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Clinical Importance of Sputum in the Respiratory Tract as a Predictive Marker of Postoperative Morbidity After Esophagectomy for Esophageal Cancer

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ABSTRACT

Background. Respiratory morbidity is common after esophagectomy and can be a major cause of surgery-related mortality. Thus, it is important to identify novel predictors that can preoperatively estimate the incidence of postoperative respiratory morbidity. Asymptomatic sputum in the respiratory tract is sometimes observed on preoperative computed tomography (CT). This study aimed to determine the clinical importance of sputum in the respiratory tract as a predictor of postoperative morbidity after esophagectomy for esophageal cancer.

Patients and Methods. The study included 609 consecutive patients who underwent three-incisional esophagectomy for esophageal cancer between April 2005 and November 2018.

Results. Among the patients, 76 (12.5%) had sputum in the respiratory tract on preoperative CT. This finding was significantly associated with older age, more extreme smoking habit, worse performance status, lower forced expiratory volume 1%, and more frequent pulmonary comorbidities. Additionally, the incidence of postoperative pneumonia was higher in these patients than in those without sputum (16 vs 8%, $p = 0.028$). Sputum in the main bronchus was associated with higher frequencies of morbidity of Clavien–Dindo classification (CDc) $\geq$ II ($p = 0.019$), severe morbidity of CDc $\geq$ IIIb ($p = 0.058$), pneumonia ($p = 0.10$), and pulmonary morbidity ($p = 0.19$) compared with the finding of sputum in the trachea alone. On multivariate analysis, sputum in the respiratory tract was an independent risk factor (hazard ratio, 2.07; 95% confidence interval, 1.019–4.207; $p = 0.044$) for postoperative pneumonia.

Conclusions. Sputum in the respiratory tract is a novel predictor of postesophagectomy pneumonia. Patients with sputum in the more distal respiratory tract might have high risk of postoperative morbidities.

Respiratory morbidity is common after esophagectomy for esophageal cancer. Most patients with esophageal squamous cell carcinoma have an extreme smoking habit.[1–3] In addition, they often have several pulmonary comorbidities, which can be potent risk factors for postoperative respiratory complications.[4] Respiratory morbidity has been reported to be a leading cause of surgery-related mortality.[5,6] Thus, it is important to predict and prophylactically address postoperative respiratory morbidity in order to improve short-term outcomes after esophagectomy.

Several risk factors for postesophagectomy respiratory morbidity have been previously reported, and notably, past smoking is a representative risk[2–4,6,7] and preoperative smoking cessation is an effective precaution.[8,9] However, it is difficult to definitively determine whether the self-reported smoking status is true.[10] Besides smoking, several pulmonary comorbidities might be risk factors for respiratory morbidity.[2–4,6,7,11] However, the severity of comorbidities highly associated with postoperative respiratory complications has not been well established. Usually, surgeons subjectively estimate the incidence of pulmonary morbidity according to information on patient background, presence of preoperative treatment, and surgical invasiveness. Thus, novel predictive markers that can objectively assess the risk of respiratory morbidity are required.

In general clinical practice for esophageal cancer, we found that a certain population of patients had sputum in the respiratory tract on preoperative computed tomography (CT), without symptoms. We hypothesized that these patients have high risk of postoperative pulmonary morbidity, as this finding might be associated with physical disadvantages, which can result in respiratory morbidity, such as high sputum output, swallowing dysfunction, and cough reflex weakness.

The present study retrospectively investigated the presence of sputum in the respiratory tract on preoperative CT in patients who underwent esophagectomy for esophageal cancer and compared short-term outcomes between patients with and those without sputum in order to elucidate the clinical value of this finding as a predictor of postoperative morbidity after esophagectomy.

PATIENTS AND METHODS

Patients

Between April 2005 and November 2018, 688 consecutive patients underwent three-incisional esophagectomy for esophageal cancer at Kumamoto University Hospital. Of these patients, 19 who underwent two-stage esophagectomy, 40 who underwent salvage esophagectomy after definitive chemoradiotherapy (CRT), 14 with insufficient CT image quality for evaluation, and 6 with insufficient clinical data were excluded. Finally, 609 patients were eligible for study inclusion (Fig. 1). Patients were divided into two groups according to the presence of sputum in the respiratory tract on preoperative CT (Fig. 2). Short-term outcomes after surgery were retrospectively compared between the two groups using an institutional clinical database, which was prospectively entered. The
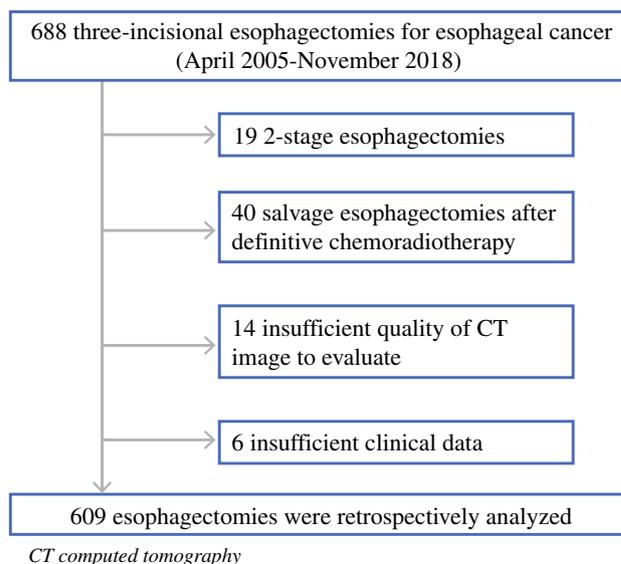

FIG. 1 Flowchart of analyzed patients (*CT* computed tomography)

study procedures were approved by the institutional ethics committee.

Evaluation of Sputum in the Respiratory Tract

Sputum in the respiratory tract was examined using multislice CT (lung window) by two individual surgeons (N.Y. and A.M.). The coincidence rate and kappa coefficient for evaluation of sputum were 97.5% (594/609) and 0.883, respectively. When evaluations between the reviewers differed, they reevaluated the data and reached a consensus via discussion. In addition to the presence of sputum, the site of sputum was classified as follows for further analysis: trachea alone and main bronchus (including both the main bronchus and trachea).

Treatment Strategy

The details of our treatment strategy are available elsewhere.[12] Neoadjuvant chemotherapy has been administered to patients with non-T4 node-positive tumors since August 2008. Neoadjuvant chemoradiotherapy (CRT) has been commonly administered to patients with T4 tumors. The pretreatment clinical stage was classified in accordance with Union for International Cancer Control tumor–node–metastasis (TNM) staging, version 7.[13]

Surgery

Esophagectomy was defined as three-incisional (neck, chest, and abdomen) esophagectomy with lymphadenectomy. The 2012 guidelines prepared by the Japan Esophageal Society were used to determine the extent of
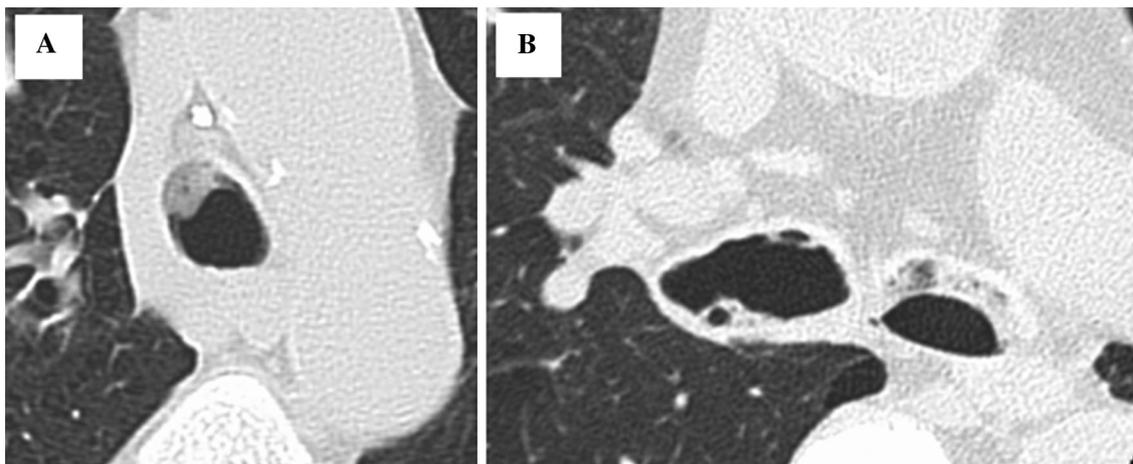
FIG. 2 Typical cases with respiratory tract sputum on computed tomography in the **a** trachea and **b** main bronchus

lymphadenectomy.[14] Chest manipulation was conducted from the right thorax. Minimally invasive esophagectomy started in May 2011.

Definitions of Morbidities

Postoperative morbidities were defined according to the definitions advocated by the Society of Thoracic Surgeons General Thoracic Surgery. Morbidity details are available elsewhere.[15] Any morbidity and severe morbidity were defined as states where the Clavien–Dindo classifications[16] (CDc) were $\geq$ II and $\geq$ IIIb, respectively. Respiratory morbidity was defined as the presence of the following postoperative conditions: initial ventilatory support for > 48 h or reintubation for respiratory failure, need for tracheostomy, and pneumonia. Pneumonia was defined as the presence of new infiltrates on chest radiography and a positive culture of bronchoalveolar lavage. Furthermore, any pulmonary morbidity requiring intervention or surgical treatment was included.

Statistical Methods

Statistical comparisons between study groups were conducted using the Chi square test. The Mann–Whitney U test was used for unpaired samples. When the matrix contained fewer than five patients, Fisher's exact test was used. The following clinical factors were adopted for the analysis of independent risk factors for the occurrence of postoperative pneumonia: age at surgery (per 10 years), sex (male vs female), body mass index (BMI) (< 18.5 vs $\geq$ 18.5 kg/m^2), Brinkman index (tobacco number/day $\times$ year, for 100 point increase), performance status (PS) (0 vs 1 and 2), American Society of Anesthesiologists physical status (1 and 2 vs 3), diabetes mellitus (yes vs no), pulmonary morbidity (yes vs no), clinical stage (0–II vs III

and IV), preoperative treatment (yes vs no), operation time (for 60 min increase), blood loss (for 100 g increase), and sputum in the respiratory tract (yes vs no). Factors with probability level $\leq$ 0.1 were selected for subsequent multivariate analysis, and variables with probability level < 0.05 were considered as independent risk factors. The software package StatView^{TM} version 5.0 (Abacus Concepts, Inc., Berkeley, CA) was used for statistical analyses.

RESULTS

Clinical Features of the Patients

Table 1 presents the patient characteristics according to the presence of sputum in the respiratory tract. Among all patients, 76 (12.5%) had sputum in the respiratory tract on preoperative CT. Patients with sputum in the respiratory tract had older age, more extreme past smoking habit, worse PS, lower forced expiratory volume (FEV) 1%, and higher frequency of pulmonary comorbidities when compared with the findings in those without sputum in the respiratory tract. The surgical procedure used was statistically equivalent between the groups.

Short-Term Outcomes After Surgery

Table 2 presents the short-term outcomes. Patients with sputum in the respiratory tract had a higher incidence of postoperative pneumonia when compared with the finding in those without sputum in the respiratory tract. Further analysis showed that sputum in the main bronchus was significantly associated with high incidence of postoperative morbidity of CDc $\geq$ II. In addition, pneumonia, pulmonary morbidity, severe morbidity of CDc $\geq$ IIIb, and reoperation were frequently observed among patients with

TABLE 1 Sputum in the respiratory tract and patient characteristics

Clinical, epidemiological, and surgical feature	Sputum in the respiratory tract		p
	Present (N = 76)	Absent (N = 533)	
Age (mean ± SD, years)	68.2 ± 7.8	65.8 ± 8.3	0.020
Sex male	69 (91%)	468 (88%)	0.45
Body mass index (kg/m²)			0.10
< 18.5	8 (11%)	66 (12%)	
18.5–25.0	62 (82%)	378 (71%)	
25.0 <	6 (8%)	89 (17%)	
Mean Brinkman index[a] ± SD	940 ± 540	750 ± 580	0.0078
Brinkman index ≥ 800	47 (62%)	239 (45%)	0.0055
Performance status			0.0064
0	60 (79%)	478 (90%)	
1, 2	16 (21%)	55 (10%)	
American Society of Anesthesiologists physical status			0.36
1	14 (18%)	119 (22%)	
2	56 (74%)	390 (73%)	
3	6 (8%)	24 (5%)	
% Vital capacity (mean ± SD)	101.2 ± 14.8	103.3 ± 14.5	0.23
Forced expiratory volume 1% (mean ± SD)	71.9 ± 10.3	74.1 ± 8.7	0.042
Comorbidity			
Diabetes mellitus	11 (14%)	101 (19%)	0.35
Pulmonary disease	39 (51%)	167 (31%)	0.0006
Cardiovascular disease	37 (49%)	268 (50%)	0.79
Clinical stage			0.84
0, I	30 (39%)	234 (44%)	
II	15 (20%)	97 (18%)	
III	27 (36%)	168 (32%)	
IV	4 (5%)	34 67%)	
Preoperative treatment			0.90
Absent	44 (58%)	314 (59%)	
Chemotherapy	23 (30%)	165 (31%)	
Chemoradiotherapy	9 (12%)	54 (10%)	
Thoracic procedure			0.99
Minimally invasive	34 (45%)	239 (45%)	
Open	42 (55%)	294 (55%)	
Conduit			0.90
Gastric tube	71 (93%)	500 (94%)	
Others	5 (7%)	33 (6%)	

SD standard deviation

[a]Brinkman index calculated as tobacco number/day × year

sputum in the main bronchus, but without significance (Supplementary Table 1).

Risk Factors for Postoperative Pneumonia

Table 3 presents the results of the multivariate analysis for the risk factors of postoperative pneumonia. The presence of sputum in the respiratory tract before esophagectomy was an independent risk factor for postoperative pneumonia (hazard ratio, 2.07; 95% confidence interval, 1.019–4.207; p = 0.044), along with high intraoperative bleeding. In addition, an extreme past smoking habit tended to be a risk factor (p = 0.055).

TABLE 2 Short-term outcomes after esophagectomy

Variable	Sputum in the respiratory tract		p
	Present (N = 76)	Absent (N = 533)	
Operative time, OE (mean ± SD, min)	535 ± 95	535 ± 109	0.98
Operative time, MIE (mean ± SD, min)	582 ± 104	592 ± 99	0.57
Bleeding, OE (mean ± SD, g)	682 ± 552	557 ± 409	0.077
Bleeding, MIE (mean ± SD, g)	212 ± 144	301 ± 366	0.16
Any morbidity of CDc ≥ II	28 (37%)	204 (38%)	0.81
Severe morbidity of CDc ≥ IIIb	11 (14%)	65 (12%)	0.57
Pneumonia	12 (16%)	43 (8%)	0.028
Any pulmonary morbidity	16 (21%)	82 (15%)	0.21
Surgical-site infection (leak included)	19 (25%)	128 (24%)	0.85
Anastomotic leakage	9 (12%)	69 (13%)	0.79
Cardiovascular morbidity	4 (5%)	35 (7%)	0.81[a]
Chylothorax	2 (3%)	10 (2%)	0.65[a]
Reoperation	5 (7%)	38 (7%)	0.86
In-hospital mortality	1 (1%)	1 (0.2%)	0.23[a]
Hospital stay (median ± SE, day)	27 ± 2.3	24 ± 0.8	0.64

OE open esophagectomy, *MIE* minimally invasive esophagectomy, *CDc* Clavien–Dindo classification, *SD* standard deviation, *SE* standard error

[a]Fisher's exact test

TABLE 3 Multivariate analysis for factors associated with postoperative pneumonia

Factor	Objective variable	Control	Univariate analysis		Multivariate analysis	
			HR (95% CI)	p	HR (95% CI)	p
Sex	Male	Female	3.83 (0.914–16.08)	0.066	2.95 (0.688–12.67)	0.145
Brinkman index	For 100 increase	–	1.06 (1.014–1.104)	0.009	1.04 (0.991–1.092)	0.055
Diabetes mellitus	Present	Absent	1.77 (0.938–3.326)	0.078	1.72 (0.896–3.287)	0.103
Bleeding	For 100 g increase	–	1.07 (1.015–1.130)	0.013	1.08 (1.017–1.138)	0.010
Respiratory tract sputum	Present	Absent	2.14 (1.071–4.264)	0.031	2.07 (1.019–4.207)	0.044

HR hazard ratio, *CI* confidence interval

DISCUSSION

The present study found that the presence of sputum in the respiratory tract before esophagectomy was a significant risk factor for postoperative pneumonia. In addition, further analysis suggested that patients with sputum in the main bronchus more frequently experienced postoperative morbidities when compared with the findings in patients with sputum in the trachea alone.

To the best of the authors' knowledge, no previous study has focused on the correlation of the presence of sputum in the respiratory tract with short-term outcomes after esophagectomy. In the present study, surprisingly, approximately 13% of patients had sputum in the respiratory tract on preoperative CT. Tumor stage, preoperative treatment, and surgical strategy, which can be associated with the incidence of postoperative morbidities, were equivalent between patients with and those without sputum. There are several reasons for the association between the presence of sputum in the respiratory tract and postoperative pneumonia. First, patients with sputum in the respiratory tract might have several physical disadvantages. In the present study, these patients had significantly older age and worse PS, which could be associated with emaciation of breathing muscles and difficulty in sputum evacuation. Second, these patients had a significantly more extreme past smoking habit, lower FEV1%, and more frequent respiratory comorbidities, which could be related to excess sputum production. Third, sputum in the respiratory tract might indicate weakness of the cough reflex. These issues could increase the incidence of postoperative pneumonia. In addition, patients with sputum in the main

bronchus had more frequent morbidities when compared with the findings in those with sputum in the trachea alone. We considered that patients with sputum in the more distal tract had more severe physical disadvantages and experienced various postoperative morbidities.

It is clinically important to identify predictive markers that can preoperatively estimate the incidence of postesophagectomy morbidities, as various precautions can be taken preoperatively based on the findings of these markers. So far, several predictors have been suggested to estimate the incidence of respiratory morbidity after esophagectomy.[2–4,6,7,11] Smoking habit is the most frequently reported risk factor associated with pulmonary morbidity. High levels of preoperative exhaled carbon monoxide at admission, which is an indicator of recent smoking status, could become a predictor of postesophagectomy severe morbidity.[10] Moreover, high mean corpuscular volume, which is etiologically associated with high tobacco consumption, could become a predictor of postesophagectomy pulmonary morbidities.[12]

In addition to these measurable markers, establishing a simple predictor based on imaging is considerably important, as the risk of postoperative morbidities can be assessed. We previously reported the significance of anatomical esophageal position (left-sided esophagus) on CT for projecting surgical difficulty and postoperative respiratory morbidity.[17] In the current study, the presence of sputum in the respiratory tract was a significant risk factor of postoperative pneumonia. The result has several clinical advantages. First, the presence of sputum can be easily determined on CT. Second, CT is routinely conducted before esophagectomy. Third, examination of sputum in the respiratory tract does not require use of any contrast agent. Thus, there are no additional economical and physical burdens.

On identifying sputum in the respiratory tract before esophagectomy, conducting possible prophylactic approaches for postoperative morbidity is considerably important. Smoking cessation at least 30 days before esophagectomy is effective for preventing postoperative pneumonia.[8,9] Preoperative respiratory rehabilitation and maintenance of oral hygiene are useful to reduce respiratory morbidity.[18,19] Enhanced recovery after surgery could reduce the incidence of pulmonary morbidity.[20,21] Additionally, minimally invasive esophagectomy is less invasive than open esophagectomy and is associated with fewer postoperative respiratory morbidities.[22,23]

The present study has several limitations. First, this was a single-institution retrospective study. Second, the observation period was long, which might have resulted in historical bias with regard to the treatment strategy, perioperative management, and surgical devices that could affect short-term outcomes after surgery. Thus, further multiinstitutional investigations with a larger cohort are required to reconfirm the usefulness of preoperative sputum in the respiratory tract as a predictive marker of postoperative morbidity after esophagectomy.

In conclusion, the presence of sputum in the respiratory tract before esophagectomy is a novel and potent risk factor for postoperative pneumonia. Notably, patients with sputum in the more distal respiratory tract might have high risk of postoperative morbidity. When sputum is preoperatively identified in the respiratory track, various prophylactic approaches should be considered during esophagectomy.

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