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ORIGINAL ARTICLE

위부분절제술 후 발생하는 담도 확장 및 담석증의 임상적 의의

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Clinical Significance of Biliary Dilatation and Cholelithiasis after Subtotal Gastrectomy

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Background/Aims: The well-organized study to support that increased cholelithiasis and bile duct dilatation can occur after gastrectomy has not been reported. The aim of this study was to determine the incidence of cholelithiasis and the degree of common bile duct (CBD) dilatation in patients undergoing subtotal gastrectomy, compared to those undergoing endoscopic treatment for gastric cancer.

Methods: Patients who diagnosed with gastric cancer and received treatment at six academic referral centers were investigated for the incidence and time of cholelithiasis and the degree of CBD dilatation after treatment by analysis of 5-year follow-up CTs. The operation group underwent subtotal gastrectomy without vagotomy, while in the control group endoscopic treatment was administered for gastric cancer.

Results: A total of 802 patients were enrolled in 5-year analysis (735 patients in the operation group and 67 patients in the control group). Cholelithiasis occurred in 47 patients (6.39%) in the operation group and 3 patients (4.48%) in the control group (p=0.7909). The incidences of cholelithiasis were 4.28% in Billoth-I and 7.89% in Billoth-II (p=0.0487). The diameter of proximal CBD and distal CBD increased by 1.11 mm and 1.41 mm, respectively, in the operation group, compared to 0.4 mm and 0.38 mm, respectively, in the control group ($p < 0.05$). Patients with increased CBD dilatation more than 5 mm showed statistically significant increases in alkaline phosphatase and gamma-glutamyltransferase.

Conclusions: The incidence of cholelithiasis was not increased due to subtotal gastrectomy without vagotomy, but the incidence was higher after Billoth-II compared to Billoth-I. In addition, significant change in the CBD diameter was observed after subtotal gastrectomy. **(Korean J Gastroenterol 2015;66:33-40)**

Key Words: Common bile duct; Biliary tract; Cholelithiasis; Gastrectomy; Stomach neoplasms

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INTRODUCTION

Widespread use of cancer screening programs has recently led to a continuous increase in the diagnostic rate of early gastric cancer. Improved outcome after gastrectomy has also contributed to long-term survival. However, long-term survival can also cause delayed complications after gastrectomy. Above all, biliary disease including cholelithiasis, caused by anatomical change after gastrectomy, is difficult to manage endoscopically with ERCP, and adhesion at the surgical site also makes surgical treatment more dangerous. In addition, clinicians frequently encounter patients with asymptomatic bile duct dilatation after gastrectomy and are faced with difficulty in choosing evaluation methods.

One of the most important hypotheses for increasing incidence rate of cholelithiasis after gastrectomy is injury to the vagus nerve, which coordinates the motion of the gallbladder (GB). Vagotomy during gastrectomy can cause sphincter of Oddi dysfunction, delayed bile circulation, increasing GB intraluminal pressure, and adverse hormonal effects. Therefore, it can be expected that gastrectomy including vagotomy may cause cholelithiasis and bile duct dilatation.[1-6] In the past, vagotomy was almost inevitable due to lymph node dissection when performing gastrectomy in patients with gastric cancer, which led to the hypothesis that cholelithiasis is increased after gastrectomy, although the number of reports is limited.[7-9] It would be necessary to determine whether the incidence of cholelithiasis has actually increased after surgery, in addition to its complications and clinical characteristics. No systematic study in a large sample, or any study investigating the incidences of cholelithiasis and bile duct dilatation after subtotal gastrectomy without vagotomy has been reported.

In the situation without vagotomy, might the incidence of cholelithiasis also be increased? Some reports have suggested that the risk of cholelithiasis differed depending on the method of gastrectomy, but the results varied among a few studies.[10-12] Exclusion of the duodenum during reconstruction or non-physiologic tract reconstruction, leading to changes in the secretion of cholecystokinin, can be a potential risk of cholelithiasis.[13] The chyme would pass directly to the jejunum, and then cause low cholecystokinin secretion, GB dyskinesia, and cholestasis. However, studies on cholecystokinin level before or after meals in patients with those situations did not support that theory.[14,15]

The aim of this study was to evaluate the incidence of cholelithiasis and the degree of CBD dilatation in patients diagnosed with gastric cancer who underwent subtotal gastrectomy without vagotomy using 5-year follow-up abdominal CT.

SUBJECTS AND METHODS

1. Study population

Patients diagnosed with gastric cancer at six academic referral centers from January 2002 through December 2007 who were alive throughout and after the 5-year follow-up period were enrolled in this multi-center study. Patients who underwent subtotal gastrectomy were included in the operation group, while those diagnosed with gastric cancer who received nonsurgical treatments — endoscopic submucosal dissection (ESD) or endoscopic mucosal resection (EMR) — were included in the control group. Only patients who underwent 5-year follow-up abdominal CT after treatment were included. Exclusion criteria were as follows: detection of cholelithiasis and/or CBD dilatation (>7 mm) on preoperative CT; subtotal gastrectomy with vagotomy; cholecystectomy state; recurrent gastric cancer; other malignant neoplasms; preoperative laboratory findings of total bilirubin >1.2 mg/dL and AST and ALT >40 IU/L, respectively; extrahepatic bile duct obstruction on CT; pancreatitis; and periampullary diverticulum on CT. Among a total of 802 patients enrolled, 735 were included the operation group and 67 were included in the control group. Retrospective cohort analysis was performed for these patients to determine the incidence of cholelithiasis and the change of bile duct diameter.

2. Methods

1) Biological and clinical parameters

Patients who met the above mentioned inclusion/exclusion criteria were investigated for the incidence and time of cholelithiasis and choledocholithiasis by analysis of 5-year follow-up CTs. The diameter of the common bile duct (CBD) was measured in Year 0 and Year 5 since the treatment, to determine the incidence and extent of dilatation. For comparison differences by gastric reconstruction method, patients were subdivided into subtotal gastrectomy and gastroduodenostomy (Billoth-I) group or subtotal gastrectomy and gas-

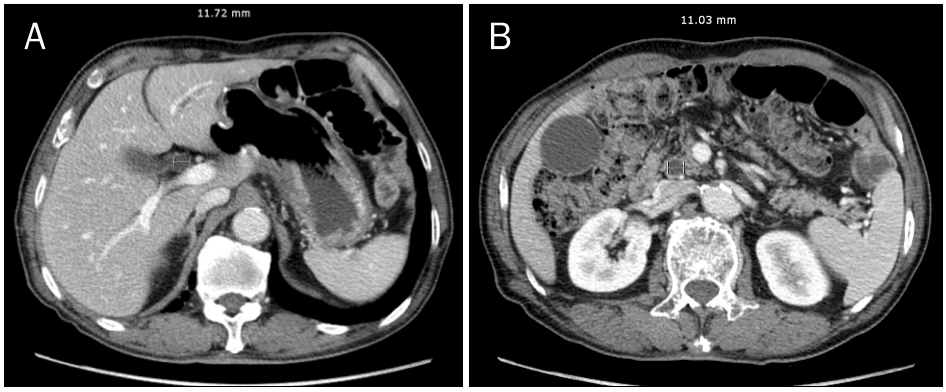

Fig. 1. Measurement of the common bile duct on abdominal computed tomography. (A) Proximal common bile duct in the porta hepatis. (B) Distal common bile duct in the pancreas head.

Table 1. Baseline Characteristics and Liver Function Tests

Characteristic	Operation group	Control group	p-value
Age (yr)	58.59±12.92	64.39±12.04	0.0038
Sex (male)	475 (64.63)	48 (71.64)	0.2484
Body weight (kg)	62.92±10.16	65.33±9.97	0.5919
AST (IU/L)	26.30±18.56	25.44±8.77	0.6032
ALT (IU/L)	23.83±39.58	24.75±16.13	0.7713
Total bilirubin (mg/dL)	0.86±1.10	0.84±0.37	0.7380
ALP (IU/L)	171.98±148.94	199.75±56.93	0.0605
GGT (IU/L)	65.41±171.48	61.00±66.62	0.8764

Values are presented as mean±SD or n (%).

trojejunostomy (Billoth-II) group and compared for the incidence of cholelithiasis and choledocholithiais as well as CBD dilatation. The operation group was compared with the control group to determine whether the gastrectomy was the cause of cholelithiasis and CBD dilatation. Patients' baseline characteristics and laboratory data were also analyzed to determine their clinical features.

2) Measurement of CBD diameter

Differentiating the CBD from the common hepatic duct can be difficult due to variability of location, or sometimes invisibility of the cystic duct. Therefore, CBD dilatation was measured by separating the proximal part and the distal part. The diameter immediately distal to the porta hepatis was measured for the proximal CBD (P-CBD), while the diameter visible in the head of the pancreas was measured for the distal CBD (D-CBD) (Fig. 1). Considering the possibility of inaccuracy when measuring long axis diameter, due to an often oblique bile duct on axial CT images, the diameter was measured on short axis view.

3) End point

The primary endpoint of this study was to evaluate the incidence and development time of cholelithiasis and choledocholithiasis after subtotal gastrectomy for stomach cancer. The secondary endpoint was to evaluate the degree of CBD dilatation.

3. Statistical analysis

Analysis of baseline characteristics and incidence was performed using independent-samples Student ttest and chi-squared test, with a logistic regression model for multivariate analysis. $p < 0.05$ was considered significant. Statistical analysis was performed using IBM® SPSS® Statistics (version 21.0.0; IBM Co., Armonk, NY, USA).

RESULTS

1. Baseline characteristics

A total of 802 patients were enrolled in 5-year analysis (735 patients in the operation group and 67 patients in the control group). Baseline characteristics of the operation group and the control group are shown in Table 1. No statistically significant difference was observed between the two groups, although patients in the operation group tended to be younger.

2. Incidence of cholelithiasis

Cholelithiasis occurred in 47 patients (6.39%) in the operation group and 3 patients (4.48%) in the control group. But, there was no statistical difference between two groups (p=0.7909) (Table 2). Interestingly, there was no occurrence of choledocholithiasis in any patients in either group.

Table 2. Incidence of Cholelithiasis between Two Groups

Group	Cholelithiasis	No cholelithiasis	p-value
Operation group	47 (6.39)	688 (93.61)	0.7909
Control group	3 (4.48)	64 (95.52)	

Values are presented as n (%).

Table 3. Relationship between Incidence of Cholelithiasis and Post-operative Duration

Duration (mo)	Operation group	Control group	p-value
0-6	13 (27.66)	0	0.7438
7-12	2 (4.26)	0	
13-24	4 (8.51)	0	
25-	28 (59.57)	3 (100)	
Total	47 (100)	3 (100)	

Values are presented as n (%).

3. Incidence of cholelithiasis by baseline characteristics

Among 735 patients in the operation group, 475 patients were male and 260 were female (1.8:1). Cholelithiasis occurred in 5.89% of male patients (28/475) and 7.31% of female patients (19/260), without statistically significant difference (p=0.0551). In the control group, the sex ratio was 2.5:1, but without statistical significance compared to the operation group (p=0.2484). Cholelithiasis occurred in 6.25% of male patients only (3/48). When adjusted for confounding factors, there were no statistically significant prognostic factors affecting the incidence of cholelithiasis.

4. Incidence of cholelithiasis by time passed after subtotal gastrectomy

Cholelithiasis after subtotal gastrectomy occurred in 27.66% (13/47) of patients within 6 months, 4.26% (2/47) from 6 months through 1 year, 8.51% (4/47) from 1 year through 2 years, and 59.57% (28/47) after 2 years. In most cases cholelithiasis occurred within 6 months or 2 years after treatment in the operation group. In contrast, all cases (3/3) occurred after 2 years in the control group. However, the between- group difference was not statistically significant (p=0.7438) (Table 3).

5. Incidence of cholelithiasis by operation method

The incidence of cholelithiasis by gastric reconstruction method was 4.28% (13/304) in Billroth-I patients and 7.89% (34/431) in Billroth-II patients (p=0.0487). In the control group, cholelithiasis occurred in 4.88% (2/41) of patients after ESD and 3.85% (1/26) after EMR, without statistically significant difference between the two procedures (p=0.8422) (Table 4).

Table 4. Incidence of Cholelithiasis according to the Operation Method

Operation method	Cholelithiasis	No cholelithiasis	p-value
Operation group (n=735)			0.0487
Billoth-I (n=304)	13 (4.28)	291 (95.72)	
Billoth-II (n=431)	34 (7.89)	397 (92.11)	
Control group (n=67)			0.8422
ESD (n=41)	2 (4.88)	39 (95.12)	
EMR (n=26)	1 (3.85)	25 (96.15)	

Values are presented as n (%).
EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.

6. Frequency and extent of CBD dilatation

Five years after the operations, P-CBD and D-CBD diameters were dilated by less than 5 mm in more than 95% of the total 802 patients (Table 5). Mean proximal CBD diameter was 6.01±2.68 mm in the operation group, compared to 5.31±1.88 mm in the control group (p=0.0063). Mean distal CBDs (6.03±2.38 mm in the operation group *vs.* 5.31±1.88 mm in the control group) also indicated statistically significant dilatation (p=0.0335). Increase in proximal CBD diameter during 5 years after treatment was 1.11 mm in the operation group, compared to 0.4 mm in the control group (p=0.0004). Changes in distal CBD diameters (1.41 mm in the operation group *vs.* 0.38 mm in the control group) also showed statistical significance (p=0.0335) (Table 6).

Results of the logistic analysis showed that reconstruction method did not have a statistically significant effect on proximal CBD dilatation (OR=0.417). In contrast, with distal CBD dilatation, Billroth-I had less effect on CBD dilatation (OR= 0.046).

7. Factors affecting CBD dilatation

When adjusted for confounding factors, age was the statistically significant prognostic factor affecting development of proximal CBD dilatation (OR=1.034 and p=0.0237, respectively). Gender and body weight were not significant prognostic factors affecting bile duct dilatation.

Table 5. Degree Categorization for Change of Common Bile Duct Diameter

Group	P-CBD Diameter change (mm)				D-CBD Diameter change (mm)			
	0-5	6-8	9-12	>13	0-5	6-8	9-12	>13
Operation group (n=735)	707 (96.19)	20 (2.72)	6 (0.82)	2 (0.27)	708 (96.33)	19 (2.59)	6 (0.82)	1 (0.14)
Control group (n=67)	66 (98.51)	1 (1.49)	0 (0)	0 (0)	67 (100)	0 (0)	0 (0)	0 (0)

Values are presented as n (%).
D-CBD, distal common bile duct; P-CBD, proximal common bile duct.

Table 6. Analysis for Change of Common Bile Duct Diameter

Variable	Operation group (n=735)	Control group (n=67)	p-value
Initial diameter (mm)			
P-CBD	4.89±1.88	4.84±1.58	0.8235
D-CBD	4.61±1.47	5.13±1.50	0.0064
Number of diameter change>5 mm			
P-CBD	34 (4.63)	1 (1.49)	0.3511
D-CBD	30 (4.09)	0 (0)	0.1663
Diameter after 5 years follow up (mm)			
P-CBD	6.01±2.68	5.31±1.88	0.0063
D-CBD	6.03±2.38	5.51±1.80	0.0335
Delta diameter change (mm)			
P-CBD	1.11±1.99	0.47±1.29	0.0004
D-CBD	1.41±1.99	0.38±1.38	0.0335

Values are presented as mean±SD or n (%).
D-CBD, distal common bile duct; P-CBD, proximal common bile duct.
Delta diameter change was defined as average diameter at initial diagnosis minus average diameter after 5 years follow up.

Table 7. Risk of Common Bile Duct Dilatation according to the Laboratory Finding

	P-CBD dilatation>5 mm		D-CBD dilatation>5 mm	
	OR	p-value	OR	p-value
AST	0.922	0.2546	1.052	0.2785
ALT	0.979	0.6667	0.977	0.4959
Total bilirubin	3.147	0.3353	0.145	0.2079
ALP	1.000	0.8324	0.996	0.3077
GGT	1.012	0.0450	1.006	0.0450

P-CBD, proximal common bile duct; D-CBD, distal common bile duct.

8. Association between laboratory findings and the incidences of cholelithiasis and CBD dilatation

Post-operative assessment of 5-year changes in AST, ALT, total bilirubin, ALP, and GGT to determine the association between post-operative incidence of cholelithiasis and laboratory findings showed no statistically significant finding. Interestingly, ALP and GGT showed statistically significant difference between the subgroup with proximal CBD dilatation of 5 mm or more and the subgroup without proximal CBD dilatation (ALP level at 5 years after operation, 303.79±229.96 IU/L *vs.* 165.58±135.9 IU/L; GGT level at 5 years after operation, 246.83±299.94 IU/L *vs.* 38.65±60.12 IU/L) (p=0.0017 and p=0.035, respectively). In logistic analysis, OR of GGT was 1.012 (p=0.045) for proximal CBD dilatation of 5 mm or more and 1.006 (p=0.045) for distal CBD dilatation of 5 mm or more, suggesting association between increased GGT and CBD dilatation (Table 7).

DISCUSSION

Vagotomy, which is inevitable during gastrectomy, is associated with increased incidence of cholelithiasis and increased bile duct diameter afterwards, although the pathophysiology is uncertain.[16-18] Old studies indicate that GB motor dysfunction due to hypomotility or hypermotility, bile acid storage in the small bowel, GB inflammation, and enterohepatic bile circulation commonly contribute to development of pigment stone, and that development of GB stones after gastrectomy is caused by GB hypomotility.[19-22] However, there are also disputes over such hypotheses, including re-

ports suggesting that the incidence of cholelithiasis does not increase, because vagus nerve injury is not the main cause of GB hypomotility.[23-26] There were also reports that not only amputated and injured vagus nerve has a fundamental effect on GB motor, but sphincter of Oddi dysfunction through cholecystokinin secretion control also causes GB hypomotility indirectly.[27,28] In addition, cholecystokinin mainly causes contraction of the GB indirectly through vagus nerve, but it works in part on the muscle directly.[29] Therefore, we aimed at determining the effect of gastrectomy without vagotomy on cholelithiasis and CBD dilatation. For reasonable comparison, gastric cancer patients who received endoscopic treatment were included in the control group.

As mentioned earlier, many cases of increased cholelithiasis and bile duct diameter after gastrectomy with vagotomy have been reported, but few involving patients who did not undergo vagotomy or cholecystectomy as possible cause of such complications, with definite results. We therefore conducted the study in such patients. Cholelithiasis occurred in 47 patients (6.39%) among 735 patients who underwent subtotal gastrectomy, and in 3 patients (4.48%) among 67 patients who received nonsurgical treatment in the control group, indicating an increasing trend of cholelithiasis after subtotal gastrectomy but without statistically significant difference. It should be noted that the incidence of cholelithiasis after gastrectomy was considerably higher than the prevalence of cholelithiasis detected during health examinations in South Korea (2.3-4.9%).[30] As it was a retrospective study, only patients who underwent gastric cancer treatment and annual follow-up abdominal CTs were included. It is possible that inclusion of patients without follow-up study in the analysis or use of abdominal sonography would have resulted in a greater increase in prevalence. In most cases the CBD was dilated by less than 5 mm, which could be associated with the normal aging process due to the passage of time. However, the diameters measured 5 years after treatment were higher with statistical significance after subtotal gastrectomy compared to the control group. This result suggests that not only vagus nerve but also other various factors affect cholelithiasis and CBD dilatation after gastric surgery.

In most cases development of cholelithiasis occurs after gastrectomy early after surgery.[2,31] In our study, cholelithiasis occurred in 27.6% (13/47) of patients within 6 months, 4.3% (2/47) from 6 months through 1 year, 8.5% (4/47) from 1 year through 2 years, and 59.6% (28/47) 2 years after surgery, most occurring within 6 months or 2 years after gastrectomy. In the control group, all cases (3/3) occurred within 2 years after treatment. The result was not statistically significant (p=0.7438), but differs from previous reports on vagotomy in that a considerable amount of cholelithiasis also occurred 2 years after treatment, suggesting the need for long-term follow-up, in addition to short-term follow-up for confirmation of incidence of cholelithiasis. Furthermore, considering the absence of choledocholithiasis within 5 years, long-term follow-up study after the 5 years is required to determine the mechanism of development from CBD dilatation to choledocholithiasis.

Gastric reconstruction method was found to be a factor that may affect cholelithiasis and bile duct dilatation after subtotal gastrectomy in gastric cancer patients, possibly because use of the duodenum bypassing method results in decreased cholecystokinin secretion, causing GB motor dysfunction. Although previous reports suggested no difference in serum cholecystokinin level between before and after food consumption,[14,15,32] one study reported markedly decreased GB contractility after Billroth-II compared to Billroth-I.[21] In our study, cholelithiasis occurred significantly more often after Billroth-II compared to Billroth-I. No statistically significant difference in P-CBD dilatation was observed between the two anastomosis methods, but Billoth-II had a statistically significant effect on D-CBD dilatation compared to Billoth-I.

For laboratory findings, 5-year changes in AST, ALT, total bilirubin, ALP, and GGT before and after treatment were investigated, which did not show statistically significant association with cholelithiasis. In terms of change in CBD diameter, increased ALP and GGT showed statistically significantly association with CBD dilatation. This might suggest that bile duct dilatation after subtotal gastrectomy has some association with biliary dysfunction, and that GGT might have a role as a predictor of CBD dilatation.

This study is relevant in that it found incidence and features of cholelithiasis after subtotal gastrectomy, objective difference of CBD dilatation by operation method, and their association with predictors and laboratory findings through a multi-center study. Limitations of this study include being a retrospective cohort analysis study; possible underestimation of actual cholelithiasis occurrence by use of CT, instead of sonography, for identification of cholelithiasis; relatively

small size of the control group (because ESD was not widely used during the study period and because there were few patients who underwent follow-up CT until 5 years after treatment); possible omission of vagotomy performance on medical record; lack of investigation on comorbidity; and lack of analysis of gastric cancer staging (the radical lymph node dissection might be an another risk factor for cholelithiasis).

In conclusion, subtotal gastrectomy itself for management of gastric cancer did not increase the incidence of cholelithiasis, but there was a difference depending on reconstruction method such that Billoth-II was associated with higher incidence than Billoth-I. In addition, significant change in the CBD diameter was observed after subtotal gastrectomy. Furthermore, CBD dilatation after gastrectomy can be associated with increased GGT level. Conduct of a large-scale, prospective study, involving more long-term follow-up, will be required in the future.

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