinoma while the CI group promoted mostly intrahepatic cholangiocarcinoma.

Ogura et al, in a study with BOP-induced cholangiocarcinoma in Syrian hamsters, demonstrated the relationship of pancreatic juice reflux into the biliary tract with the development of biliary cancer [29]. Similarly, two more animal trials with BOP-induced cholangiocarcinoma in Syrian hamsters, clearly demonstrated a strong connection between inflammation and carcinogenesis [30, 31]. In both studies, persistent cholangitis and interleukine-6 expression on the biliary epithelium accelerated malignant transformation. Tajima et al, in a BOP-induced hamster model demonstrated atypical papillary hyperplasia present within the tumor mass, in 40% of early carcinomas [32]. The authors supported an adenoma-carcinoma sequence in most polypoid tumors of the extrahepatic bile ducts.

The model of BOP-induced cholangiocarcinoma in Syrian Hamsters was used in two more trials that showed the enhancement of biliary malignancy by cholecystokinin and tauroursodeoxycholate administration [33,34]. In similar trials, several chemopreventative agents have been tested and proved efficient in reducing the cholangiocarcinoma incidence [35-37].

Spontaneous biliary carcinogenesis in animal models

Kitajima et al, in 2003 published an interesting paper regarding spontaneous biliary carcinogenesis in hamsters [38]. The aim of this study was to determine whether bilioenterostomy influences biliary carcinogenesis. Syrian hamsters were subjected to three different surgical procedures: simple laparotomy (SL), choledochoduodenostomy (CD) and choledochojejunostomy (CJ). No carcinogens were given and subjects were killed in a period of 20 to 120 weeks after surgery. The incidence of biliary carcinoma was significantly higher in the bilioenterostomy groups, especially in the CJ group (P< 0, 05) versus SL group. Persistent cholangitis and bile stasis were frequent in the bilioenterostomy groups. The proliferative cell nuclear antigen (PCNA) labeling index was also higher in the bilioenterostomy groups.

Trials after endoscopic sphincterotomy

The long-term risk of malignancy in the bile ducts, liver and/or pancreas following ES for benign disease was specifically examined by three population-based trials, two from Sweden and one from Denmark, (Table 2) [39-41].

Karlson et al in 1997 published the first population study that examined the cancer risk and relative survival following sphincterotomy for stones in the common bile duct [39]. A total cohort of 992 patients who underwent ES for stones in the common bile duct between 1977 and 1985, where followed through the Swedish Cancer Register and Swedish Death Register. End points were diagnosis of cancer (liver, gallbladder, bile ducts and pancreas), death or until 31 December 1992 (median 10 years). Statistical analysis calculated the expected number of cancers in the general population of Sweden

and a comparison was made by calculating the standardized incidence ratio (SIR). The results demonstrated 29 cancers within the first year after ES that were excluded from subsequent analysis as the authors considered them microscopic cancers not yet detectable or missed at the time of ES. After the first year only five cancers were diagnosed while at least six (SIR 0,80) were expected, hence no increased risk of malignancy after ES was identified.

Author/ year	Study design	No Patients		No of patients with malignancy (%)					
		ERC+ES Group	ERC (no ES) Group	ERC+ES Group			**ERC (no ES) Group**		
				1st year	2nd year	3rd + years	1st year	2nd year	3rd + years
Karlson et al (1997)	Population-based study	992		29[1] **(2,9%)**	5[1] **(0,5%)**		-	-	
Mortensen et al (2008)	Population-based study Case-control study	10690	10690	40[2] **(0,37%)**	7[2] **(0,06%)**	15[2] **(0,14%)**	42[2] **(0,39%)**	1[2] **(0,01%)**	6[2] **(0,06%)**
Stromberg et al (2008)	Population based study Control group	12629	15385		66[3] **(0,5%)**		156[3] **(1%)**		

Table 2: Three population-based studies assessing the risk of bile duct cancer after endoscopic sphincterotomy

[1]Malignancy of the gallbladder, liver, bile ducts and pancreas

[2] Cholangiocarcinoma

[3] Malignancy of the liver, bile ducts and pancreas

Mortensen et al published a large population-based, case control study in 2008 that specifically addressed the long-term risk of cholangiocarcinoma after ES [40]. The authors used data from Danish health-care registries and examined the incidence of cholangiocarcinoma after endoscopic retrograde cholangiography (ERC) for 10690 ERC patients who underwent ES between 1977 and 2003 and 10690 ERC patients who did not undergo ES. A control group from the general population of Denmark was matched with the total cohort of ERC patients by sex and birth year. The patients of the two groups (ES vs. non-ES) were matched for age, sex, year and indication of ERC and risk factors for malignancy. The median age of all patients at ERC was 67 years.

During follow-up, 7791 patients (36%) died and 111 patients (0,52%) were diagnosed with cholangiocarcinoma. In the matched control subjects from the general population, the cholangiocarcinoma incidence rate during follow-up period was 12 per 100.000 person-years.

The authors calculated the cholangiocarcinoma diagnoses per 100000 person-years for the first, second, third to fifth, and over fifth year after ERC in both groups. The results showed increased rates of cholangiocarcinoma during the first year in both groups (404/100000 in ES group vs. 458/100000 in the non-ES group). During year 2 and years 3-5 after ERC, the cholangiocarcinoma incidence rate for non-ES patients was similar to the general population rate (12 and 10, respectively, vs 12 per 100000 person-years), whereas the rate for the ES group remained elevated (79/100000 for second year and 42 for third to fifth year). More than 5 years after ERC, the cholangiocarcinoma incidence rate for ES patients was similar to that of the non-ES patients (27 vs 19 per 100000 person-years) and slightly higher for the matched population control subjects (12 per 100000 person-years). The authors concluded that the similar incidence rates of cholangiocarcinoma after the fifth year in the ES, non-ES group and general population exclude sphincterotomy as a risk factor of bile duct malignancy.

The third large population-based study from Sweden was also published in 2008 [41]. A total of 27708 patients undergoing ERCP for benign disease from 1976 through 2003 were included in the cohort. ES was performed in 12629 of these and follow-up was obtained through the Swedish Cancer Register to a diagnosis of malignancy, death or emigration. Statistical analysis calculated the expected number of cancers in the general population of Sweden and a comparison was made. The authors excluded all patients who had a diagnosis of malignant or benign tumor in the bile ducts, liver, or pancreas at the time of the procedure or within 2 years after ES. A total of 66 out of 12629 patients with malignancy of bile ducts, liver, or pancreas excluding gallbladder, occurred in the ES group within a mean follow-up period of 5, 9 years. In the non-ES group, malignancy occurred in 156 out of 15385 patients for a mean follow-up period of 10, 4 years. The analysis demonstrated approximately a 3-fold increase in the incidence of malignancy compared with the general population, with no significant difference between the ES and non-ES group. The authors concluded that the risk of malignancy in the bile ducts, liver, or pancreas is elevated after ERCP in benign disease but ES does not seem to affect this

risk. There are also several retrospective series that examine the late complications of ES [42-44]. In all of them except one, there is no evidence of late development of cholangiocarcinoma after ES. Only one trial by Tanaka et al reports the late occurrence of cholangiocarcinoma [45]. In this trial, a total cohort of 410 patients that underwent ES was followed for a period of one month to 20 years. Biliary carcinoma was observed in 8 patients, 5 of them during the first year after ES and the rest 3 cases after one year. The authors considered biliary carcinoma as a late complication of ES.

DISCUSSION

The first reports on late cholangiocarcinoma development after bilio-enteric procedures were published in the late 70s. Shields et al were the first to report in 1977 the occurrence of an adenocarcinoma in a 49 year-old man, at the choledochoenteric anastomosis 14 years after pancreatoduodenectomy for benign disease [7]. Haratake et al in 1983 presented the late development of a common bile duct malignancy after bilio-enteric anastomosis [8]. The author stated for the first time that the occurrence of adenocarcinoma may be one of the late complications of previous choledochojejunostomy. Herba et al in 1986 went a step further and addressed a possible mechanism of carcinogenesis. The authors suggested that choledochochoenteric anastomoses are associated with intermitted chronic obstruction with bile stasis and recurrent inflammation, factors that may predispose in the development of cholangiocarcinoma.

After five years Eleftheriadis et al, in a very interesting trial, studied changes of the biliary epithelium in patients who underwent choledochi-duodenal anastomosis for benign disease, and hyperplasia of the biliary epithelium was demonstrated [46]. The same results and atypia of biliary epithelium were reported by Kurumado et al, in mice models with choledochi-duodenal anastomosis [47].

A more clear and definite relationship of bilioenteric procedures and late cholangiocarcinoma development was established after the publications of Hakamada and Tocchi [18,19]. The biggest strengths of Tocchi trial were the large cohort of up to 1000 patients and the long follow-up of approximately 10 years. The last one is of much importance as we now know that carcino¬genesis of the bile ducts is a very slow process that involves several cellular pathways such as growth autonomy, escape from senescence, unlimited replication, blockade of growth inhibitory signals, altered microenvironment and evasion of cell death [48]. Furthermore, this trial indicated that different types of anastomosis enhance the risk of late bile duct cancer.

The same results were reproduced by animal trials [28,29,38] and that strengths the assumption that bilioenteric procedures are likely to increase the risk of late bile duct cancer. As ES causes ablation of the sphincter of Oddi several authors raised concern about the risk of late development of cholangiocarcinoma [49]. The three large population-based studies that specifically addressed this hypothesis demonstrated no clear relation between ES and late cholangiocarcinoma development.

Common facts in all three studies were the increased cholangiocarcinoma rate in the first post-ES year probably due to misdiagnosed malignancy at the time of ES and the similar cholangiocarcinoma rates in the ES and non-ES groups eventually. A point of special concern was noticed in the Denmark trial. Mortensen et al in their case-control study found that the cholangiocarcinoma rate was higher in the ES group compared with the non-ES group during the first five years. The authors justified these increased cases as possible misdiagnosed cholangiocarcinoma cases at the time of ES. But as they stated, it is unclear why undiagnosed cholangiocarcinomas might be more frequent among sphincterotomy patients. Overall, the similar cholangiocarcinoma rates in ES and non-ES groups after the fifth year led to the assumption that these malignancies could not be attributed to biliary reflux after sphincterotomy.

The function of the biliary sphincter after ES was specifically studied in a Dutch trial [50]. Bergman et al evaluated the sphincter function after ES and investigated if loss of sphincter function is associated with bacterial colonization, changes in bile composition, or inflammation of the biliary system. Eight patients who had undergone ES for bile duct stones 15 to 17 years were examined by means of biliary manometry, bile sampling, and biopsy. Results showed permanent loss of sphincter function in association with bacterial colonization, presence of cytotoxic components in the bile, and chronic inflammation of the biliary system.

Biliary reflux after ES was thoroughly studied in a well-designed trial from Japan [51]. Sugiyama et al studied the concentration of amylase in ductal bile, in 15 patients after ES and compared the results with a control group that did not undergo ES. Amylase concentration before ES was not different to the control group. Its concentration was increased 7 days after ES and then gradually decreased, returning to that before ES by the first year. In addition, bactobilia occurred in 60-80% of ES patients, although none developed acute cholangitis. The trial showed that ES causes transient pancreatobiliary reflux that is abolished after the first year and therefore is unlikely to increase the risk for development of biliary tract carcinoma as long as cholangitis or bile duct stones do not recur.

Recently, we have published a case-control study that examined the effects of ES on biliary epithelium [52]. We studied the changes in biliary epithelium of 25 patients with previous ES (median time 42 months) by means of classical and p-53 immunocytology. The conclusion was that ES causes biliary epithelial atypia that represents mostly reactive/proliferative rather than premalignant changes, mainly the first five years after ES.

The current evidence regarding sphincter function after ES is controversial. It looks like sphincter function is permanently lost after ES but bilio enteric reflux lasts only for a small period, possibly 1 year or less. That might explain the fact that almost all relative publications fail to demonstrate a positive relation between ES and cholangiocarcinoma. On the contrary, surgical sphincteroplasty clearly causes more extensive and long-lasting biliary reflux that promotes biliary inflammation

CONCLUSIONS

There are no randomized prospective trials concerning the possible correlation of bilio-enteric procedures and late bile duct cancer. Nevertheless, all the evidence from case reports, retrospective studies and animal trials show a clear correlation of cholangiocarcinoma and bilio-enteric procedures. On the contrary, large population-based studies do not show a correlation between ES and late bile duct malignancy.

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