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Risk Factors for Gallstone Formation in Resected Gastric Cancer Patients

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Abstract: Previous studies reported increased incidence of gallstone formation after gastrectomy. However, there were few reports about factors other than surgical technique. The purpose of this study is to investigate the spectrum of risk factors of gallstone formation after gastrectomy.

From June 2003 to December 2008, 1480 patients who underwent gastrectomy due to gastric cancer but had no gallstones before surgery were identified. Electronic medical records were retrospectively reviewed. Gallstones were assessed by computerized tomography or ultrasound performed as surveillance for recurrence.

There were 987 men (66.7%) and the median age was 59.0 years. The median follow-up period was 47.0 months. According to the surgical technique, 754 (50.9%), 459 (31.1%), and 267 (18.0%) underwent subtotal gastrectomy with Billroth I (STG B-I) and Billroth II (STG B-II) anastomosis, and total gastrectomy (TG). Within the follow-up period, gallstone formation occurred in 106 of 1480 patients (7.2%), the only 9 patients (0.6%) experienced symptomatic cholecystitis. By multivariate Cox regression analysis, age (HR 1.02, 95% CI 1.00–1.04), male (1.65, 1.02–2.67), diabetes mellitus (2.15, 1.43–3.24), ≥4% decrease of body mass index after surgery (1.66, 1.02–2.70), STG B-II (1.63, 1.03–2.57), and TG (2.35, 1.43–3.24) compared with STG B-I were associated with gallstone formation. Common bile duct stone formation occurred in 20 of 1480 patients (1.4%) and was only associated with gallstones.

After gastrectomy, there were considerable numbers of patients with newly developed gallstones; however, prophylactic cholecystectomy should not be routinely recommended. Gastrectomy (STG B-II or TG), old age, male sex, diabetes mellitus, and decreased body mass index were associated with gallstones.

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Abbreviations: BMI = body mass index, STG B-I = subtotal gastrectomy with Billroth I anastomosis, STG B-II = subtotal gastrectomy with Billroth II anastomosis, TG = total gastrectomy.

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INTRODUCTION

With the development of endoscopic screening, surgical techniques, and postoperative comprehensive treatment, the survival of patients with gastric cancer has become significantly prolonged after curative surgery.[1–5] Therefore, the quality of life long after surgery has attracted more attention. In this aspect, gallstone formation is one of the long-term clinical sequelae after gastrectomy,[6–8] and previous studies reported that the incidence of cholelithiasis after gastric cancer surgery is between 10 and 25%.[9,10]

However, the exact pathophysiologic mechanism for the increased incidence of gallbladder stone after gastric surgery is not fully understood. The speculative causes of postgastrectomy-associated cholelithiasis include injury of the hepatic branch of the vagus nerve,[11,12] nonphysiological reconstruction,[13,14] infection of the biliary tract,[8,15] and a distortion of the biliary tract by postoperative adhesion leading to gallbladder dysfunction.[16] In addition, there were studies that surgical methods such as subtotal gastrectomy (STG) with Billroth I (STG B-I) or Billroth II (STG B-II) anastomosis and total gastrectomy (TG) were associated with cholelithiasis, however, controversy remains.[12,14,17,18]

Besides the pathophysiology, the clinical significance of gallstone after gastrectomy is unclear. Although most of gallstones are silent in the general population, it should be considered that cholecystectomy in patients after previous gastrectomy is more complex than those without gastrectomy mainly because of postoperative adhesion.

Against this background, we investigated the risk factors for gallstone formation after gastrectomy in stomach cancer patients to gain insight into its clinical significance.

METHODS

Patients

A total of 1763 patients underwent gastrectomy because of stomach cancer from July 2003 to December 2008 at Seoul National University Bundang Hospital. Among those, 231 patients were excluded because 109 patients were followed less than 1 month after surgery, 26 previously had gallstones, 41 had already received cholecystectomy, and 55 underwent cholecystectomy at the time of gastrectomy. During the follow-up period, another 5 patients received cholecystectomy due to gallbladder cancer, pancreatic cancer, or cholangiocarcinoma. Additionally, the patients who had undergone proximal gastrectomy were also excluded due to the small sample size (n = 47). Finally, the remaining 1480 patients were retrospectively reviewed using comprehensive electronic medical records. The remaining 1480 patients received either STG B-I, STG B-II, or TG and were classified according to surgical methods. For analysis of risk factors for gallstone development, the patients were grouped according to the type of gastrectomy.

To compare the incidence of postoperative cholelithiasis according to the type of gastrectomy, a medical review of 99 patients who underwent gastric wedge resection due to gastrointestinal tumor, well-differentiated early gastric cancer, or other benign disease at our institution during the approximately same time period was done. Among those, 28 patients were excluded because 20 were followed less than 1 month after surgery, 4 had gallstones before surgery, 1 had received cholecystectomy before surgery, and 3 underwent total or subtotal gastrectomy due to gastric cancer during follow-up period. Therefore, 71 patients were eventually included as a control group in this study.

The study protocol was approved by the Institutional Review Board of Seoul National University Bundang Hospital (Institutional Review Board no. B-1505-298-103) and conformed to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008). The requirement for informed consent was waived.

Detection of Gallstones

The presence of gallstone and bile duct stone was assessed by computerized tomography or ultrasound carried out as surveillance for recurrence. The follow-up was done as follows: either abdominal computed tomography or ultrasonography was performed every 6 months for the first 2 years after gastrectomy, and annually thereafter for at least 5 years. If the patient had adjuvant chemotherapy, imaging follow-up was conducted every 3 months for the first 6 months during adjuvant chemotherapy, and every 6 to 12 months thereafter for at least 5 years. As a surveillance method of gastric cancer recurrence, 21% of patients (308 of 1480) received only computed tomography (CT) and other 79% of patients received both CT and ultrasound, alternatingly.

The presence of gallstone was also assessed by CT or ultrasound in the control group; however, there was no regular follow-up protocol in patients with benign disease.

Statistical Analysis

The cumulative incidence of gallstones after gastrectomy was evaluated by the Kaplan–Meier method and differences between groups were evaluated by the log rank test. Univariate and multivariate analysis with the Cox proportional hazards model was used to assess the risk factors for gallstone formation. Among the clinical variables included in univariate analysis, those with a 2-sided P value of less than 0.1 were chosen for multivariate analysis with stepwise selection. A 2-sided P value of less than 0.05 was considered to indicate a statistically significant difference. All statistical analyses were performed using SPSS statistics 21.0 software for Windows (IBM Corporation, Armonk, NY).

RESULTS

Baseline Characteristics

Among 1480 patients included in our analysis, there were 987 men (66.7%) and the median age was 59.0 years. The median follow-up periods were 47 months. The baseline characteristics of the participating patients according to the type of gastrectomy are shown in Table 1. There were no significant differences in age, sex, preoperative body mass index (BMI), and diabetes among these 3 groups. However, significant differences were noted in median postoperative BMI, pathological stage, and extent of lymph node dissection. In addition, there were significant differences of proportions of patients with laparoscopic gastrectomy and adjuvant chemotherapy. Therefore, patients with STG B-I were more frequently treated with laparoscopic surgery and less treated with adjuvant chemotherapy, vice versa to those with TG. Median follow-up periods were significantly longer in patients with STG B-I than those with STG B-II or TG, too. There were no significant differences in age, preoperative BMI, diabetes mellitus, and median follow-up period except sex (male 66.7% in gastrectomy group and 52.1% in control group, $P = 0.011$) and proportions of laparoscopic gastrectomy (50.0% in gastrectomy group and 93.0% in control group, $P < 0.001$).

Gallstone Formation and Cholecystitis

Cumulative gallstone formation was detected in 37 (2.5%), 56 (3.8%), and 90 (6.1%) patients at 1, 2, and 5 years after gastrectomy, respectively. In contrast, only 1 (1.4%) patient had

TABLE 1. Baseline Characteristics of Patients According to the Type of Gastrectomy

	STG B-I (N = 754)	STG B-II (N = 459)	TG (N = 267)	*P* Value
Sex (male, %)	480 (63.7)	322 (70.2)	185 (69.3)	0.066
Median age (yr)	59 (25–89)	59 (29–88)	58 (27–82)	0.139
Median preoperative BMI (kg/m^2)	23.5 (16.6–35.2)	23.6 (14.0–32.9)	23.3 (14.5–33.7)	0.173
Median postoperative BMI (kg/m^2)	22.0 (10.5–31.1)	21.6 (12.4–31.3)	19.9 (12.2–31.6)	<0.001
Stage (%)				<0.001
I and II	713 (94.6)	367 (80.0)	178 (66.7)	
III and IV	41 (5.4)	92 (20.0)	89 (33.3)	
Lymph node dissection (%)				<0.001
D0 and D1	213 (28.2)	122 (26.6)	26 (9.7)	
D2 and D3	541 (71.8)	337 (73.4)	241 (90.3)	
Diabetes mellitus (%)	156 (20.7)	95 (20.7)	56 (21.0)	0.924
Laparoscopic gastrectomy (%)	475 (63.0)	212 (46.2)	53 (19.9)	<0.001
Adjuvant chemotherapy (%)	152 (20.2)	159 (34.6)	155 (58.1)	<0.001
Follow-up period (mo)	51 (3–122)	43 (1–119)	43 (2–109)	<0.001

BMI = body mass index, STG B-I = subtotal gastrectomy with Billroth I anastomosis, STG B-II = subtotal gastrectomy with Billroth I anastomosis, TG = total gastrectomy.

developed gallstone within follow-up period in the control group. The cumulative incidence of postoperative cholelithiasis was higher in the patients with TG or STG than in the control group (Figure 1A). The cumulative incidence of gallstones after TG was significantly higher than after STG (Figure 1B). However, there was no significant difference between STG B-II and TG despite a tendency toward higher incidence of STG B-II ($P = 0.084$, Figure 1C). Of the 1480 patients, 740 (50%) underwent laparoscopic gastrectomy. The cumulative incidence of gallstone formation was not significantly different between the patients after open and laparoscopic gastrectomy ($P = 0.377$, Figure 1D).

Risk factors for gallstone formation after gastrectomy included male sex, age, decreased BMI more than 4% after gastrectomy, surgical methods including STG B-II and TG, and diabetes were identified as a significant risk factor for gallstones after gastrectomy (Table 2).

Among the 106 patients with gallstones, only 9 patients (8.4%) experienced cholecystitis and underwent cholecystectomy. In contrast, 97 patients (91.6%) did not suffer any gallstone related symptoms. Among the 1374 patients without gallstones, there were only 10 patients (0.7%) who received cholecystectomy because of acalculous cholecystitis. There was a significant difference of cholecystitis events between patients with and without stones (Figure 2).

Common Bile Duct Stone Formation

In addition to gallstones, common bile duct stone formation was observed in only 20 patients (1.4%). However, there was no difference of common bile duct stone occurrence among the 3 groups (Figure 3). Only cholelithiasis after gastrectomy was a significant contributing factor for choledocholithiasis after gastrectomy (Table 3). For stone removal, endoscopic retrograde cholangiopancreatography was performed in 6 patients, percutaneous transhepatic biliary drainage in 7 patients, and intraoperative T-tube cholangiography in 2 patients, respectively. The remaining 5 patients were observed without any procedure for a median of 33 months.

DISCUSSION

Gastric cancer is the second most prevalent cancer in Korea.[19] Because of nationwide endoscopic health screening, the patients with resectable staging gastric cancer have rapidly increased. In addition, the expected survival of gastric cancer patients has been significantly prolonged due to remarkable progress in surgical techniques.[20] As a result, many patients experienced various changes after surgery and gallstone formation is one of those changes. We therefore aimed to elucidate the relationship between gastric surgery and gallstones.

During the median 47-month follow-up, the incidence of gallstones in this study was 7.2% which is compatible with previous findings.[6,21] Considering that the prevalence of gallstones in the Korean general population is 3.6%,[22–25] the incidence in this study was much higher than in the general population, although there was no adjusted comparison. Concerning such a high incidence after surgery, a previous study[26] suggested that the absence of cyclic phasic contractions of gallbladder after antrectomy may lead to supersaturation of bile and formation of gallstones. However, the pathogenesis of gallstone formation after gastrectomy is not yet fully understood.

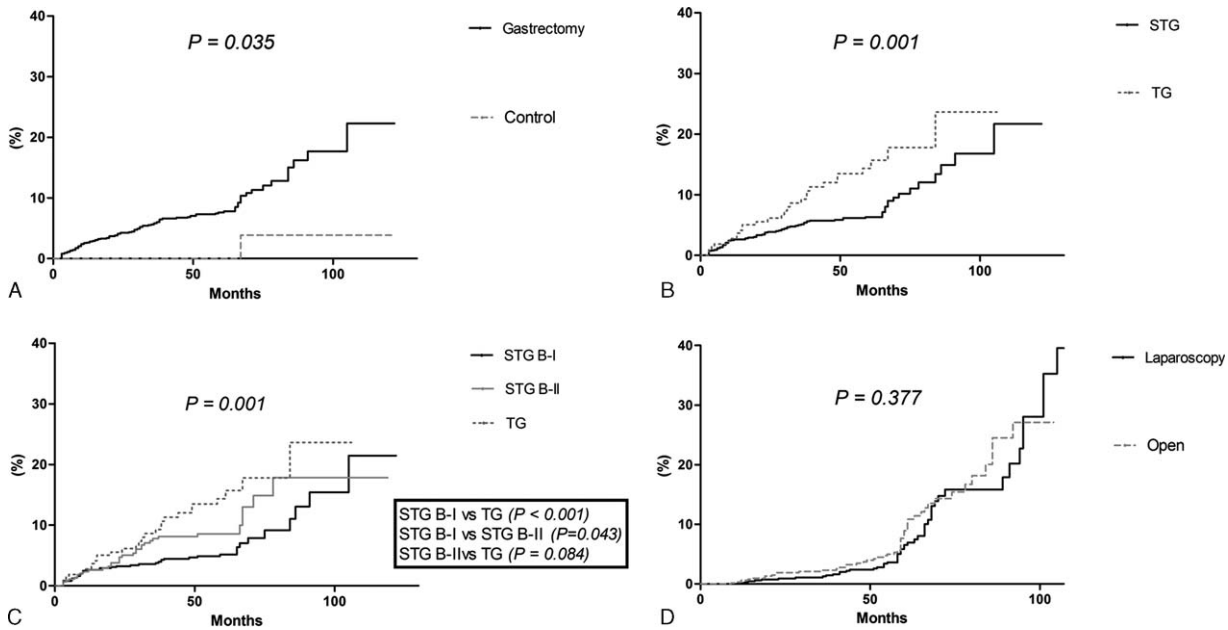

FIGURE 1. Kaplan–Meier analysis of cumulative incidence of postgastrectomy cholelithiasis according to type of surgery. A, The incidence of gallstones was significantly higher after subtotal and total gastrectomy compared with control (after wedge resection) group ($P = 0.035$). B, The incidence of gallstones was significantly higher after total gastrectomy than subtotal gastrectomy ($P = 0.001$). C, The incidence of gallstones was significantly higher after total gastrectomy or subtotal gastrectomy with Billroth II anastomosis than subtotal gastrectomy with Billroth I ananstomosis ($P < 0.001$ and $P = 0.043$). Although the incidence of gallstones tended to be higher after total gastrectomy than subtotal gastrectomy, there was no statistically significant difference ($P = 0.084$). D, The cumulative incidence of gallstone formation was not significantly different between the patients after open and laparoscopic gastrectomy ($P = 0.377$).

TABLE 2. Univariate and Multivariate Analysis of Risk Factors Using the Cox Proportional Hazard Model for Cholelithiasis After Gastrectomy

	Univariate Analysis		Multivariate Analysis	
Variables	**Hazard Ratio (95% CI)**	***P* Value**	**Hazard Ratio (95% CI)**	***P* Value**
Sex, male	2.101 (1.303–3.388)	0.001	1.650 (1.018–2.674)	0.042
Age	1.033 (1.014–1.052)	0.001	1.024 (1.004–1.044)	0.016
Preoperative BMI (kg/m^2)	1.002 (0.944–1.064)	0.941		
Decreased BMI $\geq$ 4% (kg/m^2)	2.080 (1.288–3.359)	0.003	1.658 (1.019–2.696)	0.042
Type of gastrectomy				
STG B-I	1	Ref	1	Ref
STG B-II	1.606 (1.020–2.527)	0.041	1.631 (1.034–2.571)	0.035
TG	2.418 (1.511–3.870)	<0.001	2.348 (1.455–3.790)	<0.001
Stage				
I and II	1	Ref		
III and IV	1.172 (0.654–2.101)	0.593		
LN dissection				
D0 and D1	1	Ref		
D2 and D3	1.571 (0.458–5.384)	0.472		
Diabetes mellitus	2.614 (1.764–3.875)	<0.001	2.153 (1.432–3.236)	<0.001
Liver cirrhosis	1.502 (0.369–6.111)	0.570		
Adjuvant chemotherapy	0.879 (0.584–1.324)	0.537		
Open gastrectomy	1.188 (0.810–1.050)	0.378		

BMI = body mass index, STG B-I = subtotal gastrectomy with Billroth I anastomosis, STG B-II = subtotal gastrectomy with Billroth II anastomosis, TG = total gastrectomy.

According to the surgical methods, several studies reported that the incidence of gallstone formation was affected by the gastrectomy procedure.[12,14,17,18] In these studies, TG was associated with a higher risk of gallstone formation compared to STG, which is consistent with the present study. Concerning this difference, 1 study suggested that the larger the scope of stomach resection, the greater the damage to surrounding blood vessels, nerves, and other tissues, which might affect the postoperative gallbladder contractile function.[6] Compared to the difference between TG and STG, it remains controversial whether STG B-II is more likely to cause gallstone formation than STG B-I. A previous study[18] reported a higher rate of gallstones in patients with STG B-I than that in those with STG B-II. However, more recent studies[14,17,27] reported contrary outcomes consistent with the present study. Several studies suggested this result because of the change in the pattern of cholecystokinin secretion resulting in decreased gallbladder contraction and an increased risk of gallstones.[28–30]

Except for the surgical technique, age, male sex, decreased BMI of more than 4% after gastrectomy, and diabetes were significant risk factors for gallstones after gastrectomy in this study. Among these, aging[31,32] and diabetes[33,34] are well-known risk factors for cholelithiasis. The association between BMI decrease and gallstones in this study could be explained by the fact that gallstones frequently occur after rapid weight loss as a result of gallbladder hypomotility.[35–37] Male preponderance of postgastrectomy cholelithiasis was reported in a few studies,[14,38] however, the mechanism was not clearly revealed. Further study is necessary for its clarification.

In this study, only a small proportion (8.4%) of patients with gallstones received cholecystectomy because of cholecystitis. Although the prophylactic cholecystectomy is still controversial,

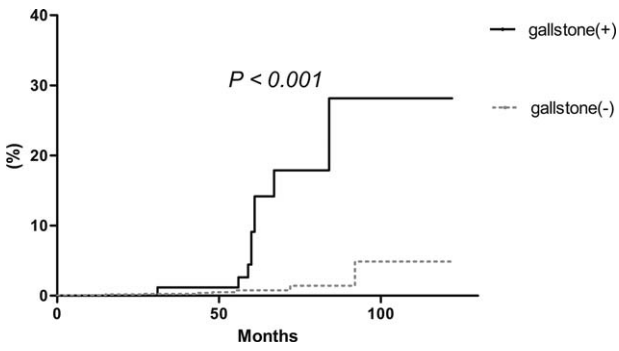

FIGURE 2. Kaplan–Meier analysis of cumulative incidence of cholecystitis revealed that postgastrectomy cholelithiasis is a significant contributing factor for cholecystitis ($P < 0.001$).

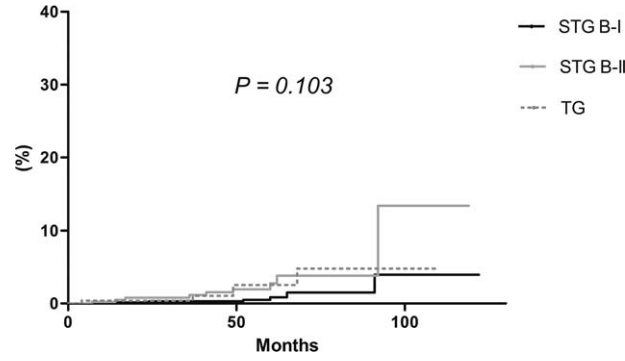

FIGURE 3. Kaplan–Meier analysis of choledocholithiasis after gastrectomy according to type of surgery revealed that there was no difference among the 3 groups ($P = 0.103$).

TABLE 3. Univariate and Multivariate Analysis of Risk Factors Using the Cox Proportional Hazard Model for Choledocholithiasis After Gastrectomy

	Univariate Analysis		Multivariate Analysis	
Variables	**Hazard Ratio (95% CI)**	***P* Value**	**Hazard Ratio (95% CI)**	***P* Value**
Sex, male	39.798 (0.932–1698.990)	0.054	261503.756 (0.000–5.602E+177)	0.951
Age	1.065 (1.017–1.114)	0.007	1.044 (0.989–1.089)	0.135
Preoperative BMI (kg/m^2)	1.032 (0.902–1.179)	0.649		
Decreased BMI ≥4% (kg/m^2)	1.532 (0.558–4.203)	0.408		
Type of gastrectomy				
STG B-I	1	Ref	1	Ref
STG B-II	2.717 (1.008–7.323)	0.048	2.254 (0.834–6.095)	0.076
TG	2.322 (0.736–7.327)	0.151	1.500 (0.464–4.844)	0.498
Stage				
I and II	1	Ref		
III and IV	1.571 (0.458–5.384)	0.472		
LN dissection				
D0 and D1	1	Ref		
D1 and D2	1.543	0.492		
Diabetes mellitus	1.741 (0.675–4.490)	0.252		
Gallstone	14.077 (5.903–33.569)	<0.001	8.731 (3.500–21.777)	<0.001
Liver cirrhosis	3.947 (0.527–29.574)	0.182		
Adjuvant chemotherapy	1.041 (0.403–2.691)	0.934		
Open gastrectomy	1.894 (0.784–4.573)	0.156		

BMI = body mass index, STG B-I = subtotal gastrectomy with Billroth I anastomosis, STG B-II = subtotal gastrectomy with Billroth II anastomosis, TG = total gastrectomy.

our results imply that most gallstones after gastrectomy are also asymptomatic. Therefore, prophylactic cholecystectomy at the time of gastrectomy is deemed unwarranted.

For the choledocholithiasis, postoperative anatomical changes may cause difficulties to access and identify the papilla in the patient after gastrectomy. Actually, among the 20 patients with postoperative choledocholithiasis in our study, only 6 patients were successfully managed by endoscopic retrograde cholangiopancreatography. Because there have been limited studies about postgastrectomy choledocholithiasis, we also try to identify the incidence and the risk factors of choledocholithiasis after gastrectomy. Although no adjusted comparison was available due to the lack of control groups, the incidence of choledocholithiasis was low (1.4%) and it was only associated with gallstones. From this, we may assume that the influence of gastrectomy to the development of choledocholithiasis is clinically insignificant.

There are limitations to the present study. First, this was a retrospective study. Second, the incidence of cholelithiasis might have been underestimated [39,40] because of the predominant use of CT to monitor recurrence. Third, there was no regular follow-up protocol in patients with benign disease.

In conclusion, there are considerable patients with newly developed gallstones after gastrectomy. In addition to well-known risk factors such as old age and diabetes mellitus, surgical methods of STG B-II and TG, male sex, and decreased body mass index are associated with gallstones. Prophylactic cholecystectomy should not be routinely recommended.

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