Exp Biomed Res 2020; 3(4): 248-254 DOI: 10.30714/j-ebr.2020463616

EXPERIMENTAL BIOMEDICAL RESEARCH
http://www.experimentalbiomedicalresearch.com

Original Article

Cholelithiasis and gastrointestinal cancer: Is there a relationship that increases the risk of developing cancer?

Bahri Ozer[1] · Oguz Catal[1] · Songul Peltek Ozer[2] · Fatih Keyif[1] · Mustafa Sit[1] · Nuri Kama[1]

[1]*Department of General Surgery, Bolu Abant Izzet Baysal University, School of Medicine, Bolu, Turkey*

[2]*Department of Pathology, Bolu AIBU Training and Research Hospital, Bolu, Turkey*

ABSTRACT

Aim: To investigate the co-existence of cholelithiasis in patients with gastrointestinal (GI) cancer both in preoperative and postoperative periods.

Methods: We retrospectively analyzed the data of patients who underwent GI tract cancer surgery in the general surgery clinic of a university hospital between January 2013 and December 2019 for the presence of 'cholelithiasis' in the preoperative and postoperative periods. Age, gender, tumor type and localization and presence of the cholelithiasis in the patients were determined. In addition, the cases were divided into two as upper GI tract and lower GI tract according to tumor location and the relationship with cholelithiasis was evaluated.

Results: A total of 680 GI cancer patients were included in the study. Localization of GI cancers were; colon in 211 cases (31%), rectum in 195 cases (28.7%), gastric in 187 cases (27.5%), periampullary region in 55 cases (8.1%), and small intestine in 32 cases (4.7%). In the preoperative period, 69 (10.1%) patients were associated with cholelithiasis. Thirty-one (5.1%) patients had accompanying cholelithiasis in the postoperative period. Coexistence of cholelithiasis according to cancer location was not statistically significant in the preoperative and postoperative periods.

Conclusions: Our available data make it difficult to distinguish the roles of cholelithiasis on gastrointestinal cancers, because no statistically causal relationship was found between cholelithiasis and gastrointestinal cancers. However, the role of asymptomatic and symptomatic stones, which may or may not require cholecystectomy, in the development of GI tract cancers should not be ignored.

Keywords: Cholelithiasis, gallbladder diseases, cholecystectomy, gastrointestinal tract cancer.

✉ *Dr. Bahri Ozer*
Department of General Surgery, Bolu Abant Izzet Baysal University, School of Medicine, Bolu, Turkey
E-mail: bahriozer@hotmail.com
Received: 2020-03-20 / Revisions: 2020-04-13
Accepted: 2020-04-28 / Publication Date: 2020-10-01

Introduction

Cholelithiasis or gallstone disease is a common problem of the digestive system. It has an 11% to 36% prevalence in different series [1]. It is more common in females and after 40 years of age, and the risk of gallbladder stone increase 2 folds in the relatives of the patients with gallbladder stone [2]. Moreover, a history of gastrointestinal surgery also increases the risk of gallbladder stone disease [3]. The most important task of the gallbladder is to store the hepatic bile necessary for digestion in the

gastrointestinal (GI) tract in adequate quantity, and discharge it into the duodenum when required. Cancers occurring in the gastrointestinal tract cause major disruptions in the physiological process depending on their localization. The problem grows even more when patients face cancer and cholelithiasis. Associations between cholecystectomy and colorectal cancer have been demonstrated previously [4,5]. On the other hand, association between small intestinal carcinogenesis and cholecystectomy is less clear and since the disease is rare data about this subject only based on 4 small studies [6]. Consequently, cancers of the GI tract have been focused on since there is a possible relation between cholelithiasis and cancer risk. In our study, we aimed to investigate the association of cholelithiasis in the preoperative and postoperative period of patients tat undergone surgery for GI tract cancer.

Materials and Methods

We retrospectively analyzed the data of patients who underwent GI cancer surgery between January 2013 and December 2019 in General Surgery Department of a University Hospital. This study was approved by the institutional directorate and ethical board (No/date: 103548508/14.10.2019). Patients who underwent cholecystectomy without a diagnosis of GI cancer were excluded from the study. The coexistence of cholelithiasis in the preoperative period and postoperative period was investigated. Patients diagnosed with cholelithiasis in the preoperative period were excluded from the group in the postoperative period. Age, gender and tumor localization of the patients were determined. The association of tumor localization and cholelithiasis was determined in the preoperative and postoperative periods. According to tumor localization, the cases were divided into two as; upper GI and lower GI (distal of the treitz ligament).

Statistical analyses

The demographic parameters and pathological results of all patients were recorded and statistically analyzed by SPSS software (SPSS 15.0 for Windows, IBM Inc., Chicago, IL, USA). The non-homogenously distributed quantitative variables in study groups were compared by the Mann-Whitney U Test and expressed as median (IQR). The qualitative variables were analyzed by the Chi-Square Test and expressed as n (%). Multivariate analysis was performed in comparison of cholelithiasis cancer association in preoperative and postoperative period. A p value less than 0.05 was considered statistically significant.

Results

The study included 680 GI cancer patients. Cholelithiasis was detected in 100 (14.7%) patients. The median ages the patients with and without cholelithiasis were 66 (35-89) and 65 (17-92), respectively ($p = 0.74$). A total of 407 (59.9%) of the patients were male and 41 (6%) of them had accompanying cholelithiasis in the preoperative period; and 273 (40.1%) of the patients were female and 28 (4.1%) of them had accompanying cholelithiasis in the preoperative period. The coexistence of cholelithiasis between male and female genders in the preoperative period was not statistically significant ($p = 0.93$). Localization of GI cancers were as follows; colon 211 (31%), rectum 195 (28.7%), stomach 187 (27.5%), periampullary region 55 (8.1%) and small intestine 32 (4.7%). In the preoperative period, 69 (10.1%) patients had accompanying cholelithiasis, and their distribution was as follows; 22 (3.2%) colon, 20 (2.9%) rectum, 18 (2.6%) gastric, 6 (0.9%) periampullary, and 3

(0.4%) small bowel cancers. According to cancer localization, cholelithiasis coexistence was not statistically significant in the preoperative period *(p = 0.94)* (Table 1).

Table1. Association of the preoperative cancer and cholelithiasis.

Parameters	Preoperative cholelithiasis		*p*
	Yes (N, %)	None (N, %)	
Age (years)	66/18	65 / 82	*0.74*
Gender			
Male	41/6	366/54	*0.93*
Female	28/4.1	245/36	
Location			
Colon	22/3.2	189/28	
Rectum	20/2.9	175/26	
Stomach	18/2.6	169/25	*0.94*
Periampullary	6/0.9	49/7.2	
Small intestine	3/0.4	29/4.2	
Upper GI tract	24/3.5	218/32	*0.88*
Lower GI tract	45/6.6	393/58	

For the postoperative period, 611 patients were included in the study. A total of 366 patients were male, 18 had cholelithiasis, and 13 of 245 female had cholelithiasis. The association with cholelithiasis in the postoperative period was not statistically significant *(p = 0.48)*. In the postoperative period, 31 (5.1%) patients were associated with cholelithiasis, and their distribution by localization were as follows; 13 (2.2%) colon cancer, 8 (1.3%) rectum cancer, 8 (1.3%) stomach cancer, 2 (0.3%) periampullary region cancer. The association of cholelithiasis in the postoperative period with localization was not statistically significant *(p = 0.35)* (Table 2).

In the preoperative period, 242 (35.6%) upper GI cancer patients (3.5%) had cholelithiasis association in 24 of 438 (64.4%) patients with lower GI cancer, and this rate was not statistically significant *(p = 0.88)*. In the

Table 2. Association of the postoperative cancer and cholelithiasis.

Parameters	Postoperative cholelithiasis		*p*
	Yes (N, %)	None (N, %)	
Age(years)	66/5	65/95	*0.74*
Gender			
Male	18/2.9	348/57	*0.48*
Female	13/2.1	232/38	
Location			
Colon	13/2.2	176/30	
Rectum	8/1.3	167/28	
Stomach	8/1.3	161/28	*0.35*
Periampullary	2/0.3	47/9	
Small intestine	0/0	29/5	
Upper GI	10/1.6	208/34	*0.68*
Lower GI	21/3.5	372/60	

Table 3. Comparison of patients with cholelithiasis in the preoperative and postoperative period.

Parameters	Preop. Chl (N, %)	Postop. Chl (N, %)	*p*
Gender			
Male (n= 407)	41/6	18/3	*0.97*
Female (n= 273)	28/3	13/2	
Location			
Colon (n=211)	22/3.2	13/2.2	
Rectum (n= 195)	20/2.9	8/1.3	
Stomach (n= 187)	18/2.6	8/1.3	*0.92*
Periampullary (n= 55)	6/0.9	2/0.3	
Small intestine (n= 32)	3/0.4	0/0	
Upper GI (n= 242)	24/3.5	10/1.6	*0.91*
Lower GI (n= 438)	45/6.6	21/3.5	

Preop. Chl: preoperative cholelithiasis. Postop. Chl: postoperative cholelithiasis.

postoperative period, cholelithiasis coexistence was detected in 10 (1.6%) of 218 (35.7%) upper GI cancer patients and in 21 (3.5%) of 393 (64.3%) lower GI cancer patients, and this rate was not statistically significant (p = 0.68). Only 1 of the patients who underwent cholecystectomy had bile leak that improved with medical treatment.

In multivariate analysis, the association of cholelithiasis and cancer in the preoperative and postoperative period was not statistically significant *(p = 0.91)* (Table 3).

Discussion

In present study, we showed that coexistence of cholelithiasis was not statistically significant in our patients with gastrointestinal cancer before and after the surgical procedures. However, the rate of cholelithiasis appears higher in the preoperative and postoperative period in patients with colon, rectum and gastric cancer. The treatment process in the gastrointestinal system cancers is difficult and takes a long time. Treatments that vary according to the stage of cancer can be quite complicated. Adding cholelithiasis to this situation before or after cancer surgery forces clinicians and the patient. There are studies showing that whether cholelithiasis is associated with GI cancers or not. Although the relation between cholecystectomy and colorectal cancer was considered in many studies, the results were equivocal; most of the case-control studies showed a positive relation, but only the two largest cohort studies showed significantly increased risks, which were restricted to women and to the proximal part of the colon [7-9]. In studies conducted in the US and Norway, gallstones were not found to be related to colorectal cancer [10,11]; whereas, in other studies conducted in the US and Japan, cholelithiasis was shown to be positively related to CRN [12,13]. In our study, the correlation of lower GI cancers in the preoperative and postoperative period was found as high as 6.6% -3.5%.

Biliary constituents were reported to be genotoxic and to cause local cellular damage which consequently increase mitotic activity of damaged tissue [14]. Therefore, most of the adenocarcinomas of the small intestine occur near the ampulla of Vater in the duodenum, which supports the hypothesis that bile was a carcinogen for the small intestinal mucosa especially in proximity with the site where bile is excreted [14]. Tavani et al suggested that there was a positive association between cholelithiasis and the risk of small intestinal cancer and provide quantitative estimates of the overall association [6]. However, in our study, the rate of cholelithiasis was very low in patients with small bowel cancer.

Increased release of bile acids into the duodenum during fasting is believed to be responsible of increased risk of colorectal cancer following gallstone disease and cholecystectomy [15,16]. The concentration of bile acids increase also by increased enterohepatic circulation [17]. Deoxycholic, a secondary bile acid which is carcinogenic especially with increasing concentrations, is increased by bacterial deconjugation and 7a dehydroxylation of primary bile acids in the proximal colon [18]. A relationship was found more often between colorectal cancer and cholelithiasis, that with cholecystectomy reported by Novell et al [19]. No significant differences in gallstone and bile composition between colon cancer patients with concomitant gallstones and control groups have been found by Gafa et al. [20]. However, a higher incidence of bile bacteria (35.7%) was observed in cancer patients with gallstones. right colon cancer patients who had pigment

stones in 75% of the cases reported to have more frequent bile bacteria. The results seem to evidence peculiarities in patients with a cancer of right colon [20]. In our study, concomittant cholelithiasis was 32% preoperatively and 42% postoperatively in patients with colon cancer.

The incidence of gallstone formation has been regarded as one of the most common complications after gastrectomy [21-23]. The underlying pathophysiology of this phenomenon for this postoperative disease has included alterations in gallbladder motility, the release of cholecystokinin (CCK), and gallbladder responses [24,25]. However, several studies have shown a higher rate of gallstone formation after gastrectomy [26]. The reported incident rate was usually around 10-25%, but rates as high as 47 and 60% had been cited in previous studies [21,26,27]. While the rate of cholelithiasis in the preoperative period was 21% in patients who are planned for obesity surgery, this rate reached 52% in the postoperative period [28]. Approximately 6% of patients undergoing upper GI surgery are expected to require cholecystectomy during follow-up [26]. In our study, the relationship between cholelithiasis in the preoperative and postoperative period was found at a rate of 3.5-1.6% in upper GI cancers. Cholelithiasis surgery has a specific morbidity and mortality burden. In the study of Cholegas, adding cholecystectomy to gastric cancer surgery did not significantly affect perioperative morbidity, mortality, and costs. However, one case (1.5%) of biliary leakage that was probably caused by prophylactic cholecystectomy was observed [29]. In our study, we found the rate of bile leakage as 0.15% in cholecystectomies that we performed with cancer surgery.

Conclusion

In conclusions, the current data make it difficult to distinguish the roles of cholelithiasis on gastrointestinal cancers, since the association of cholelithiasis and gastrointestinal cancers does not show statistical significance. Future research with larger population should focus on this subject to establish a causal link between cholelithiasis and gastrointestinal cancer. Therefore, efforts should be made to differentiate between the roles of asymptomatic and symptomatic stones, which may or may not require cholecystectomy. In addition, it is important that future studies adjust for major confounders especially studies exploring the risk of gastrointestinal cancer after exposure to gallstones.

Funding: *There is no financial support and sponsorship*

Conflict of Interest: *The authors declare that they have no conflict of interest.*

Ethical statement: *This retrospective study was reviewed and approved by institutional ethical board. (Approval Date: 14.10.2019, Decision No: 103548508).*

ORCID iD of the author(s)

Bahri Ozer / 0000-0002-4326-2102
Oguz Catal / 0000-0002-4067-251X
Songul P Ozer / 0000-0001-7334-219X
Fatih Keyif / 0000-0001-7346-1041
Mustafa Sit / 0000-0002-7475-7298
Nuri Kama / 0000-0002-7796-7493

References

[1] Brett M, Barker D. The world distribution of gallstones. Int J Epidemiol. 1976;5(4):335-41.

[2] Nakeeb A, Comuzzie AG, Martin L, et al. Gallstones: genetics versus environment. Ann Surg. 2002;235(6):842-49.

[3] Al-Jiffry BO, Shaffer EA, Saccone GT, et al. Changes in gallbladder motility and gallstone formation following laparoscopic

gastric banding for morbid obesity. Can J Gastroenterol Hepatol. 2003;17(3):169-74.

[4] Xu Y-K, Zhang F-L, Feng T, et al. Meta-analysis on the correlation of cholecystectomy or cholecystolithiasis to risk of colorectal cancer in Chinese population. Chin J Cancer. 2009; 28(7):749-55

[5] Chiong C, Cox MR, Eslick GD. Gallstone disease is associated with rectal cancer: a meta-analysis. Scand J Gastroenterol. 2012;47(5):553-64.

[6] Tavani A, Rosato V, Di Palma F, et al. History of cholelithiasis and cancer risk in a network of case–control studies. Ann Oncol. 2012;23(8):2173-178.

[7] Giovannucci E, Colditz GA, Stampfer MJ. A meta-analysis of cholecystectomy and risk of colorectal cancer. Gastroenterol. 1993;105(1):130-41.

[8] Linos D, O'Fallon WM, Heart JR R, et al. Cholecystectomy and carcinoma of the colon. The Lancet. 1981;318(8243):379-81.

[9] Chen Y-K, Yeh J-H, Lin C-L, et al. Cancer risk in patients with cholelithiasis and after cholecystectomy: a nationwide cohort study. J Gastroenterol. 2014;49(5):923-31.

[10] Nogueira L, Freedman ND, Engels EA, et al. Gallstones, cholecystectomy, and risk of digestive system cancers. Am J Epidemiol. 2014;179(6):731-39.

[11] Schmidt M, Småstuen MC, Søndenaa K. Increased cancer incidence in some gallstone diseases, and equivocal effect of cholecystectomy: a long-term analysis of cancer and mortality. Scand J Gastroenterol. 2012;47(12):1467-474.

[12] Yamaji Y, Okamoto M, Yoshida H, et al. Cholelithiasis is a risk factor for colorectal adenoma. Am J Gastroenterol. 2008;103(11):2847-852.

[13] Kahn HS, Tatham LM, Thun MJ, et al. Risk factors for self-reported colon polyps. J Gen Intern Med. 1998;13(5):303-10.

[14] Ross R, Hartnett N, Bernstein L, et al. Epidemiology of adenocarcinomas of the small intestine: is bile a small bowel carcinogen? Br J Cancer. 1991;63(1):143-45.

[15] Imray C, Radley S, Davis A, et al. Faecal unconjugated bile acids in patients with colorectal cancer or polyps. Gut. 1992;33(9):1239-245.

[16] Tocchi A, Basso L, Costa G, et al. Is there a causal connection between bile acids and colorectal cancer? Surg Today. 1996;26(2):101-104.

[17] Berr F, Stellaard F, Pratschke E, et al. Effects of cholecystectomy on the kinetics of primary and secondary bile acids. J Clin Invest. 1989;83(5):1541-550.

[18] Thomas L, Veysey M, French G, et al. Bile acid metabolism by fresh human colonic contents: a comparison of caecal versus faecal samples. Gut. 2001;49(6):835-42.

[19] Novell F, Moral A, Pascual S, et al. Is there a relationship between cholelithiasis and colorectal cancer? Rev Esp Enferm Dig. 1995;87(4):294-98.

[20] Gafà M, Sarli L, Dotti C, et al. Cancer of the colon and cholelithiasis: bile bacteria, composition of the stones and the bile. Ann Ital Chir. 1989;60(4):283-90.

[21] Hauters P, De de Roden AN, Pourbaix A, et al. Cholelithiasis: a serious complication after total gastrectomy. BJS Open. 1988;75(9):899-900.

[22] Kodama I, Yoshida C, Kofuji K, et al. Gallstones and gallbladder disorder after gastrectomy for gastric cancer. Int Surg. 1996;81(1):36-39.

[23] Wu C-C, Chen C-Y, Wu T-C, et al. Cholelithiasis and cholecystitis after

gastrectomy for gastric carcinoma: a comparison of lymphadenectomy of varying extent. Hepato-Gastroenterol. 1995;42(6):867-72.

[24] Kobayashi T, Hisanaga M, Kanehiro H, et al. Analysis of risk factors for the development of gallstones after gastrectomy. BJS Open. 2005;92(11):1399-1403.

[25] Yi S-Q, Ohta T, Tsuchida A, et al. Surgical anatomy of innervation of the gallbladder in humans and Suncus murinus with special reference to morphological understanding of gallstone formation after gastrectomy. World J Gastroenterol. 2007;13(14):2066-70.

[26] Gillen S, Michalski CW, Schuster T, et al. Simultaneous/Incidental cholecystectomy during gastric/esophageal resection: systematic analysis of risks and benefits. World J Surg. 2010;34(5):1008-14.

[27] Liang T-J, Liu S-I, Chen Y-C, et al. Analysis of gallstone disease after gastric cancer surgery. Gastric Cancer. 2017;20(5):895-903.

[28] De Oliveira CIB, Chaim EA, Da Silva BB. Impact of rapid weight reduction on risk of cholelithiasis after bariatric surgery. Obes Surg. 2003;13(4):625-28.

[29] Bernini M, Bencini L, Sacchetti R, et al. The Cholegas Study: safety of prophylactic cholecystectomy during gastrectomy for cancer: preliminary results of a multicentric randomized clinical trial. Gastric Cancer. 2013;16(3):370-76.