J Hepatobiliary Pancreat Surg (2004) 11:319–323
DOI 10.1007/s00534-004-0914-7

Journal of HBP Surgery

Increased risk of cholelithiasis after esophagectomy

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Abstract
Background/Purpose. Truncal vagotomy enhances gallstone formation. As esophagectomy involves truncal vagotomy, it was hypothesized that esophagectomy would increase the risk of cholelithiasis. This study was intended to test this hypothesis and to elucidate factors influencing the incidence of cholelithiasis after esophagectomy.
Methods. The study was a retrospective analysis of 136 patients with esophageal carcinoma who had survived for 5 years or longer after esophagectomy. Eight patients (5.9%) had cholelithiasis before esophagectomy. Of the remaining 128 patients, 113 underwent abdominal ultrasonographic examination for cholelithiasis twice a year after esophagectomy; the median follow-up time was 89.5 months (range, 60–117 months).
Results. Gallstones developed in 26 (23%) of the 113 patients undergoing regular ultrasonographic examination. The cumulative incidence of cholelithiasis reached a plateau of 34% at 10 years after esophagectomy. Reduction of body mass index after esophagectomy was the strongest independent predictor of gallstone formation after esophagectomy ($P = 0.0001$, log-rank test; $P = 0.0003$, Cox's proportional hazards model). The prevalence of cholelithiasis at 5 years after esophagectomy (18/113; 16%) was significantly higher than that before esophagectomy (8/136; 5.9%; $P = 0.012$, Fisher's exact test).
Conclusions. Esophagectomy yields an increased risk of the development of cholelithiasis. Truncal vagotomy and postsurgical malnutrition may contribute to this increased gallstone formation after esophagectomy.

Key words Cholelithiasis · Esophagectomy · Truncal vagotomy · Body mass index · Multivariate analysis

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Received: January 9, 2004 / Accepted: March 17, 2004

Introduction

Truncal vagotomy results in gallbladder hypomotility,[1–12] biliary stasis,[1,3–5,8–12] and various changes in bile composition,[5,8–15] all of which were considered to enhance gallstone formation.[1–14] Total gastrectomy involves truncal vagotomy and is a high-risk procedure for the development of cholelithiasis.[1–3] As truncal vagotomy is an integral part of esophagectomy, we hypothesized that esophagectomy would also predispose to gallstone formation. To date, there have been few reports investigating whether esophagectomy enhances gallstone formation.[16]

The aims of this study were to test the hypothesis and to elucidate factors influencing the incidence of cholelithiasis after esophagectomy.

Methods

Of 374 consecutive patients who underwent a radical esophagectomy (with truncal vagotomy) for esophageal carcinoma between January 1986 and December 1996 at Niigata University Medical Hospital, 136 survived for 5 years or longer. These 5-year survivors were selected for this retrospective study. The cohort comprised 120 men and 16 women, ranging in age from 44 to 84 years (median, 63 years) at the time of esophagectomy. The median follow-up period was 89.5 months (range, 60–177 months). All patients were Japanese. All of their esophageal tumors were squamous cell carcinomas.

Of the 136 patients, 4 had undergone cholecystectomy for gallstone disease prior to esophagectomy. The remaining 132 patients underwent ultrasonographic examination of the gallbladder before esophagectomy, which revealed gallstones in 4 patients, all of whom underwent cholecystectomy simultaneously with esophagectomy. Thus, 8 (5.9%) patients had cholelithiasis before esophagectomy in this series.

After esophagectomy, 113 patients underwent ultrasonographic examination of the gallbladder and other abdominal viscera twice a year during the follow-up period. Follow-up data of these patients were analyzed to determine the incidence of cholelithiasis after esophagectomy. The other 23 patients were excluded from this analysis, either because of lack of follow-up ultrasonographic examinations ($n = 15$) or because of cholecystectomy before or at the time of esophagectomy ($n = 8$). In this study, the development of cholelithiasis after esophagectomy was defined as the first detection of gallstones by follow-up ultrasonography.

To elucidate factors influencing gallstone formation after esophagectomy, 11 variables were examined: age, sex, history of gastrectomy, diabetes mellitus, body mass index (BMI) at the time of esophagectomy, tumor stage, type of esophagectomy, organ used for reconstruction, duration of fasting after esophagectomy, adjuvant chemotherapy, and reduction of BMI after esophagectomy (BMI at the time of esophagectomy minus BMI at 1 year after esophagectomy). These variables were selected because they are either known risk factors of cholelithiasis[17] or factors related to esophageal cancer/esophageal surgery. BMI (weight (kg)/height $(m)^2$)[18] was calculated for each patient as the time of esophagectomy and at 1 year after operation. Tumor stage was determined according to the clinical tumor-nodes-metastases (cTNM) staging system.[19]

Gallbladder stones retrieved from two patients who underwent cholecystectomy for gallstone disease after esophagectomy were analyzed for stone composition. Gross inspection of the cut surface of the gallstones,[17] and infrared spectroscopy, using the KBr-disk method,[20] were used for the composition analysis.

Statistical analysis

Cumulative incidences of cholelithiasis after esophagectomy were estimated using the Kaplan-Meier method. Differences in the incidence of cholelithiasis were evaluated using the log rank test. Cox's proportional hazards model was performed to identify factors independently associated with gallstone formation after esophagectomy. This method involved a backward stepwise variable selection with entry and removal limits of $P < 0.1$ and $P > 0.15$, respectively. Fisher's exact test was used to compare prevalences of cholelithiasis. All statistical evaluations were performed using the SPSS 9.0 J (SPSS Japan, Tokyo, Japan) software package. Values of $P < 0.05$ were considered statistically significant.

Results

Incidence of cholelithiasis after esophagectomy

Gallstones developed in 26 (23%) of the 113 patients undergoing regular ultrasonographic examination after esophagectomy; 24 with cholecystolithiasis and 2 with cholecystocholedocholithiasis. The prevalence of cholelithiasis at 5 years after esophagectomy was 16% (18/113), which was significantly higher than that before esophagectomy (8/136; 5.9%; $P = 0.012$). The cumulative incidence of cholelithiasis increased with time and reached a plateau of 34% at 10 years after esophagectomy (Fig. 1). The median interval between esophagectomy and the first detection of cholelithiasis was 26 months (range, 4–120 months). Five of the 26 (19%) patients with cholelithiasis after esophagectomy were symptomatic. Two symptomatic patients underwent a cholecystectomy; the retrieved gallstones were brown-pigment stones.

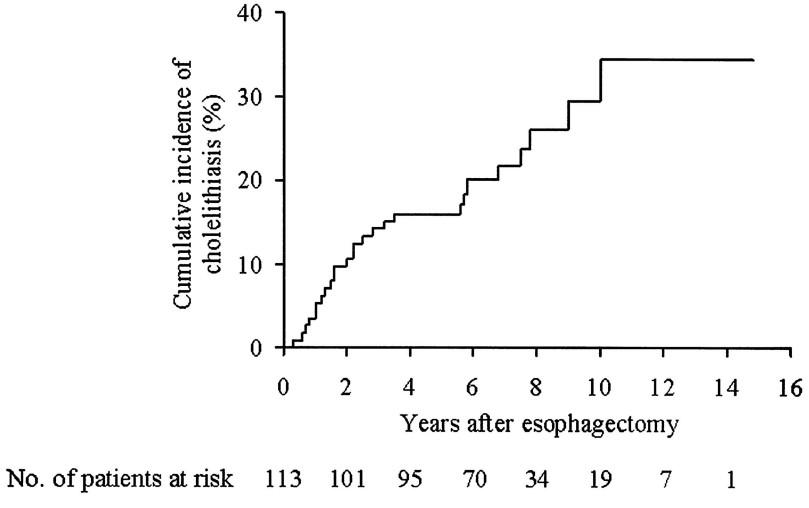

Fig. 1. The cumulative incidence of cholelithiasis after esophagectomy. It was 5.3% at 1 year, 11% at 2 years, and 16% at 5 years, and reached a plateau (34%) at 10 years after esophagectomy

Table 1. Factors influencing gallstone formation after esophagectomy, by univariate analysis

Variable	Modality	No. of patients	Incidence of cholelithiasis (%)		*P* Value
			5-Year	10-Year	
Age (years)	≤60	38	21	39	0.3822
	>60	75	13	26	
Sex	Male	99	16	28	0.4418
	Female	14	14	41	
History of gastrectomy	Absent	107	15	29	0.1794
	Present	6	33	50	
Diabetes mellitus	Absent	99	15	29	0.4895
	Present	14	21	33	
BMI at the time of esophagectomy	<25	104	14	30	0.4667
	≥25	9	33	33	
cTNM staging	I	52	14	30	0.5332
	IIA, IIB, III	61	18	31	
Type of esophagectomy	Transthoracic	75	20	33	0.2120
	Transhiatal	38	8	25	
Organ used for reconstruction[a]	Stomach	100	14	28	0.1045
	Colon	12	25	45	
Duration of fasting after esophagectomy (days)	≤14	65	9	30	0.1943
	>14	48	25	32	
Adjuvant chemotherapy	Absent	67	13	35	0.8005
	Present	46	20	26	
Reduction of BMI after esophagectomy	<2.0	61	7	11	0.0001
	≥2.0	52	27	48	

BMI, body mass index[18]; cTNM, clinical tumor-nodes-metastases staging system[19]
[a] One patient was excluded from the analysis, because the small intestine was used for reconstruction

Table 2. Independent factors influencing gallstone formation after esophagectomy among 112 patients[a]

Variable	Modality	No. of patients	RR	CI	*P* Value
Reduction of BMI after esophagectomy	<2.0	61	1.00		
	≥2.0	51	6.33	2.32–17.29	0.0003
Organ used for reconstruction	Stomach	100	1.00		
	Colon	12	3.60	1.30–9.92	0.0134

RR, relative risk; CI, 95% confidence interval
[a] One patient was excluded from the multivariate analysis, because the small intestine was used for reconstruction

Factors influencing gallstone formation after esophagectomy

Univariate analysis revealed that reduction of BMI after esophagectomy was the only significant factor predicting gallstone formation ($P = 0.0001$; Table 1). Four variables (reduction of BMI after esophagectomy, organ used for reconstruction, history of gastrectomy, and duration of fasting after esophagectomy) with a statistical value of $P < 0.2$ in the univariate analysis were entered into multivariate analysis, which revealed two variables as independent (Table 2). Reduction of BMI after esophagectomy was the strongest independent risk factor for gallstone formation after esophagectomy.

Discussion

This study is the first demonstration of the increased risk of cholelithiasis after esophagectomy. Up to 10 years after esophagectomy, one-third of the patients who had a normal gallbladder at the time of operation had developed gallstones (Fig. 1). The prevalence of cholelithiasis after esophagectomy was markedly higher than that before esophagectomy. As there is no recognized association between esophageal cancer and gallstone disease, this increased risk may have been a result of the esophageal surgery. Tachibana and colleagues[16] reported a 5.5% incidence of cholelithiasis after esophagectomy. The relatively low incidence in their report may be attributable to the short follow-up period of 18.6 months after esophagectomy,[16] and is compa-

rable to the incidence of cholelithiasis at 1 year (5.3%) or at 2 years (11%) after esophagectomy in the current series (Fig. 1). The prevalence of cholelithiasis is around 5% in the general middle-aged population in Japan[21] and increases to around 10% in the elderly.[22] This suggests that the risk of the development of cholelithiasis is much higher after esophagectomy compared with the general population of similar ages.

Gastrectomy has been considered as another risk factor for cholelithiasis.[1–6] Truncal vagotomy during peptic ulcer surgery is associated with the development of cholelithiasis.[5–12,14] Hauters et al.[1] reported a high incidence of cholelithiasis (47%) after total gastrectomy and concluded that vagotomy performed during the resection may have contributed to the development of cholelithiasis. Gafa et al.[2] and Pezzolla et al.[3] also reported similar results. Considering that truncal vagotomy is common to both total gastrectomy and esophagectomy, the increased gallstone formation after esophagectomy may be related to the vagotomy that is performed during the resection.

Truncal vagotomy leads to gallbladder hypomotility[1–12] and biliary stasis,[1,3–5,8–12] which enhance the formation of all types of gallstones. In addition, bile composition changes after truncal vagotomy, with reduced cholesterol saturation[15] and increased levels of both unconjugated bilirubin and ionized calcium.[13] These changes in bile composition after truncal vagotomy may explain the predominance of brown-pigment stones in patients with cholelithiasis after gastrectomy.[1,9,23]

Bacteribilia is essential for brown-pigment gallstone formation.[23–27] Truncal vagotomy and/or gastrectomy may increase the incidence of bacteribilia[4,9] through biliary stasis,[1,3–5,8–12,28] dysfunction of the sphincter of Oddi,[5,10,11,29,30] and hypoacidity in the duodenum.[3,7,9,10] Thus, it is very likely that bacteribilia associated with truncal vagotomy enhances brown-pigment stone formation in patients who have undergone total gastrectomy or esophagectomy. In fact, both patients in this series who underwent cholecystectomy for gallstone disease after esophagectomy had brown-pigment stones. Reduction of BMI was the strongest predictor of gallstone formation after esophagectomy; it likely represents the decreased intake of nutrients, which may enhance brown-pigment stone formation, as decreased intake of protein and fat is known to encourage bacterial β-glucuronidase activity in bile.[23–27] Therefore, truncal vagotomy combined with postsurgical malnutrition may promote brown-pigment gallstone formation in patients who have undergone esophagectomy.

Gallstones after gastrectomy are mostly asymptomatic, and prophylactic cholecystectomy at the time of gastrectomy is deemed unwarranted.[31] Although one-third on our patients developed gallstones after esophagectomy, only one-fifth of the patients became symptomatic. Thus, we think that prophylactic cholecystectomy at the time of esophagectomy is unwarranted. Cholecystectomy is indicated for gallstones after esophagectomy, provided that they are symptomatic.

The retrospective nature of this study and the exclusion of 15 patients because of incomplete follow-up were the two main limitations of this study. We feel, however, that these factors did not significantly influence the outcome of this study, as the difference shown between groups was too marked to be random or to be influenced by the above factors. This work has highlighted the impact of truncal vagotomy and nutritional status on gallstone formation after esophagectomy.

In conclusion, esophagectomy yields an increased risk of the development of cholelithiasis. Truncal vagotomy combined with postsurgical malnutrition may contribute to this increased gallstone formation in patients who have undergone esophagectomy.

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