

# Esophageal Cancer in Patients With a History of Distal Gastrectomy

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**Hypothesis:** There is an association between a history of distal gastrectomy and the development of esophageal cancer. Surgical treatment of esophageal cancer in patients with a history of gastrectomy is more complicated but will not result in increased mortality in an experienced center.

**Design:** Case-control study.

**Setting:** Tertiary care center for the treatment of esophageal cancer.

**Patients:** Forty patients with a history of gastrectomy and 1266 patients with intact stomachs who underwent esophagectomy for cancer.

**Main Outcome Measures:** Patients' demographic characteristics, tumor characteristics, operative morbidity, mortality, and long-term survival.

**Results:** There were more squamous tumors located in the lower third of the esophagus in those who had a history of gastrectomy compared with those with intact stomachs (16 [41%] of 40 patients vs 318 [25%] of 1266 patients;  $P = .04$ ). This difference was more pronounced after Billroth I vs Billroth II gastrectomy (8 [73%] of 11 pa-

tients vs 8 [29%] of 28 patients;  $P = .03$ ). Twenty-four patients (60%) in the gastrectomy group and 738 (58%) in the nongastrectomy group underwent surgical resection ( $P = .87$ ). The operative time (300 [160-465] vs 220 [90-520] minutes;  $P < .001$ ) was longer and more blood loss (1000 [300-2500] vs 700 [150-7000] mL;  $P < .001$ ) was encountered for esophagectomy after previous gastrectomy (data are given as median [range]). A colon interposition was the substitute conduit of choice in the gastrectomy group (20 [83%] of 24 patients), and the stomach was the preferred loop in those with intact stomachs (729 [99%] of 738 patients). Postoperative complication rates were similar. In-hospital mortality rates also did not differ for those with a history of gastrectomy vs those without such a history (12% for both,  $P > .99$ ). Median survival after resection was 13.8 and 12.5 months for patients who did and did not undergo prior gastrectomy, respectively ( $P = .62$ ).

**Conclusions:** A history of gastrectomy (especially the Billroth I type) is associated with more lower-third squamous cell esophageal carcinomas. Surgical resections in patients with such a history were more complicated but resulted in similar outcomes.

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**P**ATIENTS WITH a history of distal gastrectomy are an interesting group to study because duodenogastroesophageal reflux is thought to be common.<sup>1,2</sup> It has been postulated that this may contribute to the pathogenesis of esophageal cancer. However, this suggested association between the development of esophageal cancer and a history of distal gastrectomy is controversial.<sup>3-5</sup> With the increasing incidence of adenocarcinoma in the West, adenocarcinoma of the distal esophagus, attributed to gastroesophageal reflux disease and Barrett esophagus, makes up to two thirds of reported cases.<sup>6</sup> The most common histological type

for esophageal cancer in the East, however, remains squamous cell carcinoma; most of these are located in the middle third of the esophagus. Barrett cancer of the lower esophagus is uncommon, probably related to a low prevalence of gastroesophageal reflux disease.

This study determines if there is any difference in the clinicopathological features of esophageal cancer in patients with a history of distal gastrectomy compared with those without such a history. The findings are interpreted in the context of the local Chinese population, in whom the incidence of gastroesophageal reflux and Barrett esophagus is low. In addition, prior gastrectomy is expected to complicate surgical treatment

of esophageal cancer. It is hypothesized that in a center with experience in managing esophageal disease, similar morbidity, mortality, and long-term survival can be achieved compared with patients who did not undergo prior distal gastrectomy.

## METHODS

Patients with cancer of the esophagus treated at the Department of Surgery, University of Hong Kong Medical Centre, Queen Mary Hospital, were entered into a prospective esophageal cancer database. Patients with a history of distal gastrectomy were identified, and the clinicopathological data of these patients were examined. Hospital medical records were reviewed when additional information was required. Excluded from this study were patients with cancer of the gastric cardia, because in postgastrectomy patients, it would be difficult to differentiate whether they were newly developed gastroesophageal junction tumors or gastric stump cancers infiltrating the gastroesophageal junction. Also excluded were patients who underwent previous gastric surgery other than gastrectomy, such as vagotomy and pyloroplasty, and those who underwent gastrectomy for cancer of the stomach within 5 years before the diagnosis of esophageal cancer. Patients without a history of gastrectomy treated in the same period form the control group.

The tumor location in the esophagus, the histological type of tumor, and the tumor stage were determined according to the Union Internationale Contre le Cancer classification.<sup>7</sup> The lower third of the esophagus was defined as the distal half of the esophagus between the tracheal bifurcation and the gastroesophageal junction.

The choice of surgical approach depended on the location of the tumor, the extent of the tumor, and the cardiovascular assessment of the patient. The various techniques have been described in previous publications.<sup>8-10</sup> In brief, transthoracic resection via a right-sided thoracotomy was preferred. In patients with compromised cardiopulmonary functions, a transhiatal esophagectomy was performed. When the stomach was used for reconstruction for middle- and lower-third tumors, the esophagogastrostomy was usually placed in the right thoracic cavity. In those with tumors of the superior mediastinal segment, a 3-phase esophagectomy was performed, with reconstruction to the neck. For patients with a history of distal gastrectomy, a colonic conduit was most commonly used for esophageal substitution; the ascending colon, based on the right or middle colonic vessels, was preferred.

Cardiovascular complications included any arrhythmia, myocardial infarction, heart failure, and pulmonary embolus. Pulmonary complications were defined as the development of aspiration pneumonia, bronchopneumonia, respiratory failure, and shock lung. Deaths within 30 days after surgery and hospital mortality rates within the same hospital admission were reported. Patients were followed up monthly for the first year and every 3 months afterward.

Continuous variables are expressed as mean  $\pm$  SD, and non-parametric data as median (range). Statistical differences between groups were determined by analysis of variance, Mann-Whitney test,  $\chi^2$  test, and Fisher exact test, where appropriate. Survival was calculated with the Kaplan-Meier method, and differences were compared with the log-rank test. Statistical significance was set at  $P < .05$ . All calculations were performed with a computer program (SPSS, version 8.0; SPSS Inc, Chicago, Ill).

## RESULTS

From July 1, 1982, to March 31, 1999, 1306 patients with cancer of the thoracic esophagus were treated; of these

**Table 1. Patient Demographic Characteristics\***

Characteristic	Previous Gastrectomy		P Value
	Yes (n = 40)	No (n = 1266)	
Age, y	65.1 $\pm$ 10.0	63.9 $\pm$ 9.9	.42
Male-female ratio	37:3	1056:210	.19
Smoking history†	36	974	.06
Albumin level, g/dL	3.9 $\pm$ 0.5	4.0 $\pm$ 0.6	.53
Hemoglobin level, g/dL	12.4 $\pm$ 1.5	12.5 $\pm$ 1.8	.65
Body weight, kg	47.3 $\pm$ 9.0	50.0 $\pm$ 9.6	.07
Weight loss, %	12.3 $\pm$ 11.0	9.8 $\pm$ 10.0	.20
Level of tumor‡			
Esophageal			
Cervical	2 (5)	71 (6)	
Thoracic			
Upper third	3 (8)	89 (7)	
Middle third	18 (46)	756 (60)	
Lower third	16 (41)	318 (25)	.04
Double level	0	32 (3)	

\*Data are given as mean  $\pm$  SD unless otherwise indicated.

†Data are given as number of patients.

‡Data are given as number (percentage) of patients. Percentages may not total 100 because of rounding. In one patient who underwent a prior gastrectomy, the level of tumor could not be ascertained from the patient record.

patients, 40 had a history of distal gastrectomy and satisfied the inclusion criteria.

The indications for previous gastrectomy were duodenal ulcer in 9 patients, gastric ulcer in 6, unspecified peptic ulcer in 20, adenocarcinoma of the stomach in 3, a gastric leiomyoma in 1, and an unspecified gastric mass in 1. For all patients with an indication for gastrectomy other than ulcer disease, the operation was performed more than 5 years before the diagnosis of esophageal cancer. None of the esophageal tumors were judged to be recurrent or metastatic from gastric cancer. The mean interval between previous gastrectomy and diagnosis of esophageal cancer was 16.4 years (range, 1-40 years). Eleven patients underwent a Billroth I and 29 a Billroth II gastrectomy. The mean interval between gastrectomy and diagnosis of esophageal cancer was also similar for the 2 types of previous gastrectomy (18.8 years for Billroth I vs 15.5 years for Billroth II;  $P = .41$ ). Demographic characteristics of the patients are given in **Table 1**.

A significant difference in the distribution of tumor location was observed (Table 1 and **Table 2**). The proportion of lower-third tumors in patients after gastrectomy (16 [41%] of 39 patients) was significantly higher compared with that of the patients with intact stomachs (318 [25%] of 1266 patients) ( $P = .04$ ). This increase was more pronounced after Billroth I vs Billroth II gastrectomy ( $P = .03$ ).

The histological subtype for tumors after prior gastrectomy was squamous cell in 37 (92%) of the patients, mucoepidermoid in 2 (5%), and anaplastic carcinoma in 1 (2%) (percentages do not total 100 because of rounding). For those without a history of gastrectomy, squamous cell tumors were found in 1209 (95%) of the patients, adenocarcinomas in 11 (1%), and other malignant tumors in 46 (4%). For those who had lower-third tumors, none in the gastrectomy group was adenocarci-

**Table 2. Level of Tumor Distribution According to Type of Previous Gastrectomy\***

Level of Tumor	Type of Billroth Gastrectomy	
	I (n = 11)	II (n = 28)†
Esophageal		
Cervical	1 (9)	1 (4)
Thoracic		
Upper third	1 (9)	2 (7)
Middle third	1 (9)	17 (61)
Lower third	8 (73)	8 (29)

\*Data are given as number (percentage) of patients. Percentages may not total 100 because of rounding.

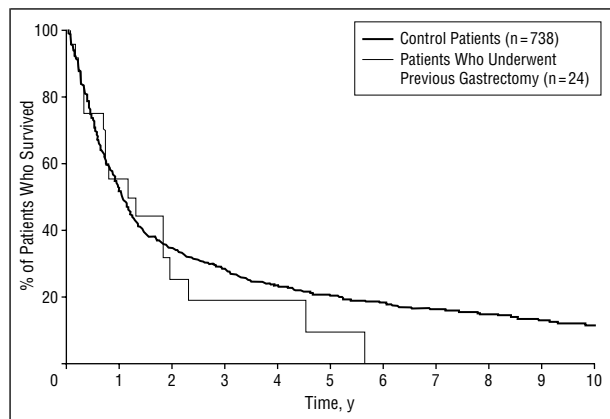
†In one patient, the level of tumor could not be ascertained from the patient record.

**Table 3. Postoperative Complications and Mortality Rates in Patients Who Underwent Resection\***

Complications	Previous Gastrectomy		P Value
	Yes (n = 24)	No (n = 738)	
Cardiac†	8 (33)	191 (26)	.48
Pulmonary†	7 (29)	153 (21)	.31
Anastomotic leak	2 (8)	25 (3)	.21
Gangrene of loop	0	5 (1)	>.99
Vocal cord paralysis	2 (8)	64 (9)	>.99
Hemorrhage	1 (4)	23 (3)	.54
Chylothorax	0	5 (1)	>.99
Thoracic empyema	1 (4)	11 (1)	.32
Intraperitoneal sepsis	0	3 (<1)	>.99
Mortality			
30 d	1 (4)	23 (3)	.54
Hospital	3 (12)	88 (12)	>.99

\*Data are given as number (percentage) of patients.

†These complications are explained in the "Methods" section.



Kaplan-Meier survival curves in patients who underwent surgical resection for those with and without a history of gastrectomy.

noma, while 6 (2%) of 318 were adenocarcinoma in those who did not undergo previous gastrectomy.

Of the 40 patients with a history of gastrectomy, 24 (60%) underwent resection, compared with 738 (58%) of the 1266 in the nongastrectomy group ( $P = .87$ ). The substitute organs for reconstruction after esophagec-

tomy for patients who underwent previous distal gastrectomy were the ascending colon in 17 (71%), the descending colon in 3 (12%), and the jejunum in 4 (17%). For the patients who did not undergo previous gastrectomy, the stomach was used for reconstruction after resection in 729 (99%), the ascending colon in 4 (<1%), the descending colon in 2 (<1%), the transverse colon in 2 (<1%), and the jejunum in 1 (<1%). The upper anastomosis was located in the cervical region in 18 (75%) of the 24 patients who underwent a previous gastrectomy and in 245 (33%) of the 738 who had intact stomachs ( $P < .001$ ). The retrosternal route for reconstruction was used in 8 (33%) of the patients who underwent a previous gastrectomy, compared with 77 (10%) of the patients with intact stomachs ( $P < .001$ ). The operative time (300 [160-465] vs 220 [90-520] minutes;  $P < .001$ ) was longer and more blood loss (1000 [300-2500] vs 700 [150-7000] mL;  $P < .001$ ) was encountered for esophagectomy after previous gastrectomy.

There was no difference in the postresection pathological staging, with the distribution for those who underwent previous gastrectomy being 2 patients with stage I, 7 with stage II, 13 with stage III, and 2 with stage IV disease. The figures for those who did not undergo gastrectomy were 50 patients with stage I, 169 with stage II, 466 with stage III, and 53 with stage IV disease ( $P = .75$ ).

Postoperative morbidity and mortality rates are given in **Table 3**. No significant differences were found. The median survival after resection was 13.8 months for patients who underwent previous gastrectomy and 12.5 months for the control group ( $P = .62$ ). The survival curves are shown in the **Figure**.

## COMMENT

The incidence of previous gastrectomy among patients with esophageal cancer in the present series is 3%, comparable to that reported in the literature.<sup>4,5</sup> The association of previous gastrectomy and esophageal cancer is controversial.<sup>2,6,11-14</sup> In 1970, it was first reported that a high incidence of gastrectomy (8.7%) was found among patients with esophageal cancer. This was associated with more distal esophageal tumors. Postgastrectomy reflux or nutritional changes after gastrectomy were proposed as a causal factor.<sup>11</sup> Maeta et al<sup>4</sup> reviewed 129 patients with esophageal cancer and found that 12 had undergone previous gastrectomy, half of whom had lower-third tumors. Population-based studies,<sup>3,15-17</sup> however, have shown no increase in the overall incidence of esophageal cancer after gastrectomy.

In the present study, for patients who had undergone distal gastrectomy, the subsequent esophageal cancers seemed to have a propensity to develop in the distal esophagus compared with those patients who did not undergo gastrectomy. The type of reconstructive method was largely responsible for the observed difference, with distal tumors more likely in the patients who underwent Billroth I vs Billroth II gastrectomy.

Clinical<sup>18</sup> and population-based<sup>19</sup> studies have shown a strong relation of gastroesophageal reflux with Barrett esophagus, with a 30 to 125 times greater risk of devel-

oping esophageal adenocarcinoma. Barrett esophagus and cancer are predominantly diseases of the West. In Asian populations, clinically significant gastroesophageal reflux disease and Barrett esophagus are rare.<sup>20</sup> In the present study, only 1% (11/1036) of the patients had adenocarcinoma of the esophagus. Patients with adenocarcinoma of the gastric stump and cardia were excluded, because gastric stump cancers are essentially stomach cancers in origin. The value of the present study is the information it provides on predominantly squamous cell cancer of the esophagus in a population in which Barrett cancers are rare.

Animal studies<sup>21-25</sup> have shown that gastroesophageal reflux can increase the incidence of esophageal squamous cell carcinoma, even without the administration of any carcinogen. Distal gastrectomy is a good model for studying the clinical effects of reflux. Symptomatic duodenogastric reflux is the most common of the postgastrectomy syndromes, with a reported frequency as high as 35%.<sup>1,20,23</sup> Possible causes include a small gastric remnant that is unable to accommodate large volumes; often the coexistence of a truncal vagotomy, which affects gastric motility; and postoperative widening of the angle of His, which may influence lower esophageal sphincter competency.<sup>26</sup>

In this study, the increased frequency of lower-third tumors was almost exclusively associated with Billroth I gastrectomy, with three quarters of the patients who underwent previous Billroth I gastrectomy having lower-third tumors; the frequency of such tumors after Billroth II gastrectomy was similar to that of patients who did not undergo gastrectomy. There may be more reflux after Billroth I compared with Billroth II gastrectomy. Following Billroth I gastrectomy, the cardia moves to the right, and the angle of His becomes more obtuse, while after Billroth II gastrectomy, the gastric remnant is drawn downward to the jejunum and not swung toward the right across the duodenum.<sup>27,28</sup> In a recent study of 38 patients postgastrectomy, 24 had symptoms of reflux. The angle of His was measured radiologically, and a reflux index was calculated by scintigraphic means. This angle was wider for asymptomatic patients after Billroth I vs Billroth II gastrectomy, and symptomatic and asymptomatic patients after Billroth I gastrectomy had the same width of angle.<sup>29</sup> Delayed gastric emptying was also more prevalent after Billroth I gastrectomy, which also resulted in a higher gastroesophageal reflux index compared with that after Billroth II gastrectomy.<sup>30</sup>

Barrett adenocarcinomas of the lower esophagus are rare in the local population, and there was no observed increase in adenocarcinomas in this study. There is no apparent explanation. In the future, it may be worth performing comparative studies on epidemiologic and pathophysiological features in our local population compared with those in the West.

The presence of prior distal gastrectomy may affect the management of subsequent esophageal cancer. Prior dissection of the stomach, including the ligation of left gastric vessels, may in theory affect lymphatic spread from esophageal cancer. In our patients, resectability for the 2 studied groups was not different, and the pathological

stage distribution in patients who underwent resection was also similar. Unfortunately, data on detailed sites of lymph node spread were not available.

The most commonly used conduit for esophageal replacement after esophagectomy for cancer is the gastric tube. Prior gastrectomy mandates use of an alternate conduit. Our preferred loop in such a situation is the ascending colon. We also favored bringing the colon loop to the neck for a cervical anastomosis. For most surgeons, colonic interposition remains an infrequently performed procedure. It was hypothesized that the more complicated procedure would be associated with a poorer postoperative outcome. The more complex procedure probably accounted for the higher blood loss and longer operative time in these patients. Postoperative morbidity and mortality rates, however, were not different compared with patients with intact stomachs.

In summary, we have shown that lower-third squamous esophageal cancers are more common in patients with a history of distal gastrectomy compared with patients with intact stomachs. This difference is almost exclusively attributed to the Billroth I type of gastrectomy. Esophageal resection after gastrectomy was more complicated and mandated an alternate conduit for reconstruction, but postoperative outcome and long-term survival were not adversely affected.

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## IN OTHER AMA JOURNALS

### ARCHIVES OF NEUROLOGY

#### Brain Damage After Coronary Artery Bypass Grafting

Martin Bendszus, MD; Wilko Reents, MD; Dorothea Franke, MD; Wolfgang Müllges, MD; Jörg Babin-Ebell, MD; Martin Koltzenburg, MD; Monika Warmuth-Metz, MD; Laszlo Solymosi, MD

**Background:** Coronary artery bypass grafting (CABG) is associated with a risk for focal neurological deficits and neuropsychological impairment postoperatively.

**Objectives:** To examine the brain damage after CABG using diffusion-weighted magnetic resonance imaging and <sup>1</sup>H-magnetic resonance spectroscopy (MRS) and to correlate the results with neurological and neuropsychological findings.

**Patients and Methods:** Thirty-five consecutive patients undergoing elective CABG were included. Patients underwent a neurological and neuropsychological examination before and after CABG. The magnetic resonance protocol was applied before and after (mean, 3 days) surgery and included a diffusion-weighted sequence and single-voxel MRS measurements in the frontal lobes.

**Results:** None of the patients revealed a new focal neurological deficit after surgery. Diffusion-weighted magnetic resonance imaging demonstrated new ischemic lesions in 9 (26%) of the patients. The presence of an ischemic lesion was not related to impaired postoperative test performance ( $P > .50$ ). The apparent diffusion coefficient values in the cerebellum and the centrum semiovale exhibited an increase after surgery ( $P < .01$ ), consistent with vasogenic edema. Following surgery, MRS revealed a significant decrease in the metabolite ratio of *N*-acetylaspartate-creatinine (mean  $\pm$  SD,  $1.69 \pm 0.20$  vs  $1.52 \pm 0.19$ ;  $P < .001$ ). The extent of deterioration in neuropsychological test performance after surgery was closely related to the degree of the *N*-acetylaspartate-creatinine ratio decrease ( $P < .01$ ). A follow-up MRS scan revealed a normalization of the *N*-acetylaspartate-creatinine ratio, which accompanied the recovery in psychological test performance.

**Conclusions:** Postoperative impairment in neuropsychological test performance is associated with a transient metabolic neuronal disturbance. Focal ischemic lesions after CABG are more frequent than the apparent neurological complication rate; however, they are not related to the diffuse postoperative encephalopathy. (2002;59:1090-1095)

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