Original Article

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Changes in Acidity Levels in the Gastric Tube After Esophagectomy for Esophageal Cancer

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Summary: Reflux esophagitis and gastric tube ulcer sometimes cause severe clinical problems in patients undergoing esophagectomy with gastric tube reconstruction. We previously reported that acidity in the gastric tube was decreased for 1 year after esophagectomy, and that lower acidity levels were associated with Helicobacter pylori (H. *pylori*) infection. However, the long-term changes in gastric acidity remain unknown. We aimed to investigate the long-term changes in gastric acidity after surgery. Eighty-nine patients who underwent esophagectomy with gastric tube reconstruction for esophageal cancer were analyzed. They underwent 24-hour pH monitoring, serum gastrin measurement, and H. *pylori* infection examination before surgery, at 1 month, 1 year, and 2 years after surgery. The gastric acidity at 1 month and 1 year after surgery was significantly lower than that before surgery ($p=0.003$, $p=0.003$). However, there was no difference in gastric acidity before and 2 years after surgery. The gastric acidity in H. *pylori*-infected patients was significantly lower in comparison to non-infected patients at each time point ($p=0.0003$, $p<0.0001$, $p<0.0001$, $p<0.0001$, respectively). In H. *pylori*-infected patients, gastric acidity was decreased for 1 year after surgery, and recovered within 2 years after surgery. However, no significant differences were observed in the acidity levels of non-infected patients during the 2-year follow-up period. The serum gastrin level increased after esophagectomy. The acidity levels in the gastric tube recovered within 2 years after surgery. Periodic endoscopy examination is recommended for early detection of acid-related disease, such as reflux esophagitis or gastric tube ulcer, after esophagectomy with gastric tube reconstruction.

Keywords esophageal cancer, gastric acidity, gastric tube, *Helicobacter pylori*, 24-h pH monitoring

INTRODUCTION

A gastric tube is generally used as an esophageal substitute after esophagectomy for cancer [1]. There have been several reports about patients with reflux esophagitis or gastric tube ulcer after esophagectomy for cancer [2-5]. We previously reported that the acidity levels in the gastric tube used for esophageal reconstruction after esophagectomy decreased for a year after surgery and that the acidity in the gastric tube after surgery is influenced by the incidence of *Helicobacter pylori* (*H. pylori*) infection [6]. Although there were many reports on the acidity levels in the gastric tube after esophagectomy for cancer [7-10] , they in-

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Abbreviations: H. pylori, Helicobacter pylori; UBT, urea breath test.

clude results from various patients who received pH monitoring at different time points. Furthermore the long-term changes of acidity in the gastric tube after esophagectomy for cancer are not clearly understood. The purpose of this study was to investigate the long-term changes in gastric acidity after esophageal surgery.

MATERIALS AND METHODS

Study Population and Protocol

The study included 89 patients who underwent esophagectomy followed by gastric tube reconstruction for esophageal cancer at Kurume University Hospital between 2002 and 2013. The clinical characteristics of 89 patients are summarized in Table 1. All patients received endoscopic examination, 24-h pH monitoring and examination for *H. pylori* infection preoperatively, and at 1 month, 1 year, and 2 years after surgery. Reflux esophagitis was classified according to the Los Angeles classification. The 24-h pH monitoring data was analysed to assess gastric acidity. The method of 24-h pH monitoring in the gastric tube is as follows. A monitoring catheter (Zinetics 24 ME MultiUse External Reference pH catheter, Medtronic A/S, Skovlunde, Denmark) with a sensor probe was connected to a portable pH monitor (DIGITRAPPER pH 400, Medtronic A/S, Skovlunde, Denmark). The pH sensor probe was calibrated in pH 7.01 and pH 1.07 buffer solutions (Medtronic A/S, Skovlunde, Denmark) before the examination. The pH sensor was introduced transnasally using fluoroscopy and placed in the gastric tube 7.5 cm below the esophagogastric junction or the esophagogastric anastomosis. The percentages of time during which the gastric pH was < 4 (% time of pH < 4) over the total monitoring period were noted. The data were analyzed using a commercially available software package (Polygram 98, Medtronic Functional Diagnostics A/S, Skovlude, Denmark). Antacid therapy, if any, was discontinued at least 3 days before 24-h pH monitoring.

H. pylori infection was examined using the 13C-urea breath test (UBT) and the pathological examination of endoscopic biopsy specimens from the antrum and stomach body. *H. pylori* infection positivity was defined as the detection of *H. pylori* by any examination.

The serum gastrin level was measured using fasting blood samples. Written informed consent for participation in the study was obtained from the patients. This study was approved by the Kurume University Ethics Review Board.

Statistical analysis

The patient characteristics in each *H.pylori* group were summarized by the median with IQR for the continuous variables and the count with proportion. The continuous variables between groups were compared by the Wilcoxon signed tests, and the categorical variables were compared by the Chi-squared tests. The gastric acidities/gastrin levels between the baseline and each monitoring time point after the operation were compared by the Wilcoxon signed rank test. The significance levels were adjusted to preserve an overall level of significance of 0.05 by the Bonferroni method to correct for multiple testing.

The gastric acidities measured at 1 month, 1 year and 2 years post-operation, and the amount of those changes from baseline were compared between *H. pylori* groups by a linear mixed-effect model with the patient as a random effect for the slope of the groups and the intercept to allow for within-patient correlation of repeated measures over time. Fixed effects included the main effects for the group and times (1 month post-operation, after 1 year and 2 years) and interactions for those. The data were analyzed by the linear mixed model without and with adjustment of the covariates summarized in Table 2 and 3, except that the route of reconstruction included some categories without enough patients. By applying these linear mixed effects models, the unadjusted and adjusted least squared means of baseline covariates were calcu-

TABLE 1.
Patient Characteristics

		n (%)
Age / years	Median (range)	64 (39-78)
Gender	Male	76 (85)
	Female	13 (15)
pStage	0/1/2/3/4	10/17/32/27/3
Esophagectomy	Subtotal	74 (83)
	Lower	15 (17)
Route of reconstruction	Posterior mediastinal	44 (50)
	Retrosternal	9 (10)
	Subcutaneous	36 (40)
Antacid therapy	Preoperative	11 (12)
	Postoperative	18 (20)
Anti *H. pylori* therapy		4 (4)
Chemotherapy		27 (30)

TABLE 2.
Comparison of gastric acidity according to H. pylori infection considering the influence of clinical factors– univariate and multivariate logistic analysis*

Period	*H. pylori*	Univariate		Multivariate	
		Adjusted mean [95%CI]	P-value	Adjusted mean [95%CI]	P-value
1 month	Positive	26.6 [15.6, 37.7]	<.0001	26.7 [10.8, 42.5]	<.0001
	Negative	81.4 [72.4, 90.4]		65.7 [48.6, 82.7]	
1 year	Positive	20.8 [9.6, 32.1]	<.0001	20.6 [4.7, 36.6]	<.0001
	Negative	73.8 [64.8, 82.8]		58.1 [41.0, 75.1]	
2 years	Positive	31.8 [20.8, 42.9]	<.0001	31.9 [16.0, 47.7]	0.0001
	Negative	77.7 [68.7, 86.7]		61.9 [44.9, 79.0]	

*age (≧ 65 vs. < 64 years), gender, stage, extent of esophagectomy, antacid therapy and chemotherapy

TABLE 3.
*Influence of clinical factors*on change in gastric acidity– univariate and multivariate logistic analysis*

H. pylori	Period	Univariate		Multivariate	
		Adjusted mean [95%CI]	P-value	Adjusted mean [95%CI]	P-value
Positive	pre vs. 1m	-13.9 [-25.0, -2.8]	0.016	-29.3 [-45.2, -13.5]	0.0006
	pre vs. 1y	-20.4 [-31.7, -9.1]	0.0008	-35.4 [-51.3, -19.4]	<.0001
	pre vs. 2y	-8.7 [-19.8, 2.4]	0.122	-6.1 [-15.4, 3.3]	0.203
Negative	pre vs. 1m	9.3 [-0.8, 19.4]	0.069	58.1 [41.0, 75.1]	0.258
	pre vs. 1y	1.7 [-8.4, 11.8]	0.732	31.9 [16.0, 47.7]	0.808
	pre vs. 2y	5.6 [-4.5, 15.7]	0.268	61.9 [44.9, 79.0]	0.484

*age (≧ 65 vs. < 64 years), gender, stage, extent of esophagectomy, antacid therapy and chemotherapy

lated and compared among groups and monitoring times.

RESULTS

H. pylori infection

The incidence of *H. pylori* infection is shown in Table 4. A total of 43 (48%) patients showed the same results at all four observation points (positive, n=23; negative, n=20).

Gastric acidity

Figure 1 shows the changes in the gastric acidity level according to time in all 89 patients. The gastric acidity at 1 month and 1 year after surgery was significantly lower than that before surgery ($p = 0.003$ and $p = 0.003$, respectively). However, the gastric acidity at 2 years after surgery was not significantly

TABLE 4.
Incidence of Helicobacter pylori Infection

Time after surgery (n)		n (%)
Before Surgery (89)	Positive	56 (63)
	Negative	33 (37)
1 month (68)	Positive	38 (56)
	Negative	30 (44)
1 year (89)	Positive	53 (60)
	Negative	36 (40)
2 years (88)	Positive	50 (57)
	Negative	38 (43)

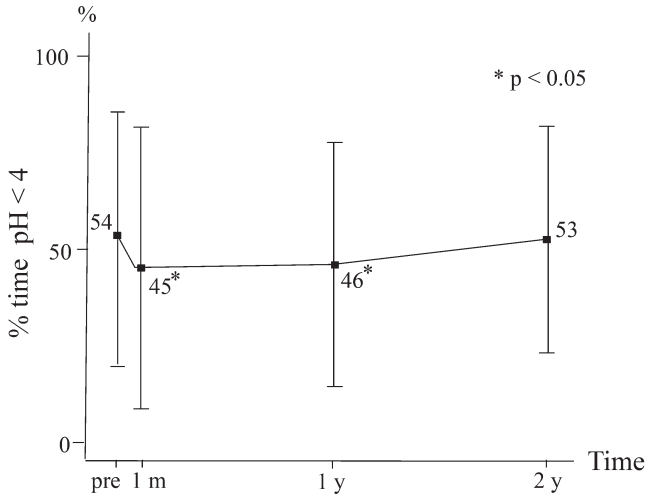

Fig. 1. Changes in the gastric acidity in 89 patients. The gastric acidity values of 45% at 1 month and 46% at 1 year after surgery were significantly lower than that of 54% before surgery ($p = 0.003$, $p = 0.003$). There was no significant difference between the value of 54% before surgery and 53% at 2 years after surgery ($p = 0.893$).

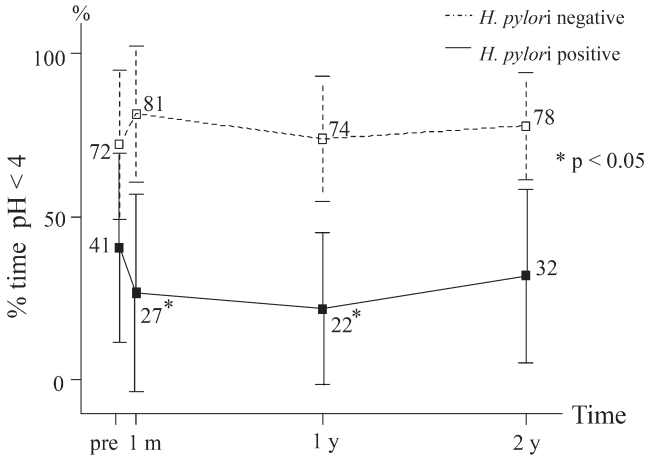

Fig. 2. Changes in the gastric acidity according to *H. pylori* infection status.
At each point in time, the gastric acidity in those who were positive for *H. pylori* infection was significantly lower than that in uninfected patients ($p = 0.0003$, $p < 0.0001$, $p < 0.0001$, $p < 0.0001$). In patients with *H. pylori* infection, the gastric acidity at 1 month and 1 year after surgery were significantly lower than before surgery ($p = 0.004$, $p = 0.010$). However, there was no significant difference in the gastric acidity at 2 years after surgery and that before surgery ($p = 0.334$). There was no significant difference in gastric acidity compared to preoperative level in patients without *H. pylori* at any time point in the 2-year follow-up period.

different from that before surgery ($p = 0.893$).

Figure 2 shows the changes in gastric acidity level according to *H. pylori* infection status. At each time point, the gastric acidity level in the *H. pylori* infection-positive patients was significantly lower than that in the *H. pylori* infection-negative patients ($p = 0.0003$, $p < 0.0001$, $p < 0.0001$, and $p < 0.0001$, respectively). In patients with *H. pylori* infection, the gastric acidity at 1 month and 1 year after surgery was significantly lower in comparison to before surgery ($p = 0.004$ and $p = 0.010$, respectively). However, there was no significant difference between the gastric acidity at 2 years after surgery and that before surgery ($p = 0.334$). In contrast, there was no significant difference in the gastric acidity compared to the preoperative level in patients without *H. pylori* at any time point in the 2-year follow-up period ($p = 0.216$, $p = 0.202$, and $p = 0.312$, respectively). In addition, univariate and multivariate analyses were performed for the effects of age ($\geq$65 vs. <64 years), gender, stage, extent of esophagectomy, antacid treatment, and chemotherapy on gastric tube acidity in both *H. pylori* -positive and -negative patients. None of these factors were found to be significant in either group (Table 2 and 3).

Serum gastrin levels

Figure 3 shows the changes in the serum gastrin levels. The serum gastrin levels at 1 month, 1 year, and 2 years after surgery were significantly higher than those before surgery ($p < 0.0001$, $p < 0.0001$, $p < 0.0001$).

Figure 4 shows the changes in the serum gastrin levels according to the *H. pylori* infection status. Irrespective of the *H. pylori* infection status, the serum gastrin levels at 1 month, 1 year, and 2 years after surgery were significantly higher in comparison to before surgery.

Reflux esophagitis and gastric tube ulcer

In the study patients, 27 (30%) patients developed reflux esophagitis during the follow-up period. Among these, 18 (20%) patients were diagnosed grade A/B and 9 (10%) were grade C/D. Three (3%) patients developed a gastric tube ulcer.

DISCUSSION

In this study, we found that the acidity level in the gastric tube recovered after esophagectomy. The gastric acidity at 1 year after surgery was decreased in comparison to that before surgery, but recovered with-

in 2 years after surgery. Furthermore, changes in gastric acidity differed according to *H. pylori* infection. To our knowledge, this is the first long-term study showing the change in gastric tube acidity after esophagectomy in the same patients over a 2-year period.

It has long been believed that the acidity in the gastric tube decreases because of the truncal vagotomy or gastric gland area reduction. Lam et al. have noted that gastric acidity was reduced after esophagectomy [11]. Bonavina et al. also reported that the acidity levels of gastric tube in patients who underwent esophagectomy for cancer were significantly less than in healthy controls [12]. On the other hand, some reports have suggested that acidity recovered with time after esophagectomy [7-9,13]. Gutschow et al. reported that the gastric acidity recovered and thus demonstrated a normal pH profile during follow-up of at least 3 years [14]. However, in those cross-sectional studies, study patients were only examined once to determine gastric acidity at a single time point with various intervals after surgery.

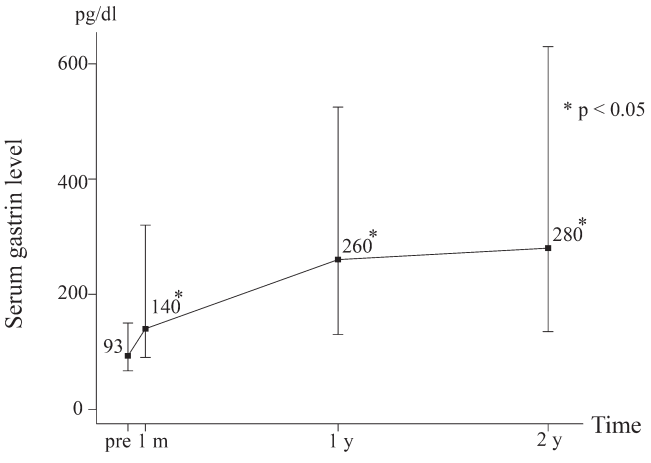

Fig. 3. Changes in the serum gastrin levels in 89 patients. The serum gastrin levels at 1 month, 1 year, and 2 years after surgery were significantly higher than those before surgery ($p < 0.0001$, $p < 0.0001$, $p < 0.0001$).

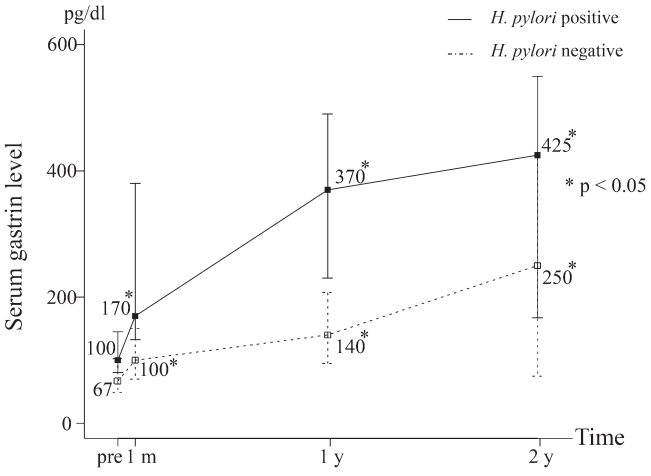

Fig. 4. Changes in the serum gastrin levels according to *H. pylori* infection status. The serum gastrin level in patients with *H. pylori* infection was significantly higher than in uninfected patients at any time point in the 2-year follow-up period.

It remains unclear whether the gastric tube acidity after esophagectomy decreases day by day or not. In our study, patients who underwent esophagectomy for esophageal cancer were serially examined for gastric acidity before surgery, at 1 month, 1 year, and 2 years after surgery. Thus, the present study identifies the serial changes in gastric acidity after surgery.

It is well known that there is a close association between *H. pylori* infection and acidity in the stomach [15,16]. *H. pylori* infection reduces gastric acid secretion. However, there are few reports about the correlation between acidity in the gastric tube and *H. pylori* infection after esophagectomy for cancer. We previously reported that the level of gastric acidity after esophagectomy was strongly influenced by *H. pylori* infection [10]. The present study showed that at each time point, the gastric acidity in patients with *H. pylori* infection was significantly lower than that in patients without *H. pylori* infection. Furthermore, this report shows that the change in acidity in the gastric tube differed according to the *H. pylori* infection status. Positive rates of *H. pylori* changed after surgery. Although the mechanisms of the change remain unclear, false negatives due to postoperative antibiotics and proton pump inhibitor use might be partially involved.

Gastrin is a peptide hormone that stimulates the secretion of gastric acid. It is released by G cells in the pyloric antrum of the stomach and duodenum. It has been reported that the reduction of gastric acidity after esophagectomy caused an increase in serum gastrin levels [8,17]. We also now know that *H. pylori*-infected individuals have increased levels of basal, meal-stimulated, and gastrin-releasing peptide-stimulated gastrin concentrations in comparison to *H. pylori*-negative individuals [18,19]. With regard to the recovery of gastric acidity, the present study demonstrated a feedback mechanism wherein the acidity and gastrin levels were correlated in patients with *H. pylori* infection. Gastric acidity was decreased after esophagectomy for a year, thereafter, the serum gastrin levels increased. While there are various factors involved in gastric acid secretion, such as vagotomy, and histamine and acetylcholine levels [20,21], the present

study suggested that gastrin played a role in the recovery of gastric acidity in the gastric tube.

Acidity-related diseases such as gastric ulcer and reflux esophagitis sometimes develop in the gastric tube or remnant esophagus after esophagectomy. In this study, among the 89 patients, 3 (3.4%) patients developed a gastric tube ulcer. Regarding the development of a gastric tube ulcer, Koide et al. reported that *H. pylori* infection could be an important cause [22,23]. In our previous report, severe gastric tube ulcers developed irrespective of the *H. pylori* infection [2,3]. Therefore, *H. pylori*-positive patients with low gastric acidity are also at risk for ulcers. The incidence of reflux esophagitis including severe esophagitis has been reported to increase with time [4,5,13]. In the present study, 30% of patients developed reflux esophagitis. Changes in the gastric tube acidity are therefore clinically important issues for patients who have undergone esophagectomy for cancer.

CONCLUSION

Gastric tube acidity recovered to the preoperative level 2 years after esophagectomy for cancer. Patients after esophagectomy are at risk for acid-related diseases.

CONFLICT OF INTEREST: The authors have no conflicts of interest directly relevant to the content of this article.

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