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ORIGINAL ARTICLE

The impact of cervical lymph node dissection on acid and duodenogastroesophageal reflux after intrathoracic esophagogastrostomy following transthoracic esophagectomy

Soichiro Asai[1] · Masahide Fukaya[1] · Kazushi Miyata[1] · Keita Itatsu[1] · Ryoji Miyahara[2] · Kazuhiro Furukawa[2] · Tomoki Ebata[1] · Masato Nagino[1]

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Abstract

Purpose The aim of this study was to evaluate the impact of cervical lymph node dissection on acid reflux and duodenogastroesophageal reflux (DGER) in patients undergoing transthoracic esophagectomy with gastric tube reconstruction and intrathoracic esophagogastrostomy.

Methods Thirty-one patients receiving transthoracic esophagectomy with gastric tube reconstruction by intrathoracic esophagogastrostomy were divided into the following two groups: a two-field lymph node dissection group (2F group) and a three-field lymph node dissection group (3F group). All patients underwent 24-h pH and bilirubin monitoring and gastrointestinal endoscopy at 1 year after surgery. The 24-h pH and bilirubin monitoring results, endoscopic findings, and reflux symptoms were compared between the 2 groups.

Results No acid reflux was observed in the 2F group, whereas it was observed in 6 (40%) patients in the 3F group ($p=0.007$). DGER was found in 2 patients (13%) in the 2F group and in 8 (53%) in the 3F group ($p=0.023$). Four patients (25%) in the 2F group and 9 (60%) in the 3F group ($p=0.048$) had reflux esophagitis.

Conclusion Cervical lymph node dissection increases acid reflux and DGER and can lead to an increase in the incidence of reflux esophagitis in patients undergoing intrathoracic esophagogastrostomy.

Keywords Cervical lymph node dissection · Duodenogastroesophageal reflux · Intrathoracic esophagogastrostomy

Introduction

Thoracic esophageal cancer can metastasize to regional lymph nodes from the neck to the abdomen. Therefore, three-field lymph node dissection with cervical lymph node dissection, including bilateral cervical para-recurrent laryngeal nerve lymph node dissection and bilateral supraclavicular lymph node dissection, is often performed.

However, despite an improved prognosis with three-field lymph node dissection, complication and mortality rates are high [1–4]. Furthermore, three-field lymph node dissection has been reported to decrease the quality of life of patients compared with two-field lymph node dissection (without cervical lymph node dissection). For example, Nakamura et al. reported that three-field lymph node dissection is associated with greater postoperative gastrointestinal dysfunction than is two-field lymph node dissection, particularly with regard to decreased physical activity and reflux symptoms [5]. However, no reports have compared the postoperative endoscopic findings between two- and three-field dissections. In addition, no detailed study has been conducted using 24-h pH and bilirubin monitoring to compare the extent of acid reflux and duodenogastroesophageal reflux (DGER) between these two groups.

The aim of this study was to evaluate the impact of cervical lymph node dissection on acid reflux and DGER in patients undergoing transthoracic esophagectomy with gastric tube reconstruction and intrathoracic esophagogastrostomy.

✉ Masahide Fukaya
mafukaya@med.nagoya-u.ac.jp

[1] Division of Surgical Oncology, Department of Surgery, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan

[2] Department of Gastroenterology and Hepatology, Nagoya University Graduate School of Medicine, Nagoya, Japan

Patients and methods

Patients

Of 135 patients who underwent right transthoracic subtotal esophagectomy for esophageal cancer in our department between January 1997 and December 2011, 62 underwent gastric tube reconstruction and intrathoracic esophagogastrostomy. A total of 19 patients who refused simultaneous pH and bilirubin monitoring were excluded from this study. We previously reported that the location of esophagogastrostomy is closely associated with acid reflux and DGER [6]; therefore, to preclude the impact of the esophagogastric location, 12 patients who underwent esophagogastrostomy below the center of the aortic arch were excluded.

The remaining 31 patients were subjected to an analysis, including 26 males and 5 females with a median age of 67.5 years old (range 52–74 years old). We evaluated simultaneous pH and bilirubin monitoring data, endoscopic findings, and reflux symptoms. The 31 patients were divided into a 2-field lymph node dissection group (2F group, $n = 16$) and a 3-field lymph node dissection group (3F group, $n = 15$), and the results of the above examinations were compared between the 2 groups. The tumor location and clinical stage were estimated according to the UICC, 7th edition. Postoperative complications were assessed based on the Clavien–Dindo classification [7]. The ethics committee of Nagoya University Hospital approved our study (No2016-0442).

Surgical procedure

The abdomen was explored through an upper midline incision. After perigastric and celiac lymph node dissection, a gastric tube was constructed using a linear cutting stapler (Proximate Linear Cutter 75; Ethicon Endo-Surgery, Cincinnati, OH, USA). The stapler was fired as many times as necessary to divide the stomach from the lesser curvature at the anastomosis between the right and left gastric arteries along the axis of the greater curvature, creating an approximately 4-cm-wide tube. Digital dilatation of the pyloric ring was performed in all patients. Esophagectomy with mediastinal lymphadenectomy, including bilateral recurrent laryngeal nerve lymph node dissection, was performed through a right transthoracic approach. A gastric tube was placed in the posterior mediastinum, and intrathoracic esophagogastrostomy was performed on the anterior wall of the gastric tube using a circular stapler (CEEA 25; Medtronic, Minneapolis, MN, USA). Between 1997 and 2005, cervical lymph node dissection was performed in patients with a tumor deeper than T2 in the upper thoracic esophagus; except for those with a T1 lower thoracic and abdominal tumor without upper mediastinal lymph node metastasis, all patients underwent cervical lymph node dissection between 2006 and 2011. Cervical lymph node dissection was performed simultaneously with the abdominal operation. The supraclavicular, deep cervical, and cervical paraesophageal lymph nodes were dissected through a cervical collar incision. Cervical paraesophageal lymph node dissection was performed by separating the left and right anterior cervical muscles; the sternocleidomastoid, sternohyoid, sternothyroid, and omohyoid muscles were preserved.

Simultaneous 24-h pH and bilirubin monitoring

Simultaneous monitoring of the esophageal pH and bilirubin levels was performed for 24 h in all subjects. After an antimony catheter with pH sensors (Medtronic, Skovlunde, Denmark) was inserted pernasally, the proximal sensor was positioned 2 cm above the site of esophagogastrostomy. The distal pH sensor was positioned 10 cm below the proximal sensor in the gastric tube. The pH information was recorded by a portable digital data recorder (Digitrapper Mark III; Medtronic). Esophageal bilirubin levels were monitored with a fiberoptic sensor (Bilitec 2000; Medtronic) placed at the same position as the proximal pH sensor. Data were recorded by a portable opticoelectric recorder.

The pH and bilirubin monitoring data were subsequently transferred to a personal computer for an analysis with the EsopHogram Reflux Analysis software program (Medtronic). An esophageal pH less than 4.0 indicated acid reflux, whereas an alkaline shift was defined as an esophageal pH above 7.0. The presence of acid reflux was defined as an esophageal pH below 4.0 for more than 4.4% of the total monitoring time [8]. A bilirubin absorbance that exceeded 0.14 indicated bile reflux. The presence of DGER was defined as a bilirubin absorbance exceeding 0.14 for more than 1.8% of the total monitoring time [9, 10]. Patients were instructed to consume a low-residue liquid diet (500 mL of Ensure Liquid; Dinabot, Tokyo, Japan) three times daily at their usual mealtimes during the monitoring period. Only water was allowed in addition to the diet. Some patients complained of nasal or pharyngeal discomfort, but all patients tolerated this monitoring. Although ten patients took antacids for gastroesophageal reflux disease after esophagectomy, all drugs that could potentially affect gastrointestinal motility and secretion were discontinued at least 1 week prior to the pH and bilirubin monitoring.

Endoscopy

Preoperative endoscopy was used to confirm that the squamous epithelium in the cervical esophagus was normal and that Barrett's epithelium was absent in all patients. Postoperative endoscopy was performed to observe mucosal changes in all patients within 1 month before or after the pH and bilirubin monitoring. Of the 10 patients who used antacids before this study, 5 each underwent endoscopy before antacid discontinuation and after restarting antacid use. Reflux esophagitis was graded according to the Los Angeles Classification System.

Symptoms

Reflux symptoms, such as pharyngeal regurgitation, cervical heartburn or pain, and thoracic discomfort associated with sleep disturbance or a nocturnal cough were categorized as follows: absent and mild (can or cannot be ignored but does not affect lifestyle, respectively) and severe (affects lifestyle, including the inability to lie flat and contributing to sleep deprivation, even after the use of antacids).

Identification of the esophagogastrostomy location

The esophagogastrostomy location was identified by tracing the remnants of the circular staples on a computed tomography (CT) image. In addition, the length of the remnant esophagus was measured between the cricoid cartilage and esophagogastrostomy on the CT image.

Statistical analyses

The results are expressed as medians (range). The Chi-squared test, Fisher's exact test, and Mann–Whitney *U* test were used where appropriate to assess differences between the two groups. All statistical analyses were performed using the SPSS software program, version 21.0 J (SPSS Inc., Chicago, IL, USA). Two-sided *p* values were calculated, and the results are presented. A p value of < 0.05 was considered to indicate statistical significance.

Table 1 Patients' characteristics

Variables	2F group ($n=16$)	3F group ($n=15$)	p
Age, years (range)	69.5 (52–73)	64 (55–74)	0.830
Gender, male/female	12/4	14/1	0.333
Body mass index, kg/m^2 (range)	17.9 (14.6–24.0)	19.9 (16.0–25.3)	0.110
Tumor location, *n*			
Ut/Mt/Lt	1/9/6	0/9/6	0.616
Clinical stage (UICC 7th)			
I/II/III	6/6/4	3/6/6	0.504
Histological type, *n*			
Squamous cell carcinoma/adenocarcinoma	15/1	15/0	1.000
Use of antacids, *n* (%)	3 (18%)	7 (47%)	0.135

Table 2 Short-term surgical outcomes

Variables	2F group ($n=16$)	3F group ($n=15$)	p
Operative time, min (range)	445 (335–645)	600 (427–660)	0.006
Blood loss, ml (range)	550 (172–1210)	1062 (224–1530)	0.022
Number of mediastinal lymph nodes dissected, *n*	19 (11–28)	22 (10–27)	0.118
Length of the remnant esophagus, mm (range)	46 (35–70)	48 (25–75)	0.796
Postoperative complications, *n* (%)			
Vocal cord palsy	6 (38)	6 (40)	0.886
Postoperative pneumonia (CD grade ≥ 2)	6 (38)	5 (33)	0.809
Re-intubation	1 (6)	0	1.000
Anastomotic leakage, *n* (%)	2 (13)	1 (7)	1.000
Any complication (CD grade $\geq$ 3a), *n* (%)	4 (25)	4 (27)	1.000
Postoperative hospital stay, days (range)	28 (18–68)	30 (16–55)	0.387

CD Clavien–Dindo classification

Table 3 Relationship between cervical lymph node dissection and acid and duodenogastroesophageal reflux

Variables	2F group ($n=16$)	3F group ($n=15$)	p
Acid reflux	0	6 (40%)	0.007
Duodenogastroesophageal reflux	2 (13%)	8 (53%)	0.023

Table 4 A comparison of endoscopic findings and reflux symptoms between the two groups

Variables	2F group ($n=16$)	3F group ($n=15$)	P
Reflux esophagitis			
Present	4 (25%)	9 (60%)	0.048
Mild (A or B)	3 (19%)	7 (47%)	
Severe (C or D)	1 (6%)	2 (13%)	
Barrett's esophagus	1 (6%)	1 (7%)	1.000
Stenosis	4 (25%)	4 (27%)	1.000
Reflux symptoms			
Present	8 (50%)	9 (60%)	0.576
Mild	8 (50%)	8 (53%)	
Severe	0	1 (7%)	

Results

The patient characteristics are summarized in Table 1. No significant difference in the age, gender, tumor location, body mass index at the time of this study, clinical stage, histological type, or use of antacids before the study was observed between the two groups. Short-term surgical outcomes are shown in Table 2. The operative time was significantly longer in the 3F group than in the 2F group (600 min vs. 445 min, $p=0.006$), and blood loss was also greater in the 3F group than in the 2F group (550 ml vs. 1062 ml, $p=0.022$). However, there was no significant difference in the following parameters between the two groups: number of mediastinal lymph nodes dissected; length of the remnant esophagus; incidence of vocal cord palsy; rate of postoperative pneumonia of grade ≥ 2 as determined by the Clavien–Dindo classification; rate of re-intubation; rate of anastomotic leakage; rate of any complication of grade $\geq 3a$ as determined by the Clavien–Dindo classification; and duration of postoperative hospital stay. All patients but one in the 3F group had recovered from postoperative vocal cord palsy by the time of pH and bilirubin monitoring. The proportion of patients with acid reflux was significantly higher in the 3F group than in the 2F group (40% vs. 0%, $p=0.007$) (Table 3), and the proportion of patients with DGER was also significantly higher in the 3F group than in the 2F group (53% vs. 13%, $p=0.023$). Four patients (25%) in the 2F group and 9 (60%) in the 3F group ($p=0.048$) had reflux esophagitis (Table 4). In contrast, no between-group differences were observed in the incidence of severe reflux esophagitis, Barrett's esophagus, or stenosis, and the proportion of patients with reflux symptoms was similar in the 2F and 3F groups (50% vs. 60%, $p=0.576$). Only one patient in the 3F group had severe symptoms.

The percentage times of acid and bile reflux to the remnant esophagus are shown in Fig. 1. The percentage time of acid reflux was significantly greater in the 3F group than in the 2F group (median 0.8% vs. 0%, $p=0.008$), as was that of bile reflux (median 2.6% vs. 0%, $p=0.027$).

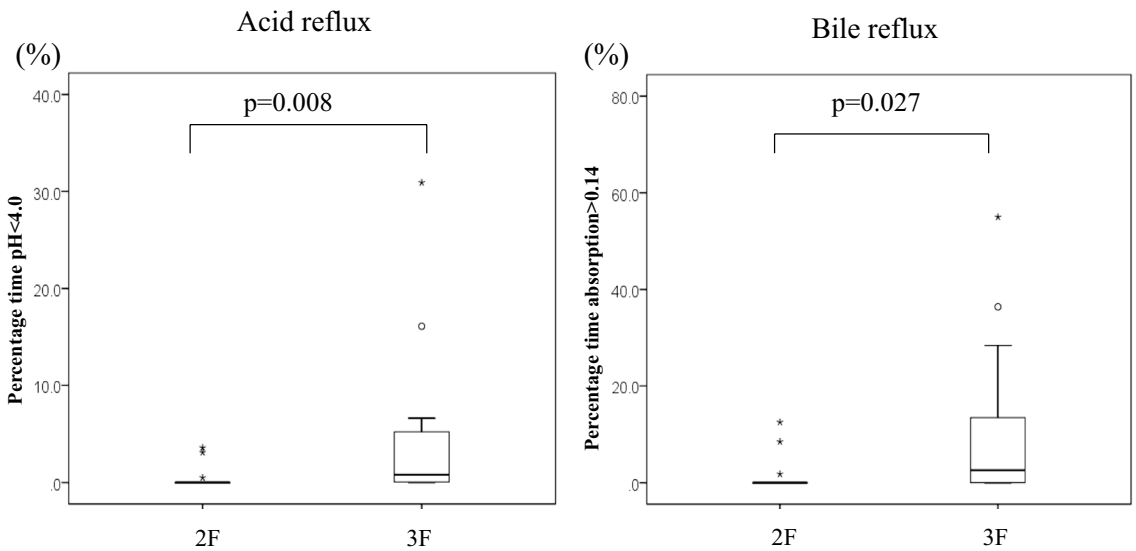

Fig. 1 A comparison of the percentage times of acid and bile reflux to the remnant esophagus between the 2F and 3F groups

Discussion

In patients who undergo intrathoracic esophagogastrostomy after esophagectomy, the location of the esophagogastrostomy is closely associated with the occurrence of acid reflux and DGER. In addition, the incidence of DGER and percent time of bile reflux to the remnant esophagus increases as the location of the esophagogastrostomy becomes lower, as we previously reported [6]. A unique point of this study is that the impact of the esophagogastrostomy location was removed to accurately investigate the impact of cervical lymph node dissection. Therefore, patients whose esophagogastrostomy location was below the center of the aortic arch were excluded from this study. As a result, there was no significant difference in the length of the remnant esophagus between the two groups.

Some reports have compared 2F and 3F groups of patients with cervical anastomosis [5, 11]. However, when performing cervical anastomosis, cervical incision, partial splitting or transection of the anterior cervical muscles, and dissection of the remnant esophagus further to the oral side are necessary, which can impair the swallowing function. Therefore, such studies are strongly affected by the cervical maneuver used for the anastomosis and examine only the impact of supraclavicular lymph node dissection. Our study targeted patients who underwent intrathoracic esophagogastrostomy, which is commonly performed in Western countries. Since this cervical maneuver was not performed in the 2F group, this study specifically compares the impact of cervical lymph node dissection, including cervical paraesophageal lymph node dissection and supraclavicular lymph node dissection, between the groups.

Our findings demonstrated that cervical lymph node dissection increases acid reflux and DGER to the remnant esophagus as well as the incidence of postoperative reflux esophagitis. The possible reasons are as follows: denervation and scarring of the remnant esophagus secondary to cervical paraesophageal lymph node dissection may reduce the remnant esophageal peristaltic movement. In addition, separating the left and right anterior cervical muscles for cervical paraesophageal lymph node dissection may cause scarring and rigidity of these muscles, which prevents larynx elevation, impairs the swallowing function, and reduces swallowing pressure. Adhesions among the skin flap, anterior cervical muscles, and larynx can also prevent larynx elevation. Supraclavicular lymph node dissection requires the creation of a wide skin flap and dissection of the sternocleidomastoid muscle, which may cause scarring in a broad area of the anterior cervical region and impair larynx elevation and the swallowing function. In fact, Yasuda et al. reported that cervical lymph node dissection did indeed prevent larynx elevation and impair the swallowing function [11]. The reflux is attributed to the balance of pressures, including swallowing pressure, peristaltic pressure of the remnant esophagus, negative pressure of the thoracic cavity, and positive pressure of the abdominal cavity. Overall, a decrease in swallowing pressure and peristaltic pressure of the remnant esophagus due to cervical lymph node dissection may reduce clearance of the remnant esophagus and increase acid reflux and DGER to the remnant esophagus.

Although cervical lymph node dissection has been reported to be beneficial for improving the prognosis of thoracic esophageal cancer [1–4], this approach is not necessary in all patients with this cancer. For example, Udagawa et al. reported that cervical lymph node dissection has a high efficiency index in patients with upper and middle thoracic esophageal cancer but a low efficiency index in those with lower thoracic esophageal cancer [12]. Taniyama et al. reported that the status of the recurrent laryngeal nerve lymph node can be used as an indicator of supraclavicular lymph node dissection in upper esophageal cancer and advanced cases of middle and lower esophageal cancer [13]. Since cervical lymph node dissection can lead to a prolonged operative time and increased blood loss and also impair the patient's quality of life, it is important to properly select patients who can benefit from this strategy.

Several limitations associated with the present study warrant mention. First, this was a retrospective study that included only a small number of patients. Second, the study period was very long, from 1997 to 2011, during which the indication of cervical lymph node dissection had changed. Third, antacids were discontinued at least 1 week before the pH and bilirubin monitoring, and they, therefore, did not influence the monitoring results. However, all 10 patients who used antacids before this study underwent endoscopy while using antacids, which may have influenced the incidence of reflux esophagitis; accordingly, the true incidence of reflux esophagitis without antacids might have been higher. Fourth, although the decrease in swallowing pressure in the pharynx and peristaltic pressure in the remnant esophagus was presumed to reduce the clearance of the remnant esophagus and increase acid reflux and DGER to the remnant esophagus in patients with cervical lymph node dissection, a proper evaluation of this hypothesis will require comparing changes in these pressures between the 2F and 3F groups using high-resolution manometry.

In conclusion, cervical lymph node dissection increases acid reflux and DGER and can lead to an increase in the incidence of reflux esophagitis in patients who undergo intrathoracic esophagogastrostomy. It is necessary to properly select esophageal cancer patients who can benefit from cervical lymph node dissection.

Compliance with ethical standards

Conflict of interest None of the authors have financial incentives or conflicts of interest associated with the material or methods in this report.

Ethical standards The ethics committee of Nagoya University Hospital approved our study (No2016-0442).

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