Fukushima J. Med. Sci.,
Vol. 68, No. 2, 2022

[Original article]

Preoperative bacterial culture can predict severe pneumonia in patients receiving esophagectomy

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(Received February 16, 2022, accepted July 7, 2022)

Abstract

Background : Postoperative pneumonia is one of the major complications after esophagectomy. The aim of this study was to determine whether bacterial cultures before esophagectomy could predict occurrence of postoperative pneumonia and help treatment strategies for postoperative pneumonia.

Methods : Sixty-nine patients who underwent subtotal esophagectomy at Fukushima Medical University Hospital between January 2017 and May 2021 were included in this study. We collected sputum, oral, and/or nasopharyngeal swabs for bacterial culture preoperatively from all patients and from those who were suspected of postoperative pulmonary infections. We compared cultured pathogenic bacteria obtained preoperatively and postoperatively from patients who developed postoperative pneumonia, and investigated their association with incidence of postoperative pneumonia.

Results : Postoperative pneumonia occurred in 22 of 69 patients (31%), including 13 cases of severe pneumonia with a Clavien-Dindo classification of grade IIIa or higher. Multivariate analysis revealed that longer operative duration (for 30 minutes increase ; odds ratio 1.27, 95% CI 1.01-1.51, $p=0.039$) and positivity for preoperative bacterial culture (odds ratio 5.03, 95% CI 1.31-19.2, $p=0.018$) were independent risk factors for severe postoperative pneumonia, but not for all incidences of postoperative pneumonia. Of note, in only 5 of the 22 patients with pneumonia, the same pathogenic species were detected preoperatively and after the onset of pneumonia.

Conclusions : Our results imply that preoperative bacterial culture may be useful to predict severe postoperative pneumonia. However, it may not be useful in determining pathogenic bacteria responsible for postoperative pneumonia.

Key words : bacterial culture, pneumonia, esophageal carcinoma, esophagectomy

Introduction

Esophagectomy for esophageal cancer is a highly invasive surgery. Even though surgical techniques and perioperative management have improved, a number of complications after esophagectomy persist[1-3]. Respiratory complications are among the most common complications after esophagectomy (17.9-38.9%) and can lead to prolonged hospital stay and increased mortality[2-6]. Several studies reported that respiratory complications after esophagectomy, including pneumonia, affect not only short-term outcomes, but also, survival[4,7]. Thus, improvement of perioperative management for patients undergoing esophagectomy is required to prevent such complications.

It is generally considered that aspiration of oropharyngeal pathogens is one of the main causes of postoperative pneumonia[8,9]. Several studies identified pathogens in the oral cavity, dental plaque, and tracheal sputum as risk factors for respiratory infections after esophagectomy[10,11]. When esophagec-

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tomy patients develop postoperative pneumonia, it is mandatory to identify the causative bacteria and to administer effective antibiotics as soon as possible. If pathogens identified preoperatively from sputum or oral cavity are identical to the bacteria responsible for postoperative pneumonia, appropriate antibiotics can be started immediately. However, the clinical usefulness of bacterial culture before esophagectomy is not yet fully elucidated.

This study aimed to assess whether bacteria cultured before esophagectomy were identical to those responsible for postoperative pneumonia, and whether preoperative bacterial cultures could predict the incidence of postoperative pneumonia.

Materials and methods

Patients and data collection

This study included consecutive patients who underwent subtotal esophagectomy for esophageal or esophagogastric junction cancer at Fukushima Medical University Hospital between January 2017 and May 2021. We excluded patients who underwent partial cervical esophagectomy, pharyngo-laryngo-esophagectomy, and salvage surgery after definitive chemoradiotherapy. Also, patients without any preoperative bacterial culture were excluded. Patients were divided into two groups, *Positive* and *Negative*, according to the results of their preoperative bacterial culture. Clinicopathological data were retrospectively collected from medical records. These data included patients' background, surgical procedure, operative duration, operative blood loss, postoperative complications, and tumor pathological factors. We used the controlling nutritional status (CONUT) score – calculated from serum albumin, lymphocyte count, and total cholesterol – to evaluate the preoperative nutrition status[12]. Pathological diagnoses were based on the Union for International Cancer Control TNM staging, version 7.

Written informed consent was obtained from all patients. This study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the institutional review board of Fukushima Medical University (registry number 30169).

Surgical procedure

Esophagectomy was defined as esophagectomy with two- or three-field lymphadenectomy requiring three incisions (neck, chest, and abdomen). Open thoracic esophagectomy or minimally invasive esophagectomy (MIE) was performed. Open transthoracic esophagectomy by right thoracotomy was performed with the patient in the left lateral decubitus position. Thoracic manipulation of MIE, including video-assisted thoracic surgery and robotic assisted thoracoscopic surgery, was performed through the right thorax with the patient in a prone position. We performed MIE using artificial pneumothorax under two-lung ventilation. MIE-approach was mainly selected for esophagectomy, while open-approach was selected for patients with borderline resectable tumor factors. We primarily selected the gastric tube as a reconstructive conduit through the retrosternal route, and performed esophagogastrostomy through a cervical incision. A feeding catheter jejunostomy was created for postoperative enteral nutrition in all cases.

Perioperative management

All patients received respiratory rehabilitation and oral care before surgery. The oral care included oral assessment and extractions of carious teeth by dentists in the Division of the Dentistry and Oral Surgery. We administered cefazolin as a prophylactic antibiotic, 1 g every 3 hours, only during the esophagectomy. All patients were routinely extubated in the operating room after the surgery, unless contraindicated by problems during surgery. We gave enteral nutrition through the catheter jejunostomy on the next day after surgery. Oral intake was started after confirmation of the absence of anastomotic leakage by radiography on the 7th postoperative day. Physical and respiratory rehabilitation were started on the first postoperative day, unless prevented by a patient's general condition. Swallowing rehabilitation was performed after postoperative day 7 only in cases with dysphagia or recurrent laryngeal nerve palsy.

Bacterial cultures

We routinely collected sputum, oral, nasal, and/or pharyngeal swabs within 7 days before esophagectomy. The samples were cultured, and identification of normal flora and pathogens was performed in our microbiology laboratory. Postoperative sputum culture was not carried out routinely, but only in cases of suspicious for pulmonary infections. Patients were defined as *Positive* if pathogenic bacteria were detected, and those with normal flora or non-pathogenic bacteria were defined as *Negative*.

Postoperative pneumonia

We defined postoperative pneumonia as devel-

Table 1. Patients' characteristics and surgical outcomes

	Preoperative bacterial culture		
	Negative (n = 49)	Positive (n = 20)	p-value
Age†	68 ± 8.3	69 ± 6.6	0.63
Sex (male/female)	37/12	19/1	0.09
Brinkman index†	500 ± 443	727 ± 446	0.058
%VC†	100 ± 15	103 ± 20	0.59
FEV1 (L)†			
Male	2.79 ± 0.53	2.65 ± 0.74	0.30
Female	2.05 ± 0.67	1.83	0.59
FEV1%†	74 ± 8.2	72 ± 6.0	0.35
Comorbidity			
COPD	8	3	0.60
Diabetes mellitus	8	3	0.60
CONUT score			0.37
Normal (0-1)	20	8	
Light malnutrition (2-4)	28	10	
Moderate malnutrition (5-8)	1	2	
Location of tumor			0.86
Ut	9	3	
Mt	24	8	
Lt	10	6	
Ae	6	3	
Histological type			0.90
Squamous cell carcinoma	38	7	
Adenocarcinoma	6	10	
Others	5	3	
Neoadjuvant therapy			0.17
None	21	7	
Neoadjuvant chemotherapy	13	10	
Neoadjuvant chemoradiotherapy	15	3	
Thoracic surgical approach			1.0
Open	13	5	
MIE	36	15	
3-field lymphadenectomy	33	12	0.58
Operative duration (minutes)†	529 ± 96	571 ± 103	0.11
Blood loss (g)†	283 ± 417	390 ± 545	0.67
pStage			0.60
0, I	16	3	
II	15	9	
III	12	5	
IV	6	3	
Anastomotic leakage	18	8	0.79
Recurrent laryngeal nerve palsy	12	6	0.76
Dysphagia	13	7	0.37
Postoperative pneumonia	12	10	0.05
Severe postoperative pneumonia (≥ IIIa)	5	8	0.007

†Plus-minus values are means ± standard deviation.
%VC, vital capacity as percent of predicted ; FEV1, forced expiratory volume in 1 second ; FEV1%, forced expiratory volume % in 1 second ; COPD, chronic obstructive pulmonary disease ; CONUT, controlling nutritional status ; Ut, upper thoracic esophagus ; Mt, middle thoracic esophagus ; Lt, lower thoracic esophagus ; Ae, abdominal esophagus ; MIE, minimally invasive esophagectomy.

opment of new infiltrations on chest radiography and/or computed tomography, and the presence of at least one of the following two clinical features as previously reported : increase in body temperature to 38℃ or higher ; and/or increase in white blood cell count to 9,000/mm^3 or higher[13,14]. Postoperative pneumonia was documented according to Clavien-Dindo classification, with severe pneumonia defined as grade IIIa or higher[15].

Statistics

The software package STATA15 (STATA Corp., College Station, TX, USA) was used for statistical analysis. Fisher's exact test was used to compare categorical variables between groups, and the Wilcoxon test was used to compare continuous variables. Risk factors for postoperative pneumonia and severe pneumonia were analyzed using univariate and multivariate logistic regression models. The following factors were adopted for analyses of postoperative pneumonia : age (for 10-year increase), sex (male vs female), Brinkman index (for 100 increase), vital capacity as percent of predicted (for 10% increase), forced expiratory volume in 1 second (FEV1 ; for 1 L increase), forced expiratory volume % in 1 second (FEV1% ; for 10% increase), comorbidity (present vs absent), CONUT score (normal vs light or moderate malnutrition), neoadjuvant treatment (surgery alone vs neoadjuvant chemotherapy or chemoradiotherapy), thoracic surgical procedure (MIE vs open esophagectomy), lymphadenectomy (3-field vs 2-filed), operative duration (for 30 minutes increase), blood loss (for 50 g increase), tumor stage (0 or I vs II-IV), anastomotic leakage (present vs absent), recurrent laryngeal nerve palsy (present vs absent), dysphagia (present vs absent), and preoperative bacterial test (*Negative* vs *Positive*). *P*-values less than 0.05 were considered significant.

Results

Patient characteristics and postoperative pneumonia

Sixty-nine patients were included in this study. Among them, pathogenic bacteria were detected from at least one culture of sputum, oral swab, nasal swab, and/or pharyngeal swab obtained preoperatively in 20 patients (29%), defined as *Positive*. The remaining 49 patients (71%) were defined as *Negative*. Clinical characteristics and surgical outcomes of these two groups are summarized in Table 1. Although the Brinkman index of the positive group was marginally higher than that of the negative group ($p=0.058$), the background data did not differ among the two groups.

Postoperative pneumonia occurred in 22 of 69 patients (32%), with 13 of the 22 classified as having severe pneumonia (including 1 with acute respiratory distress syndrome). Postoperative pneumonia was more frequently observed in the positive group than the negative group ($p=0.05$), and the incidence of severe pneumonia was also higher in the positive group than the negative group ($p=0.007$). No significant differences were observed in age, preoperative comorbidity, respiratory function, preoperative nutritional status, location and stage of the tumor, neoadjuvant therapy, thoracic surgical approach, range of lymphadenectomy, anastomotic leakage, or recurrent laryngeal nerve palsy, between the two groups.

Perioperative bacterial culture

Table 2 shows the detection rate of pathogenic bacteria in preoperative cultures from each site. The positive rate was 22% in sputum culture, 18% in nasal swab culture, 5% in oral swab culture, and 11% in pharyngeal swab culture. Among patients with positive preoperative bacterial cultures, those who developed postoperative pneumonia were 5 of 10 for sputum culture, 6 of 11 for nasal swab culture, and 2 of 3 for oral swab culture. No patient positive by pharyngeal swab culture developed postoperative pneumonia.

Figure 1 shows the number of pathogenic bacterial species detected in pre- and postoperative cultures. In preoperative cultures, methicillin-susceptible Staphylococcus aureus was detected most frequently, followed by Klebsiella pneumoniae. Twenty-three bacteria were identified in postoperative cultures of sputum from the 22 patients with postoperative pneumonia. Eleven of the 22 postoperative pneumonia patients were positive for postoperative sputum culture, and in 5 of those 11 cases, pathogenic bacteria in postoperative sputum culture were identical to those in preoperative culture.

Table 2. Detection rate of pathogenic bacteria in preoperative bacterial cultures

	Positive rate	
Sputum	10/45	(22%)
Nasal swab	11/58	(18%)
Oral swab	3/56	(5.3%)
Pharyngeal swab	1/9	(11%)

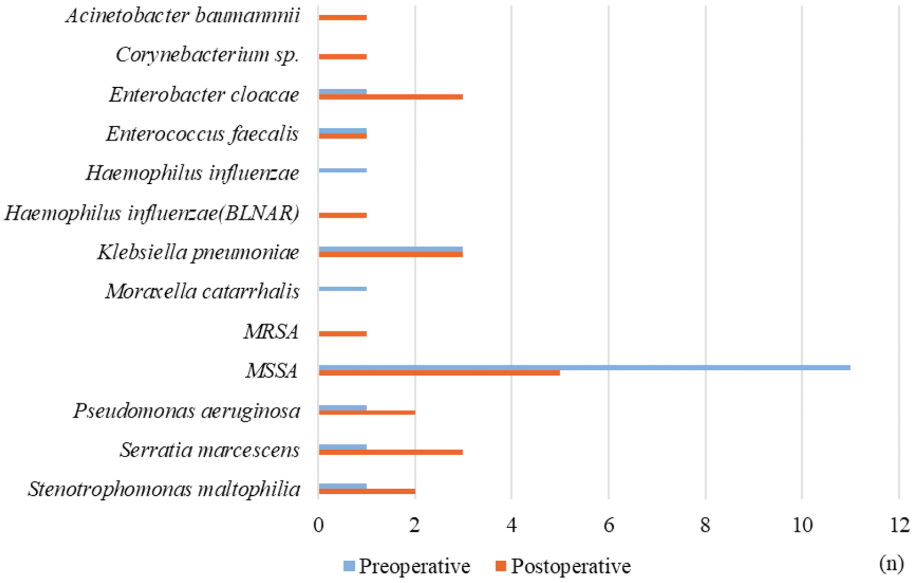

Fig. 1. Number of pathogenic bacterial species detected in pre- and postoperative bacterial cultures.

Table 3. Logistic regression analysis for postoperative pneumonia

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age (for 10-year increase)	0.93 (0.49-1.79)	0.84		
Male	7.20 (0.87-59.4)	0.067		
Brinkman index (for 100 increase)	1.04 (0.93-1.16)	0.48		
%VC (for 10% increase)	0.82 (0.60-1.12)	0.23		
FEV1 (for 1 L increase)	0.87 (0.41-1.86)	0.72		
FEV1% (for 10% increase)	0.39 (0.18-0.85)	0.018	0.31 (0.12-0.76)	0.011
Comorbidity				
COPD	1.26 (0.32-4.89)	0.72		
Diabetes mellitus	0.17 (0.02-1.47)	0.10		
CONUT score (normal vs light and moderate malnutrition)	0.74 (0.26-2.07)	0.57		
Neoadjuvant therapy (vs surgery alone)	2.34 (0.78-7.04)	0.12		
Neoadjuvant chemotherapy (vs surgery alone)	2.82 (0.83-9.57)	0.096		
Neoadjuvant chemoradiotherapy (vs surgery alone)	1.83 (0.48-6.94)	0.37		
Thoracic surgical approach (open vs MIE)	2.92 (0.95-8.94)	0.06		
3-field lymphadenectomy (vs 2-field)	0.90 (0.31-2.60)	0.85		
Operative duration (for 30 minutes increase)	1.20 (1.02-1.41)	0.023	1.16 (0.96-1.41)	0.12
Blood loss (for 50 g increase)	1.10 (1.01-1.20)	0.024	1.08 (0.98-1.18)	0.09
pStage (2-4 vs 0 and 1)	1.59 (0.49-5.13)	0.43		
Anastomotic leakage	0.92 (0.32-2.62)	0.87		
Recurrent laryngeal nerve palsy	1.48 (0.57-3.84)	0.41		
Dysphagia	2.38 (0.79-7.15)	0.12		
Preoperative bacterial culture test (Positive vs Negative)	3.08 (1.03-9.18)	0.043	2.36 (0.68-8.17)	0.20

OR, odds ratio ; CI, confidence interval ; %VC, vital capacity as percent of predicted ; FEV1, forced expiratory volume in 1 second ; FEV1%, forced expiratory volume % in 1 second ; COPD, chronic obstructive pulmonary disease ; CONUT, controlling nutritional status ; MIE ; minimally invasive esophagectomy.

Risk factors associated with postoperative pneumonia

Table 3 shows the risk factors associated with postoperative pneumonia. By univariate analysis, postoperative pneumonia was associated with low FEV1% ($p=0.018$), longer operative duration ($p=0.023$), extensive blood loss ($p=0.024$), and positivity for preoperative bacterial culture ($p=0.043$). Multivariate analysis showed that low FEV1% (for a 10% increase ; odds ratio 0.31, 95% confidence interval 0.12–0.76, $p=0.011$) significantly impacted the risk of postoperative pneumonia.

Table 4 shows the multivariate logistic regression analysis for risk factors of severe postoperative pneumonia. Of note, longer operative duration (for 30 minutes increase ; odds ratio 1.27, 95% confidence interval 1.01–1.51, $p=0.039$) and positivity for preoperative bacterial test (odds ratio 5.03, 95% confidence interval 1.31–19.2, $p=0.018$) were significant independent risk factors for developing severe postoperative pneumonia.

Discussion

It is generally accepted in theory that bacteria in the oral cavity could cause postoperative pneumonia. In practice, there are only a few studies about the relationship between oral cavity bacteria and postoperative pneumonia, and the clinical significance of preoperative bacterial culture is not well established. This study revealed that the presence of pathogenic bacteria in the oropharyngeal cavity and sputum before esophagectomy was a predictive factor for the development of severe postoperative pneumonia, but not for all incidences of pneumonia. Moreover, the concordance rate of bacterial species in preoperative screening culture and postoperative diagnostic culture for pneumonia was very low.

Previous studies report conflicting results about the relationship between the presence of pathogenic bacteria detected in perioperative routine cultures and postoperative pneumonia[8,14,16]. Jimbo *et al.* and Matsunaga *et al.* reported that perioperative bacteri-

Table 4. Logistic regression analysis for severe postoperative pneumonia

Variables	Univariate analysis		Multivariateanalysis	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age (for 10-year increase)	1.51 (0.65–3.54)	0.33		
Male	3.27 (0.38–27.7)	0.27		
Brinkman index (for 100 increase)	1.07 (0.93–1.22)	0.31		
%VC (for 10% increase)	0.74 (0.51–1.07)	0.12		
FEV1 (for 1 L increase)	0.63 (0.26–1.54)	0.31		
FEV1% (for 10% increase)	0.62 (0.27–1.41)	0.25		
Comorbidity				
COPD	0.94 (0.17–5.02)	0.95		
Diabetes mellitus	0.38 (0.04–3.29)	0.38		
CONUT score (normal vs light and moderate malnutrition)	1.11 (0.32–3.84)	0.86		
Neoadjuvant therapy (vs surgery alone)	1.11 (0.32–3.84)	0.86		
Neoadjuvant chemotherapy (vs surgery alone)	1.27 (0.31–5.10)	0.72		
Neoadjuvant chemoradiotherapy (vs surgery alone)	0.92 (0.19–4.43)	0.91		
Thoracic surgical approach (Open vs MIE)	3.14 (0.88–11.1)	0.076		
3-field lymphadenectomy (vs 2-field)	0.82 (0.23–2.85)	0.75		
Operative duration (for 30 minutes increase)	1.26 (1.04–1.52)	0.015	1.27 (1.01–1.51)	0.039
Blood loss (for 50 g increase)	1.06 (1.00–1.13)	0.045		
pStage (2–4 vs 0 and 1)	2.60 (0.52–13.0)	0.24		
Anastomotic leakage	1.54 (0.45–5.22)	0.48		
Recurrent laryngeal nerve palsy	1.08 (0.34–3.43)	0.88		
Dysphagia	1.21 (0.32–4.62)	0.77		
Preoperative bacterial culture test (Positive vs negative)	5.86 (1.61–21.2)	0.007	5.03 (1.31–19.2)	0.018

OR, odds ratio ; CI, confidence interval ; %VC, vital capacity as percent of predicted ; FEV1, forced expiratory volume in 1 second ; FEV1%, forced expiratory volume % in 1 second ; COPD, chronic obstructive pulmonary disease ; CONUT, controlling nutritional status ; MIE ; minimally invasive esophagectomy.

al culture could not predict postoperative pneumonia after esophagectomy[8,14]. On the other hand, Matsui *et al.* showed that detection of bacterial species by sputum culture on the first postoperative day was an independent risk factor of postoperative pneumonia[17], although, this study did not focus on severity of pneumonia. Yuda *et al.* revealed that severe postoperative pneumonia was more common when antibiotic-resistant bacterial species were detected in saliva cultures[18], which might support our results. However, to our knowledge, no previous report has shown that perioperative bacterial culture might be an independent risk factor for severe postoperative pneumonia after esophagectomy. Additionally, our results suggest that it might be possible to identify patients at high risk for postoperative pneumonia *preoperatively*. In general, bacterial culture takes a few days to obtain the results. Therefore, preoperative indicators of risk for postoperative pneumonia, especially severe pneumonia, could facilitate better postoperative situational awareness and care to mitigate pneumonia after esophagectomy.

Of note, pathogenic bacteria species cultured from sputum of patients with postoperative pneumonia did not match those in preoperative cultures in the present study. In only 5 of 22 patients (23%) with pneumonia, pathogens detected preoperatively were identical to pathogenic bacteria responsible for postoperative pneumonia. It is reported that the concordance rate between bacteria detected before and after esophagectomy was relatively low (7-40%)[8,14,19]. Sok *et al.* reported that pathogens in sputum found in the early postoperative period and implicated in postoperative infective complications were different from those found in preoperative bacterial cultures[20]. Such findings in the present study and previous studies suggest that preoperative bacterial culture is not able to determine causative pathogenic bacteria, and thus, may not be useful to select appropriate antibiotics immediately after onset of postoperative pneumonia.

This study has some limitations. First, it was a retrospective study of a small cohort at a single institution. Second, in contrast with preoperative cultures, we did not routinely collect sputum culture after esophagectomy unless patients showed signs of postoperative pneumonia. Therefore, the timing of postoperative sputum culture varied among the patients, which might have affected the detection rate and concordance of pathogenic bacteria.

In conclusion, our results imply that preoperative bacterial culture may be useful to predict severe postoperative pneumonia. However, it may not be useful in determining pathogenic bacteria responsible for postoperative pneumonia.

Abbreviations

CONUT : COntrolling NUTritional status (score) ; FEV1, forced expiratory volume in 1 second ; FEV1%, forced expiratory volume % in 1 second ; MIE : minimally invasive esophagectomy.

Author contributions

Conceptualization, AK and KK ; methodology, AK and ZS ; formal analysis, AK, YW, HH, and SH ; investigation, AK, TS, HN, TM, and TT ; resources, AK, TS, HN, TM, TT, YW, HH, and SH ; data curation, AK ; writing – original draft preparation, AK ; writing – review and editing, ZS and KK ; visualization, AK ; supervision, ZS and KK ; project administration, AK and KK.

Acknowledgments

Not applicable.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

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