

Reflux of Duodenal Content Develop Esophageal Squamous Cell Carcinoma

Naoki Hashimoto

Abstract—The incidence of esophageal cancer patients who have undergone distal gastrectomy is increasing recently. Distal gastrectomy is a good model for studying the clinical effects of duodenal content reflux. Individuals with a history of gastrectomy often suffer from severe alkaline reflux esophagitis. A history of gastrectomy is associated with an increased rate of lower third esophageal squamous cell carcinoma. Therefore, I made a rat model, a total gastrectomy followed by esophagoduodenostomy (n=27) was performed to induce chronic duodenal content reflux esophagitis. Esophageal squamous cell carcinoma (SCC) (40%) developed in places distant from the anastomosis compared to Esophageal adenocarcinoma (ADC) (30%). This means that histological features may depend on the volume of reflux contents; small amounts of reflux causes SCC and a large volume of reflux causes ADC. I concluded reflux of duodenal contents developed not only ADC but also SCC from clinical and experimental data.

Index Terms— Distal Gastrectomy, SCC, ADC, Reflux of Duodenal Content, Esophagoduodenostomy.

I. INTRODUCTION

Recently, the prognosis of patients with gastric cancer has improved with early detection and advances in perioperative management. The incidence of esophageal cancer patients who have undergone distal gastrectomy is increasing recently¹. Distal gastrectomy is a good model for studying the clinical effects of reflux. Owing to a truncal vagotomy, which affects gastric motility, postoperative widening of the angle of His, which may influence lower esophageal sphincter competency² and a small gastric remnant that is unable to accommodate large volumes, the gastric and duodenal contents, including bile, would reflux into the esophagus³.

I will make a review about esophageal squamous cell carcinoma with distal gastrectomy and esophageal squamous cell carcinoma with reflux of duodenal content.

II. ESOPHAGEAL SQUAMOUS CELL CARCINOMA WITH A HISTORY OF DISTAL GASTRECTOMY

Gastro-esophageal scintigraphy was performed for the patient suffering from heartburn. She was reconstructed Billroth II for early gastric cancer twenty years ago.

Gastro-esophageal scintigraphy⁴: A small meal of bread was then taken and 400 μ Ci of Tc 99m DTPA diluted in 100 ml of juice were taken up through a straw. Following this, the subject was instructed to lie under the gamma camera {RCIC-1635 LD, Hitachi} which had already been positioned to image the remnant stomach and the lower two-thirds of the

esophagus. We evaluated the extent of regurgitation from the remnant stomach to the esophagus using 120 scans obtained at 30 s intervals over 60 min.

Gastro-esophageal scintigraphy showed prominent regurgitation of gastroduodenal content into esophagus at 5, 7, 20 and 25 minutes (Fig 1).

In general, the incidence of gastrectomy in Japanese was 0.8%⁵. On the other hand, esophageal cancer after gastrectomy occurred in the range from 4.4%-10.4%, with an obviously higher incidence than in the general population^{6,7}.

Individuals with a history of gastrectomy often suffer from severe alkaline reflux esophagitis. We retrospectively evaluated 153 patients who underwent subtotal esophagectomy for thoracic esophageal cancer for the past three years. They were divided into two groups, according to whether or not they had previously undergone a gastrectomy: group 1, comprising 14 patients who had undergone gastrectomy and group 2, comprising 139 patients who had not. Clinical profiles of the patients were obtained from the medical records and the whole resected esophagus was histopathologically examined. Seven patients underwent Billroth I, six patients underwent Billroth II gastrectomy and one patient underwent total gastrectomy. The interval between gastrectomy and esophagectomy in group 1 was significantly shorter in the patients who had undergone gastrectomy for gastric cancer (10.5 ± 4.2 years) (n=4) than in those who had undergone gastrectomy for a peptic ulcer (28.9 ± 3.0 years) (n=10). The interval was also somehow shorter in the patients for whom anastomosis had been performed by Billroth I (21.3 ± 5.6 years) (n=7) compared with Billroth II (29.7 ± 3.2 years) (n=6), although the difference did not reach its statistical significance (P = 0.11). 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^{9,10}. Therefore, the frequency of reflux is much higher in Billroth I gastrectomy than Billroth II gastrectomy. Moreover, the proportion of lower third tumors in patients after gastrectomy was significantly higher compared with that of the patients with intact stomach. These findings suggest that a history of gastrectomy is associated with more lower-third squamous cell esophageal carcinoma (Table 1). Alexandrou¹¹ checked an association between a history of distal gastrectomy and the development of esophageal cancer. They concluded that there were more squamous tumors located in the lower third of the esophagus in those who had a history of gastrectomy compared with

Reflux of Duodenal Content develop Esophageal Squamous Cell Carcinoma

those with intact stomachs(16 [41%] of 40 patients vs 318 [25%] of 1266 patients; $p=0.04$).This difference was more pronounced after Billroth I vs Billroth II gastrectomy (8 [73%] of 11 patients vs 8 [29%] of 28 patients; $p=0.03$).

H H Li²also investigated the clinicopathological characteristics and surgical outcome of thoracic esophageal cancer after gastrectomy, and compare with these without gastrectomy. Among 1411 esophageal cancer patients who underwent curative operation,48(3.4%) had a history of distal gastrectomy, the proportion of lower third tumors was significantly higher compared with that of the non-gastrectomized patients (50% vs 33.1% $p=0.033$). They concluded that gastrectomy (especially Billroth-1) precipitated subsequent chronic gastroesophageal reflux and induced the development of squamous dysplasia and carcinoma in the esophagus. Esophageal mucosal changes resulting from persistent regurgitation of gastric and duodenal contents, including bile, into the lower esophagus may occur at higher frequency in patients with partial gastrectomy or gastroenterostomy than in patients with intact stomach. In this study, the histologic subtype for tumors was SCC in all cases-gastrectomized and nongastrectomized. None of the patients had adenocarcinoma.

III. DOES DUODENAL CONTENTS EXPOSURE CAUSE CHRONIC INFLAMMATION, ESOPHAGEAL INJURY AND ESOPHAGEAL CARCINOGENESIS?

Therefore, I made a rat model, a total gastrectomy followed by esophagoduodenostomy (n=27) was performed to induce chronic duodenal content reflux esophagitis. A total gastrectomy was performed with the removal of the entire stomach and end-to-end anastomosis of the esophagus and duodenum. The abdominal incision was closed in two layers (Figure 2). The animal was sacrificed at 40th week after surgery. Although it is widely accepted that duodenogastric esophageal reflux is directly linked to Barrett's esophagus and to the development of adenocarcinoma(ADC), a risk of squamous cell carcinoma(SCC) is reported not to be associated with gastroesophageal reflux. SCC is generally associated with smoking and alcohol consumption^{13,14}. Individuals with long standing and sever symptoms of reflux display odds ratios of 43.5 for ADC and 1.1 for SCC¹⁵. In our experimental study, sever dysplasia in the lower esophagus occurred in 100% (27/27), SCC was observed in 40% (10/27), and ADC was observed in 30%(8/27) at the 40th week. It is unclear what factors lead to the formation of carcinoma of specified histology. ADC is near the site of anastomosis, SCC is distant from the site of anastomosis (Fig 3) . SCC developed in places distant from the anastomosis compared to ADC. This means that histological features may depend on the volume of reflux contents; small amounts of reflux causes SCC and a large volume of reflux causes ADC. In conclusion, reflux of duodenal contents developed not only ADC but also SCC. Therefore, these experimental findings suggest that a history of gastrectomy is associated with more lower-third SCC.

Reflux of Gastroduodenal Content

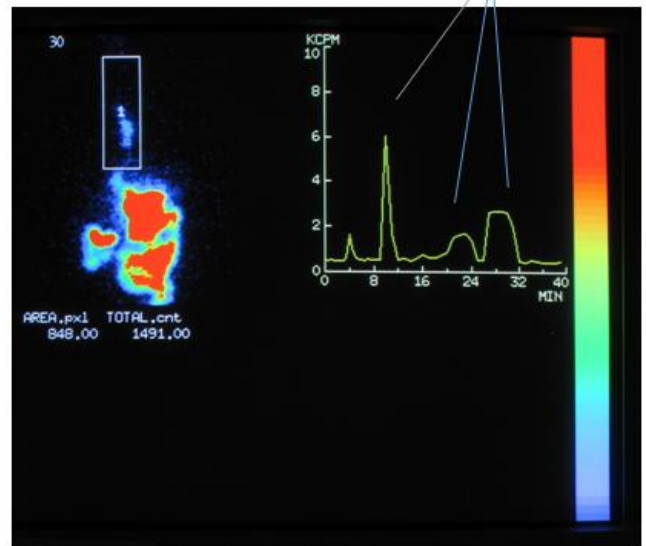


Fig1: Gastro-esophageal Scintigraphy showed prominent regurgitation of gastroduodenal content into esophagus.

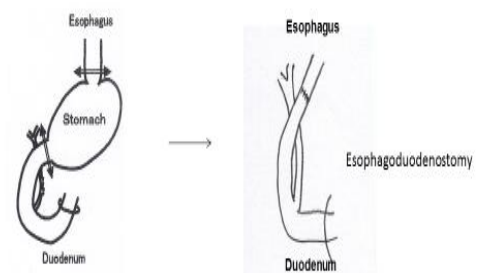


Fig 2: Surgical model, esophagoduodenostomy with total gastrectomy

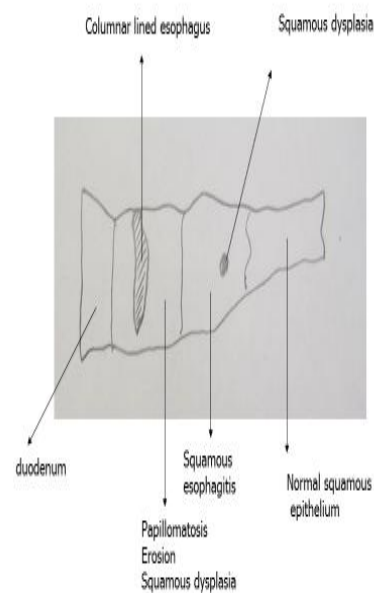


Fig 3: Schematic diagram indicating the relationship between each type of carcinoma and background epithelial patterns in rats with duodeno-esophageal reflux.

Table 1: Datas on patients with esophageal cancer who had, or had not, undergone gastrectomy.

	Gastrectomized pts (n=14)	Non gastrectomized pts (n=139)
Age	63±2.1	61.9±2.5
Cancer site		
Cervical	0 (0%)	15 (11%)
upper thoracic	1 (7%)	9 (6%)
Middle thoracic	5 (30%)	85 (61%)
Lower thoracic	8 (62%) *	30 (22%)
Histology		
SCC	14(100%)	139(100%)
Adenocarcinoma	0(0%)	0(0%)

* P<0.05

Table 1



Naoki Hashimoto graduate Kobe University on 1975. With a medical degree in Japan, upon PhD in 1984 at Hyogo Medical College. Over the last 10 years, he has focused his scientific interests on the topics related to “Reflux of duodenal contents induces esophageal carcinogenesis and reflux esophagitis” from the point of experimental and clinical studies. With his expertise in biomedical imaging, surgical treatment and chemoradiotherapy for advanced esophageal cancer. He was received many academic honors including European Conference on General Thoracic Surgery(2012), OESO(2013) and OESO(2015). Innovative, translational and longstanding research has been a pursuit in his academic career.

REFERENCE

- [1] Aiko S, Yoshizumi Y, Sugiura Y. Clinical characteristics of esophageal cancer after gastrectomy and the pertinence of chemoradiotherapy. *Nihon Rinsho Geka Gakkai Zasshi* 2002;63:813-820
- [2] Stein HJ, Peters JH, Smyrk TC. Gastric juice protects against the development of esophageal adenocarcinoma in the rat. *Ann Surg* 1996;224:358-371
- [3] Pera M, Trastek VF, Carpenter HA. Influence of pancreatic and biliary reflux on the development of esophageal carcinoma. *Ann Thorac Surg* 1993;55:1386-1393
- [4] Fujiwara Y, Hashimoto N, Nakagawa K et al. Scintigraphic evaluation of gastroesophageal reflux following gastrectomy. *Hepato-Gastroenterology* 1993;40:262-266
- [5] Tachibana M, Abe S, Yoshimura H et al. Squamous cell carcinoma of the esophagus after partial gastrectomy. *Dysphagia* 1995;10:49-52
- [6] Kuwano H, Matsuda H, Nagamatsu M et al. Occurrence of esophageal carcinoma after gastrectomy. *J Surg Oncol* 1989;41:77-80
- [7] Wada H, Doki Y, Nishioka K et al. Clinical outcome of esophageal cancer patients with history of gastrectomy. *J Surg Oncol* 2005;89:67-74
- [8] Hashimoto N, Inayama M, Fujishima M et al. Esophageal cancer after distal gastrectomy. *Dis Esophagus* 2006;19:468-472
- [9] Endo A, Okamura S, Kono N et al. Esophageal reflux after gastrectomy: a hazard after Billroth-1 subtotal gastrectomy. *Int Surg* 1978;63:52-58
- [10] Windsor CWO. Gastroesophageal reflux after partial gastrectomy. *BMJ* 1064;5419:1233-1234
- [11] Alexandrou A, Davis P A, Mchir M M et al. Esophageal cancer in patients with a history of distal gastrectomy. *Arch Surg* 2002;137:1238-1242
- [12] H H Li, Q Z H Zhang, L Xu et al. Clinical outcome of esophageal cancer after distal gastrectomy: A prospective study. *Int Journal of Surgery* 2008;6:129-135
- [13] Nozoe T, Korenaga D, Kabashima A et al. Smoking-related increase of O(6)-methylguanine-DNA methyltransferase expression in squamous cell carcinoma of the esophagus. *Cancer Lett* 2002;8:49-55
- [14] Yokoyama A, Ohmori T, Muramatsu T et al. Cancer screening of upper aerodigestive tract in Japanese alcoholics with reference to drinking and smoking habits and aldehyde dehydrogenase-2 genotype. *Int J Cancer* 1996;68:313-316
- [15] Lagergren J, Bergstrom R, Lindgren A et al. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med* 1999;340:825-831