Gallstone formation after gastrectomy for adenocarcinoma of the stomach

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Abstract  Background/Introduction: An increased incidence of gallstones after gastrectomy has been reported, but with varying risk factors. Purposes/Aims: To delineate the incidence of and risk factors for gallstone formation after gastrectomy. Methods: We retrospectively analyzed patients with Stages 0, I, and II adenocarcinoma of the stomach who had undergone curative gastrectomy with routine lymph node dissection between August 1996 and November 2010. We reviewed the clinical factors, radiographic presentation of the gallstones, and follow-up records. Results: We included 215 patients (124 men and 91 women), with a median age of 53 years (range, 16–89 years). Gallstones were observed in 46 patients (21.4%) during follow-up periods of 6 months–14.5 years. Gallstones were diagnosed at a median of 2.3 years after gastrectomy. The cumulative incidence of gallstones at 5 years and 10 years was 18% and 20%, respectively. Total gastrectomy, Billroth II reconstruction (vs. Billroth I), age ≥60 years, and diabetes mellitus (multivariate odds ratios of 3.8, 3.3, 2.7, and 2.6, respectively) were the risk factors for gallstone formation. Complicated cholelithiasis was identified in seven patients (15.2% of patients with gallstones and 3.3% of all patients) and was more prevalent in patients who had undergone total gastrectomy (5 of 14; 35.7%) than in those who had undergone subtotal gastrectomy (2 of 32; 6.2%; \( p = 0.02 \)). Conclusion: The incidence of gallstone formation was 21.4%. Total gastrectomy, Billroth II reconstruction, age ≥60 years, and diabetes mellitus were risk factors for gallstone formation. Total gastrectomy is also a risk factor for complicated gallstone.

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KEYWORDS
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1. Introduction

A cross-sectional study conducted in a rural Taiwanese village reported a 5.0% prevalence of gallstones, with a slight propensity for the female sex. Risk factors for gallstone disease in both sexes included age and fatty liver. In females, diabetes mellitus, a history of gallstone disease in first-degree relatives, and the use of oral contraceptives were additional risk factors. Liu et al reported a 5.3% prevalence of gallstones in a Taiwanese population that had undergone a paid health examination. In their study, older age, higher body mass index, and type 2 diabetes mellitus were associated with an increased prevalence of gallstone disease.

A higher incidence of gallstones has been reported in gastrectomy patients than in the general population. Wu et al reported cholelithiasis in 30% of patients receiving radical gastrectomy. The pathophysiology remains unclear, but the current theories posit that the surgical dissection of the vagal trunk affects gallbladder contractility and that a nonphysiological reconstruction of the gastrointestinal tract, such as duodenal exclusion, results in increased gallstone formation. The present study evaluated the incidence of gallstone formation after gastrectomy for stomach cancer and identified risk factors for gallstones.

2. Methods

The medical records of patients who had undergone radical gastrectomy for gastric adenocarcinoma were reviewed, and clinical information was retrospectively collected. This study was approved by the Institutional Review Committee of Koo Foundation Sun Yat-Sen Cancer Center, Taipei, Taiwan.

In total, 657 patients had undergone gastrectomy with lymph node dissection between August 1996 and November 2010 at our cancer institute. Curative resection (R0) without microscopic or macroscopic residual diseases was achieved in 503 patients with Stage 0, I, or II cancer [pathologically staged according to the American Joint Committee on Cancer (AJCC) Staging Manual, 7th Edition]. Patients with Stage III and IV cancer were excluded owing to poor survival and early recurrence. Moreover, patients with previous cholecystectomy or cholecystectomy combined with gastrectomy (n = 159); gallstones diagnosed preoperatively or within 6 months of gastrectomy (n = 29); previous partial gastrectomy (n = 7); a history of cholecystitis and obstructive jaundice (n = 3); and insufficient clinical data, imaging, and follow-up (n = 57) and those who underwent reconstruction methods other than Billroth I, Billroth II, Roux-en-Y, and uncut Roux-en-Y (n = 33), were excluded.

In total, 215 patients (124 men and 91 women), with a median age at operation of 53 years (range, 16–89 years) were included. Pathological staging according to the seventh edition of the AJCC Manual showed Stages 0, I, and II for three patients, 142 patients, and 70 patients, respectively. Overall, 180 distal subtotal gastrectomies and 35 total gastrectomies were performed. All patients had undergone lymph node dissections [D1 or more (over D1), 197 patients; D0, 18 patients]. The extent of lymph node dissection was classified according to the Japanese gastric cancer treatment guidelines 2010 (version 3). Lymph node dissection around the liver hilum was not routinely performed in our patients. Moreover, splenectomy was also not a routine procedure accompanying total gastrectomy. Thirty-seven patients received postoperative concurrent chemoradiation therapy; 24 patients had type 2 diabetes mellitus.

Gallstones were identified through abdominal ultrasonography or abdominal computed tomography. According to the in-house guidelines, radiographic imaging after radical gastrectomy for gastric cancer was performed every 6 months for the first 2 years and annually thereafter. Gallstone-related symptoms and complications include typical biliary colic, acute cholecystitis, common bile duct stones with obstructive jaundice, and gallstone pancreatitis.

Clinical factors—age at gastrectomy, sex, cancer stage, diabetes mellitus, method of gastrectomy, extent of lymph node dissection, method of reconstruction, and postoperative concurrent chemoradiation therapy—were recorded for analysis.

The cumulative incidence of gallstones after gastrectomy was evaluated using the Kaplan–Meier method. Univariate analysis of risk factors for gallstone formation was performed using the Chi-square and Fisher’s exact tests for categorical variables and Student t test for numerical variables. Multivariate analysis was performed using a logistic regression model. A p value < 0.05 was considered statistically significant. Statistical analyses were performed using SAS software, version 9.3 (SAS Institute, Cary, NC, USA).

3. Results

Gallstones were detected in 46 of the 215 patients (21.4%) during a median follow-up period of 3.5 years (range, 0.5–14.5 years). Gallstones were diagnosed at a median of 2.3 years (range, 0.5–11.5 years) after gastrectomy. Half of the patients with gallstones were diagnosed within 2 years after surgery, mostly during routine abdominal ultrasonography. The incidence of new cases peaked 1–2 years after gastrectomy and then gradually decreased (Figure 1). The cumulative incidence of gallstones at 5 years and 10 years after gastrectomy was 18% and 20%, respectively (Figure 2).

Furthermore, univariate and multivariate analyses revealed that an age at operation of ≥ 60 years, type 2 diabetes mellitus, total gastrectomy, and Billroth II reconstruction (vs. Billroth I) were independent risk factors for gallstone formation (Tables 1 and 2).

Seven patients with complicated gallstones, accounting for 3.3% of all gastrectomy patients and 15.2% of patients with newly diagnosed gallstones, were clinically diagnosed with acute cholecystitis. Three patients had undergone cholecystectomy soon after visiting the emergency department of other hospitals, three patients had undergone urgent operations in our hospital, and one patient refused surgery. Moreover, three patients had common bile duct stones with associated bile duct obstruction and infection. An episode of acute cholecystitis occurred at a median of 4.3 years (range, 1.7–6 years) after the initial surgery. This event was more
significant in patients who had undergone total gastrectomy (5 of 14; 35.7%) than in those who had undergone distal subtotal gastrectomy (2 of 32; 6.2%; \( p < 0.02 \)).

Diabetes mellitus and age at operation were unassociated with complicated gallstone.

## 4. Discussion

Our study showed a cumulative incidence of gallstones in 21.4% (46 of 215 patients), which is consistent with previous reports.\(^3\)\(^-\)\(^7\) A pooled analysis of 16 studies on gallstone formation after upper gastrointestinal surgery reported an incidence of 17.5%.\(^3\) Moreover, a Peruvian observational case series analyzed the frequency and development of gallbladder stones after subtotal and total gastrectomy and reported a 19.6% incidence, with a mean development period of 3.1 years.\(^4\) In this study, the cumulative incidence of gallstones at 5 years and 10 years after gastrectomy was 18% and 20%, respectively, which is consistent with the report of Kobayashi et al\(^5\) (13.6% and 22.1%, respectively).

Factors associated with gallstone formation after gastrectomy include lymph node dissection, extent of gastrectomy, and method of reconstruction. Increased gallstone formation has been observed after radical gastrectomy compared with that after simple gastrectomy.\(^6\)\(^-\)\(^10\) More extensive lymph node dissection results in higher incidences of gallstone formation.\(^6\)\(^,\)\(^7\) In our study, almost all patients had undergone an over-D1 dissection; therefore,
this difference was not observed. Kobayashi et al\textsuperscript{5} reported that the dissection of lymph nodes in the hepatoduodenal ligament was the most significant risk factor for gallstones. However, a thorough dissection of the nodes of the hepatoduodenal ligament was not routinely performed in our patients.

Furthermore, Kobayashi et al\textsuperscript{5} reported that the incidence of gallstones was significantly higher after total gastrectomy than after partial gastrectomy; our study presented similar findings (40\% vs. 17.8\%; odds ratio, 3.8). Furthermore, an increased incidence of acute cholecystitis was observed in patients who had undergone total gastrectomy compared with those who had undergone distal subtotal gastrectomy [35.7\% (5 of 14 patients) vs. 6.2\% (2 of 32 patients); \(p = 0.02\)]. However, the difference between total gastrectomy and distal gastrectomy was nonsignificant in the study of Fukagawa et al.\textsuperscript{7} Gastrectomy as a risk factor might be affected by the extent of lymph node dissection.

The reconstruction method applied affects the risk of gallstone formation. Segawa et al\textsuperscript{10} and Ikeda et al\textsuperscript{11} reported no difference between Billroth II and Billroth I reconstruction in terms of the risk of gallstones. Similarly, Inokuchi et al\textsuperscript{12} found no difference between Roux-en-Y and Billroth I reconstruction after laparoscopic distal gastrectomy. However, Kobayashi et al\textsuperscript{5} identified duodenal exclusion as a crucial risk factor for gallstone formation. Our results showed that Billroth II was associated with an increased incidence of gallstones compared with Billroth I (31.4\% vs. 10.7\%). The differences in the effects of Roux-en-Y, uncut Roux-en-Y, and Billroth I reconstruction were nonsignificant.

We observed gallstone formation in half of the analyzed patients within 2 years of gastrectomy; this incidence gradually decreased in the following years (Figure 2). Fukagawa et al\textsuperscript{1} reported that 64.7\% of the detected gallstones appeared within 1 year of radical gastrectomy.

A prospective observational study conducted by Inoue et al\textsuperscript{13} showed that 42\% of 46 patients had gallbladder sludge formation and significantly decreased gallbladder contractility 1 month after radical gastrectomy. However, most sludge disappeared within 12 months, in tandem with the gradual recovery of gallbladder contractility. Nevertheless, further follow-up revealed that 18.8\% of the patients developed gallstones, mostly at > 6 months after gastrectomy. Gallbladder stones evolved in only two patients who had received intravenous hyperalimentation.\textsuperscript{13} Gallbladder enlargement and suddenly decreased contractile dysfunction in the early postgastrectomy period is closely associated with the formation of debris echogenicity in the gallbladder, but it is not presumed to be the essential factor in the pathogenesis of gallstone formation.\textsuperscript{14} In our study, a subgroup analysis of 35 patients diagnosed with gallstones at > 6 months after gastrectomy showed that almost all radiographic findings demonstrated small stones with or without sludge. These stones typically persisted throughout the follow-up period, and gallstones could not be visualized later in only one patient.

Gallbladder stones development is considered a multifactorial process. The motility of the gallbladder is controlled by both neural and hormonal interactions, such as vagal signaling and cholecystokinin (CCK)\textsuperscript{15}; both factors induce gallbladder contraction, and the disruption of either pathway can potentially cause gallbladder dysfunction. Yi et al\textsuperscript{16} conducted an anatomical study of the human gallbladder and showed three pathways of nerve innervation of the gallbladder: through the anterior hepatic plexus, posterior hepatic plexus, and phrenic nerve. In particular, the preservation of the neural pathway from the anterior hepatic plexus through the cystic artery and duct is crucial for maintaining gallbladder innervation.\textsuperscript{16} Because patients with total gastrectomy typically undergo the division of both vagal trunks, vagal signaling would be blocked at the proximal site.

CCK, a peptide secreted in the duodenum, stimulates the release of digestive enzymes from the pancreas and bile from the gallbladder. Masclee et al\textsuperscript{17} reported significantly delayed gallbladder emptying after the ingestion of a fatty meal in patients who had undergone partial gastrectomy compared with normal patients. Both groups exhibited the same basal CCK levels, but gastrectomy patients had a lower CCK peak after oral intake. However, an analysis of CCK levels an hour after meal ingestion showed that both groups had comparable CCK levels and gallbladder emptying.\textsuperscript{17} The correlation between CCK levels and gallstone formation has not yet been reported, possibly because of its minor role or other compensatory mechanisms.

Whether prophylactic cholecystectomy is indicated for patients with adenocarcinoma of the stomach undergoing radical gastrectomy remains unclear. Fukagawa et al\textsuperscript{1} examined 672 patients and reported that 173 (25.7\%) patients developed gallstones after surgery, and only 12 (6.9\% of 173) were symptomatic and required cholecystectomy. They found that prophylactic cholecystectomy is not beneficial for most patients, and that only patients with extensive lymph node dissection should be considered for prophylactic cholecystectomy. Kobayashi et al\textsuperscript{5} demonstrated that most patients with gallstones were asymptomatic after radical gastrectomy, and < 0.5\% of the patients required cholecystectomy. Gillen et al\textsuperscript{18} reviewed concurrent cholecystectomy during gastric and esophageal resection and reported higher calculated additional morbidity compared with late cholecystectomy. However, the preliminary report of the CHOLEGAS (Gastrectomy Plus Prophylactic Cholecystectomy in Gastric Cancer Surgery) study, a multicenter randomized study examining the safety of prophylactic cholecystectomy during gastrectomy for cancer, found no increase in perioperative morbidity, mortality, and costs.\textsuperscript{18,19} Cholecystectomy is an uncomplicated procedure; the theoretical advantage of prophylactic cholecystectomy is that it avoids reintervention for cholecystitis.\textsuperscript{15} In our study, total gastrectomy was a crucial factor for postoperative gallstone formation and subsequent complications. However, most patients do not benefit from combined cholecystectomy. Prophylactic cholecystectomy is definitely not indicated in patients with distal subtotal gastrectomy. Furthermore, the widespread application of minimally invasive gastrectomy may reduce the necessity of prophylactic gallbladder removal for preventing future open cholecystectomy. For early gastric cancer management, procedures for preserving the vagus nerve may be an alternative.

In summary, the incidence of gallstone formation after gastrectomy for adenocarcinoma of the stomach was 21.4\%.
Half of the gallstones were detected within 2 years of gastrectomy. The cumulative incidence of gallstone formation at 5 years and 10 years after gastrectomy was 18% and 20%, respectively. Total gastrectomy, Billroth II reconstruction (vs. Billroth I), age at operation ≥ 60 years, and type 2 diabetes mellitus were the independent risk factors for gallstone formation. Furthermore, gallstones observed 6 months after gastrectomy were typically small and persistent. Only seven patients had acute cholecystitis, and three had common bile duct stones. Total gastrectomy may be the most crucial risk factor for complicated cholelithiasis.

References