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Postoperative recurrent laryngeal nerve palsy is associated with pneumonia in minimally invasive esophagectomy for esophageal cancer

Short running head: Recurrent laryngeal nerve palsy in MIE

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Abstract

Background

During the past decade, minimally invasive esophagectomy (MIE) for esophageal cancer has been adopted worldwide with expectations of lower invasiveness. However, the rate of postoperative pneumonia, which is an independent risk factor for oncological prognosis in esophageal cancer, remains high. The aim of this retrospective follow-up study is to clarify whether there is a strong correlation between recurrent laryngeal nerve (RLN) palsy and postoperative pneumonia in MIE.

Methods

This retrospective follow-up study included 209 patients with esophageal cancer who underwent thoracoscopic esophagectomy in the prone position (TEP) at Kobe University between 2011 and 2017. Inclusion criteria included age 18–85 years; cT1–3, cN0–3 disease; upper mediastinal lymphadenectomy; and ability to undergo simultaneous esophagectomy and reconstruction of the gastric conduit or pedicled jejunum. Univariate and multivariate logistic regression were conducted to identify independent risk factors for pneumonia.

Results

Among 209 TEPs, pneumonia of Clavien-Dindo classification grade >II occurred in 44 patients (21%). In the pneumonia positive and negative groups, there were significant differences in age (67.9 ± 7.5 vs. 64.9 ± 8.6 years), 3-field lymph node dissection (27 (61%) vs. 67 (41%)), transfusion (20 (45%) vs. 41 (25%)), left RLN palsy (19 (43%) vs. 18 (11%)), and any RLN palsy (20 (45%) vs. 18 (11%)). In multivariate analysis, any RLN palsy was associated with a higher incidence of pneumonia (odds ratio (OR), 6.210; 95% confidence interval (CI), 2.728–14.480; $P < 0.0001$). In addition, age was associated with a higher incidence of pneumonia (OR, 1.049; 95% CI, 1.001–1.103; $P = 0.046$). Changes in the rate of any RLN palsy over time were quite similar to changes in the incidence of pneumonia.

Conclusions

There is a strong correlation between RLN palsy and pneumonia in MIE for esophageal cancer. Prevention of RLN palsy may reduce the incidence of pneumonia, leading to better oncological prognosis.

Key words: minimally invasive esophagectomy (MIE), thoracoscopic esophagectomy in the prone position (TEP), pneumonia, recurrent laryngeal nerve (RLN) palsy

Introduction

For localized esophageal carcinoma, esophagectomy with extended lymphadenectomy is the mainstay of treatment [1-3]. However, this procedure is invasive and associated with high mortality [4]. During the past decade, minimally invasive esophagectomy (MIE) in the form of thoracoscopic surgery has been adopted around the world with expectations of lower invasiveness [5,6]. However, the rates of postoperative complications for MIE such as pneumonia, recurrent laryngeal nerve (RLN) palsy, and anastomotic leakage remain high [7,8].

Recently, some investigators have reported that postoperative pneumonia is an independent risk factor for worse oncological prognosis in esophageal carcinoma [9,10]. Consequently, reducing the incidence of post-MIE pneumonia is a matter of utmost importance. Recognizing the risk factors for pneumonia associated with the operative procedure will be the first step to improving esophageal cancer prognosis. We hypothesized that RLN palsy may impact the incidence of pneumonia because RLN palsy induces aspiration leading to pneumonia. Thus, we planned a retrospective follow-up study to clarify whether there is a strong correlation between RLN palsy and postoperative pneumonia after MIE.

Materials and Methods

Patient population

This retrospective follow-up study included 209 patients with esophageal cancer who underwent thoracoscopic (Mckeown) esophagectomy in the prone position (TEP) at Kobe University between 2011 and 2017. The diagnosis of esophageal cancer was based on the seventh edition of the Union for International Cancer Control (UICC) tumor node metastasis (TNM) cancer staging system [11]. Prior to surgery, two cycles of cisplatin and 5-fluorouracil were administered as preoperative chemotherapy to patients with clinical (c)-Stage II or III disease. None of the patients received preoperative chemoradiotherapy. In this study, inclusion criteria included age 18–85 years; cT1–3, cN0–3 disease [11]; histologically proven thoracic esophageal squamous cell carcinoma, adenocarcinoma, carcinosarcoma, or basaloid-squamous cell carcinoma; upper mediastinal lymphadenectomy; and ability to undergo simultaneous esophagectomy and reconstruction of the gastric conduit or pedicled jejunum. Every patient underwent preoperative oral management. Sarcopenia was defined as low muscle mass plus low muscle strength and/or low physical performance according to the Asian consensus definition [12].

At our institution, it is common practice for all surgical candidates with esophageal cancer to undergo TEP. Three-field (neck, chest, and abdomen) lymph node dissection was performed when a cT2or3 tumor was located in the upper or middle esophagus.

This study was approved by the Ethics Committee of Kobe University.

Surgical procedures

Thoracic procedure

All patients underwent TEP with radical esophagectomy and total mediastinal lymphadenectomy. To permit easy retraction of the trachea, a single-lumen tracheal tube was inserted into the trachea and a blocker was inserted into the right bronchus for one-lung ventilation anesthesia before the procedure. The patient was initially placed in the prone position. Five 5-mm or 12-mm ports were inserted into the third intercostal space (ICS) on the posterior midaxillary line, the fifth and seventh ICSs on the posterior axillary line, the sixth and eighth ICSs on the midaxillary line, and the ninth ICS on the scapular line. The chest cavity was inflated via the ports with a carbon dioxide insufflation pressure of 6–8 mmHg. The endoscope was usually inserted through the ninth ICS [13].

Abdominal and neck procedures

The abdominal procedure was performed with laparoscopic surgery or open laparotomy (OL). Laparoscopic surgery was designated as the first choice, and OL was the second procedure to be considered in some patients with a past medical history of laparotomy. Gastric mobilization, abdominal lymphadenectomy around the left gastric pedicle and the celiac axis, and excision of the entire isolated thoracic esophageal specimen and dissected LNs through the esophageal hiatus were performed first. Next, a gastric conduit of 3–4 cm in width was typically created outside of the wound and raised via the posterior mediastinum. In some patients in whom gastric conduits were not available due to past gastric resection or synchronous gastric cancer, pedicled jejunum reconstruction via the presternal route was performed. The neck was the site of the anastomosis. For 3-field lymph node dissection, the cervical nodes were removed through a collar incision.

Mediastinal lymphadenectomy

For lymphadenectomy along the RLNs, a standardized procedure (Bascule method [13,14] and Pincers maneuver [15,16]) was adopted starting in 2015.

Specifically, the fundamental concept of Bascule method in the left upper mediastinum is to draw the proximal portion of the divided esophagus and two-dimensional membrane that includes the left RLN and lymph nodes via dorsal side. Using this technique, a two-dimensional membrane will be easily recognizable. Identification and reliable cutting of the tracheoesophageal artery and distinguishing the left RLN from the lymph nodes should be easy [13, 14]. In the right upper mediastinum, exfoliation of the two-dimensional membrane, which includes the right RLN, LNs along the right RLN, and the primary esophageal artery, from the right side of the trachea toward the neck is performed at first. Closing in from the inner and outer sides of the two-dimensional membrane, lymphadenectomy along the right RLN toward the right inferior thyroid artery should be easy [15, 16].

Outcomes

Evaluation of the postoperative clinical course

The following parameters were assessed: operative time for the entire procedure and the thoracic portion; overall estimated blood loss; transfusion; and complication rates for RLN palsy, pneumonia, and anastomotic leakage. Postoperative morbidity was analyzed according to the Clavien-Dindo (C-D) classification system [16].

Assessment of laryngopharyngeal function

Regarding the diagnosis of RLN palsy, each patient was routinely referred to the Department of Otolaryngology on postoperative day 7, regardless of the presence or absence of hoarseness, for evaluation of vocal cord mobility with flexible laryngoscopy.

Assessment of pneumonia

We defined pulmonary infection as the presence of clinical manifestations of pneumonia or bronchopneumonia confirmed by thoracic radiography or computed tomography (CT) and a positive sputum culture within the first 2 weeks after surgery.

Assessment of anastomotic leakage

We diagnosed anastomotic leakage based on the nature of the drain discharge as well as CT and esophagogastroduodenoscopy findings.

Statistical analysis

All continuous data are presented as medians (range) or means [± standard deviation (SD)] based on the distribution. All categorical data are presented as number (percentage). Differences between the 2 groups were analyzed using the χ^2 test, Mann-Whitney U test, or Student's t-test, as appropriate. Univariate and multivariate logistic regression was conducted to assess the association between RLN palsy and pneumonia. All variables with $P < 0.1$ in the univariate analysis were entered in multivariate analyses. $P < 0.05$ was considered statistically significant. All statistical computations were performed using JMP® 11 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

Baseline characteristics of the 209 patients who underwent TEP are provided in Table 1. The mean (SD) age was 65.6 (±8.5) years and 85% of patients were male. Sarcopenia was seen in 28% of patients. Tumors were located in the upper esophagus (Ut) (18%), middle esophagus (Mt) (47%), and lower esophagus (Lt) (35%). Regarding depth of tumor invasion, 40% of the patients had cT1 disease, 15% had cT2 disease, and 45% had cT3 disease. With regards to clinical lymph node metastasis, 54% of patients were cN positive (+) and 46% were cN negative (-). UICC c-stage III or IV disease was present in 39% of patients and c-stage I or II disease was present in 61%. Most patients (94%) had scc. In 67% of patients, preoperative chemotherapy was performed (Table 1).

Among the 209 patients who underwent TEP, pneumonia of C-D grade >II occurred in 44 patients (21%). The pneumonia positive (+) group and negative (-) groups differed significantly in age (Table 1).

Treatment-related characteristics and outcomes

Treatment-related characteristics and outcomes are shown in Table 2. The laparoscopic approach was used for the abdominal procedure in 73% of patients. Most patients (93%) were reconstructed with a gastric conduit via the posterior mediastinum route (88%). Three-field lymph node dissection was performed in 45% of patients. The mean (SD) operative time was 701 (±115) minutes for the entire procedure and 318 (±66) minutes for the thoracic procedure. The median (range) blood loss was 266 (30–11,000) ml. Transfusions were given to 29% of patients. Left RLN palsy occurred in 39% of patients (C-D grade >II, 18%). Right RLN palsy occurred in 9% of patients (C-D grade >II, 6%). RLN palsy on either or both sides (any RLN palsy) occurred in 43% of patients (C-D grade >II, 18%). Anastomotic leakage of C-D grade >II occurred in 16% of patients (Table 2).

There were significant differences between the pneumonia (+) and (-) groups in terms of lymph node dissection, transfusion, left RLN palsy, and any RLN palsy (Table 2). Univariate and multivariate analyses were performed to identify independent risk factors for pneumonia. Results are shown in Table 3. In multivariate analysis, any RLN palsy was associated with a higher incidence of pneumonia (Table 3) (odds ratio (OR), 6.210; 95% confidence interval (CI), 2.728–14.480; $P < 0.0001$). In addition, age was associated with a higher incidence of pneumonia (OR, 1.049; 95% CI, 1.001–1.103; $P = 0.046$). Lymph node dissection and transfusion were not independent risk factors for pneumonia.

Changes in RLN palsy rates over time and correlation between RLN palsy and pneumonia rates

Changes in RLN palsy rates are shown in Figures 1–3. Rates of left, right, and any RLN palsy decreased from 2011 to 2018 (Figure 1–3). The incidence of pneumonia also decreased over time (Figure 4). The line graph for any RLN palsy was quite similar to the graph for the incidence of pneumonia (Figures 3, 4).

Discussion

Our hypothesis that RLN palsy associated with MIE for esophageal cancer may affect the incidence of pneumonia was supported by the findings of this study. Multivariate analysis showed that there is a significant correlation between any RLN palsy and pneumonia. Scholtemeijer et al. reported that RLN palsy after McKeown esophagectomy is associated with an increased rate of pulmonary complications [18]. The other independent risk factor for pneumonia in this study was age. These two factors have qualities in common. Bhattacharyya et al. reported that 23.4% of 64 patients with unilateral vocal cord immobility due to RLN palsy had aspiration [19]. Périé et al. assessed the incidence of aspiration in patients with unilateral RLN palsy after head and neck or thoracic surgery. In their study, 20% of patients with unilateral RLN palsy had silent or symptomatic aspiration [20]. Age was also reported to be an independent factor associated with aspiration leading to pneumonia in esophagectomy [21]. Early postoperative arterial pressure and higher maximum intraoperative pH, those might be also responsible for postoperative pneumonia, were unrelated in this study (data not shown). Namely, both RLN palsy and age are strongly associated with aspiration. Patients with tracheobronchial aspiration in any setting are significantly more likely to develop pneumonia than patients with normal swallowing function [22]. Consequently, our results showing that RLN palsy and age are both independent risk factors for pneumonia seem reasonable. In this study, there is tendency towards older in patients with RLN palsy than in others (data no shown). This is why, incidence of pneumonia with RLN palsy might be slightly higher (20/38; 53%) than other reports.

In univariate analysis, other factors were also predictors for pneumonia, including transfusion. The association between blood transfusion and infectious complications was examined among 14,875 patients who underwent resection of upper gastrointestinal cancer. Multivariate analysis showed that blood transfusion was independently associated with pneumonia (OR, 1.98; 95% CI, 1.74–2.26) [23]. As represented by transfusion-related acute lung injury, blood transfusion sometimes causes lung damage. Histological findings include pulmonary edema, capillary leukostasis, and neutrophil extravasation [24]. In our study, transfusion was not an independent risk factor for pneumonia. However, unnecessary transfusion should be avoided.

In our institution, TEP started in 2011. Since then, surgical skills improved according to the learning curve. Moreover, standardized procedures for lymphadenectomy around the RLN, consisting of the Bascule method for the left side and the Pincers maneuver for the right side, were introduced in 2015 [13–16]. Consequently, the RLN palsy rate with TEP decreased over time. Interestingly, the line graph for the rate of any RLN palsy is quite similar to the graph for the incidence of pneumonia. Consequently, a strong correlation between RLN palsy and pneumonia in TEP can be confirmed statistically and visually. Conversely, prevention of RLN palsy should contribute to reducing the incidence of pneumonia. Since pneumonia significantly worsens the oncological prognosis [9,10], prevention of RLN palsy might be important for not only short-term but also long-term outcomes in esophageal cancer. Additionally, medical equipment like as intraoperative nerve monitoring system might also contribute to reduce RLN palsy [25]. Unfortunately, it remains controversial whether MIE is superior to open esophagectomy in terms of preventing pneumonia [8,26]. While standardizing the procedure to reduce pneumonia associated with TEP, other techniques such as subcarinal lymphadenectomy, which spares the pulmonary branches of the vagus nerve, might also be important [27]. This study has some limitations, including its retrospective design and participation from only one center. Therefore, prospective or retrospective analysis using larger number of patients will be required to reach a conclusion.

Conclusion

In conclusion, there is a strong correlation between RLN palsy and pneumonia in MIE. Prevention of RLN palsy may reduce the incidence of pneumonia, thus leading to better oncological prognosis.

Disclosures

Conflicts of interest: Taro Oshikiri, Gosuke Takiguchi, Hiroshi Hasegawa, Masashi Yamamoto , Shingo Kanaji, Kimihiro Yamashita, Takeru Matsuda, Tetsu Nakamura, Satoshi Suzuki, and Yoshihiro Kakeji have no conflicts of interest or financial ties to disclose.

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Figure legends

Figure 1

The left recurrent laryngeal nerve (RLN) palsy rate decreased from 2011 to 2018. Since 2015, a standardized procedure for lymphadenectomy around the left RLN (Bascule method) was used at our institution. Total includes all cases of left RLN palsy, including Clavien-Dindo classification Grade I.

Figure 2

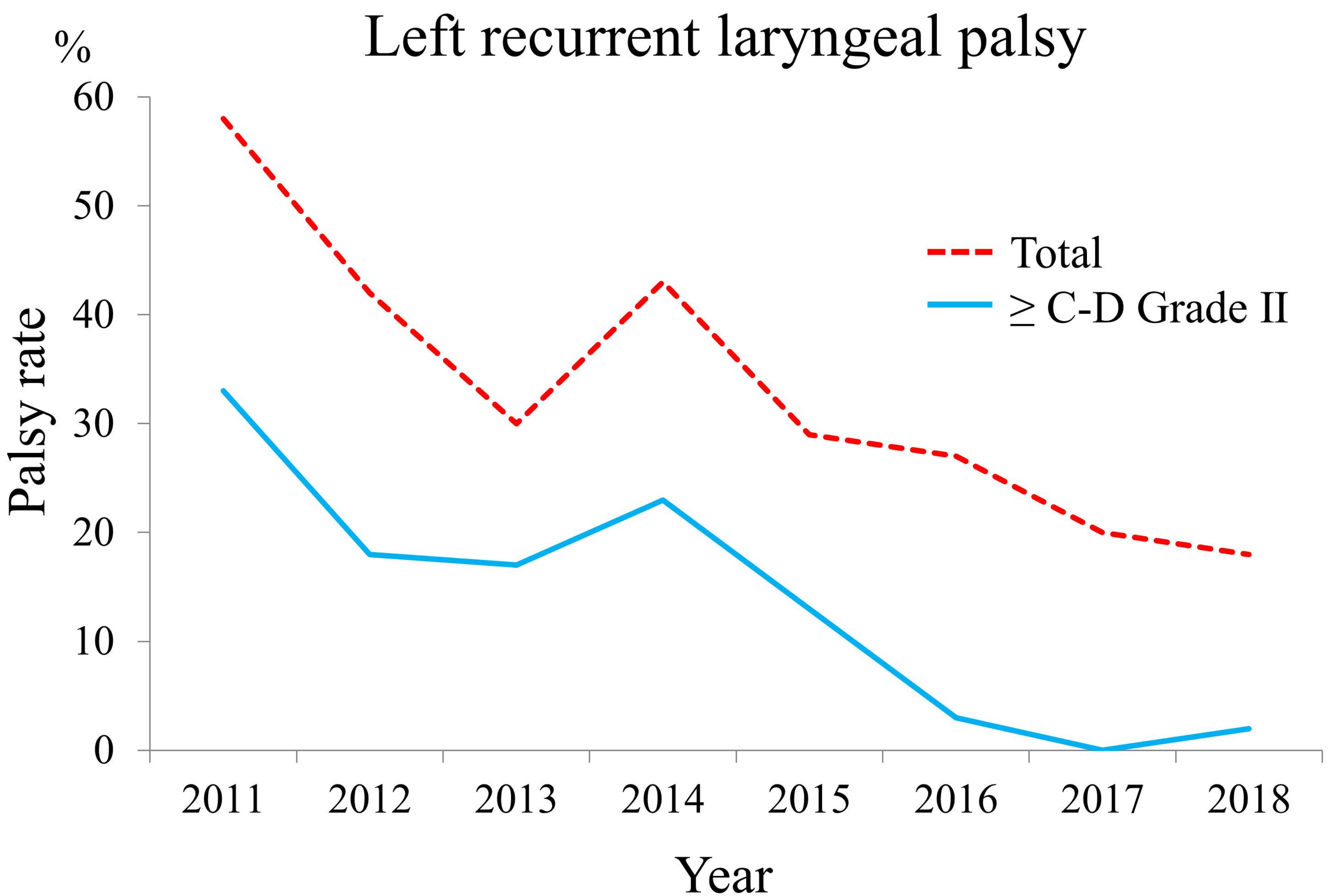
The right recurrent laryngeal nerve (RLN) palsy rate decreased from 2011 to 2018. Since 2015, a standardized procedure for lymphadenectomy around the right RLN (Pincers maneuver) was used at our institution.

Figure 3

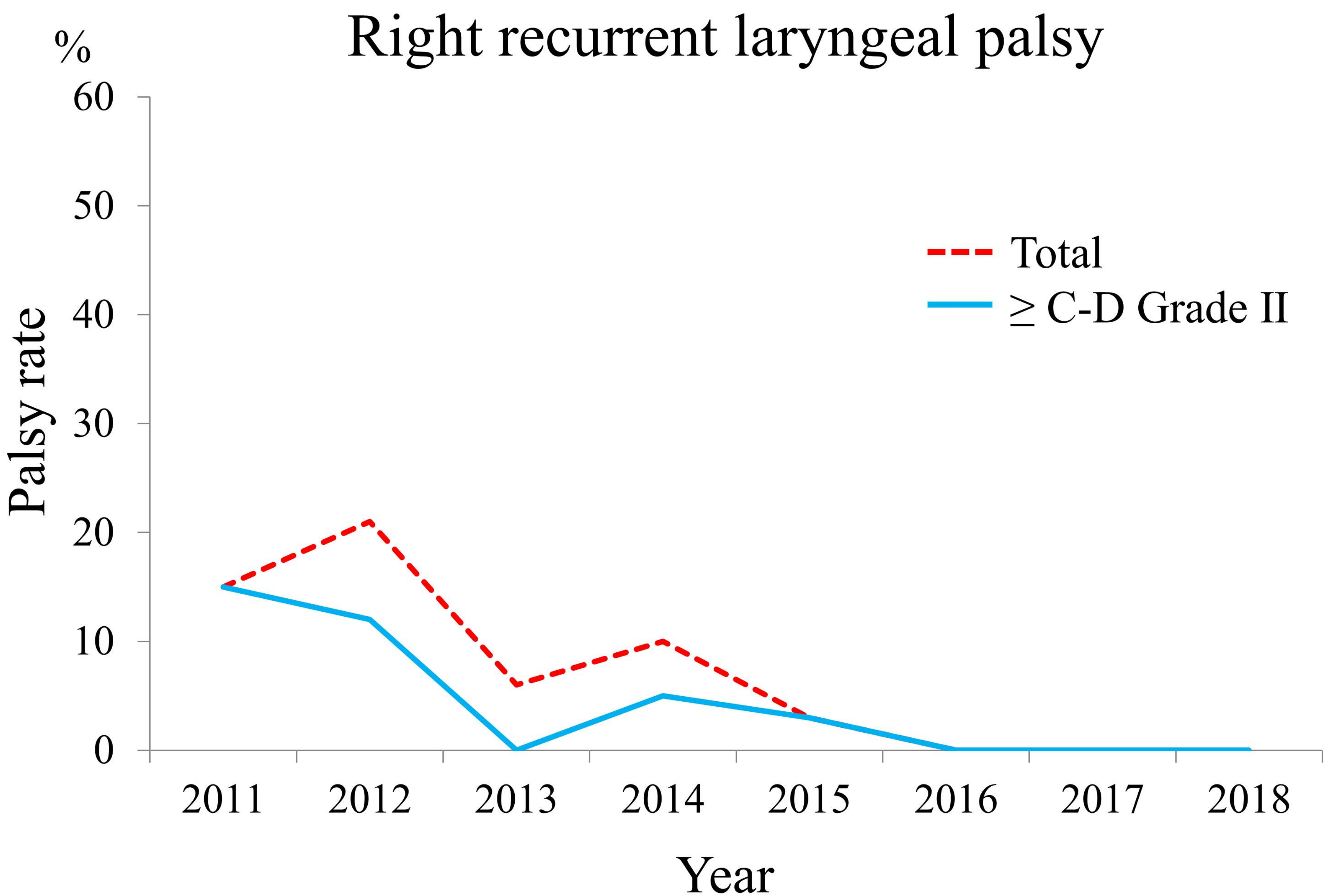
The rate of any recurrent laryngeal nerve palsy decreased from 2011 to 2018.

Figure 4

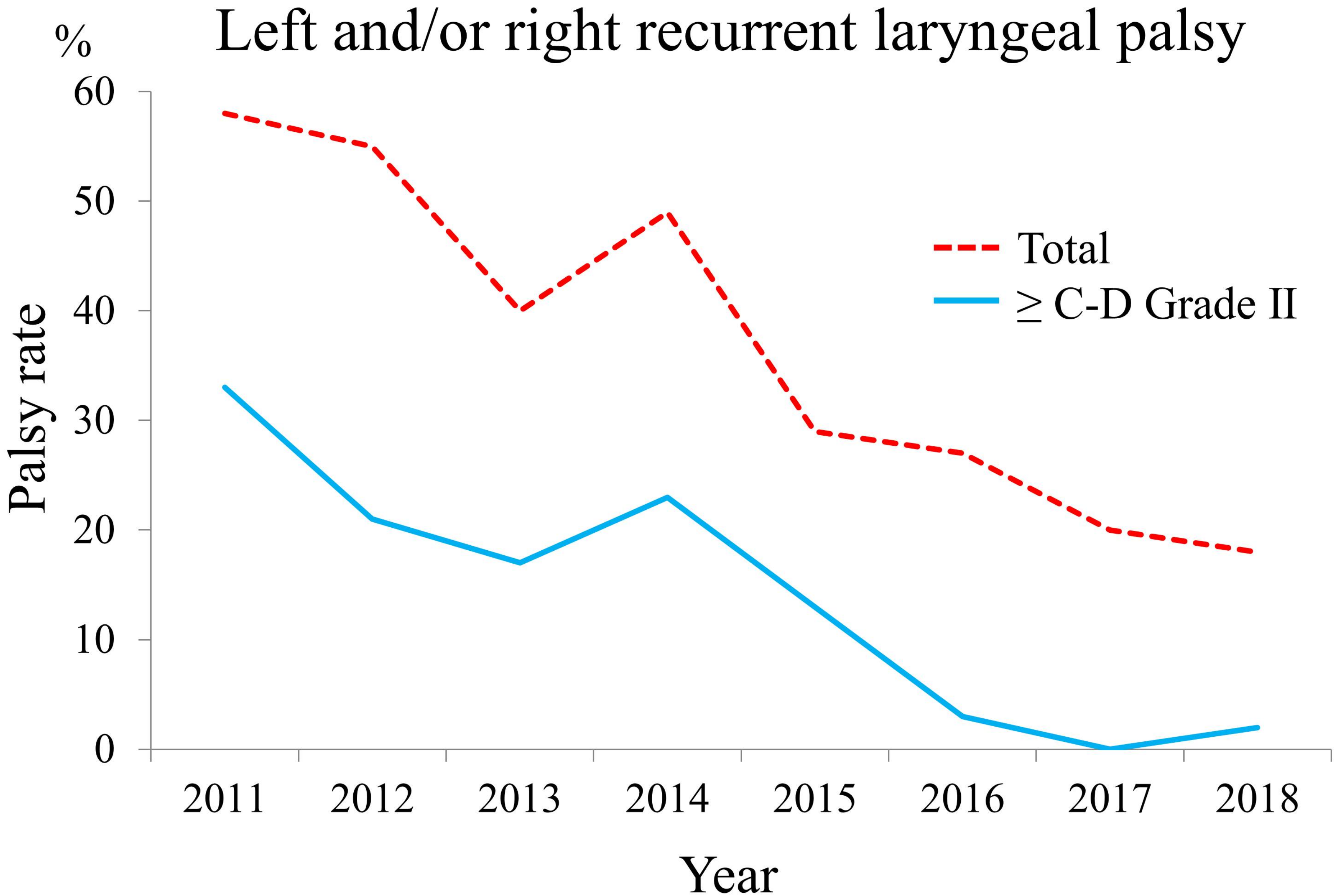
The incidence of pneumonia decreased from 2011 to 2018. The line graph is quite similar to the graph for the rate of any recurrent laryngeal nerve palsy in Figure 3.



Left recurrent laryngeal palsy
%
60
50
40
30
20
10
0
Palsy rate
Total
≥ C-D Grade II
2011
2012
2013
2014
2015
2016
2017
2018
Year



Right recurrent laryngeal palsy
%
60
50
40
30
20
10
0
Palsy rate
Total
≥ C-D Grade II
2011
2012
2013
2014
2015
2016
2017
2018
Year


Left and/or right recurrent laryngeal palsy
%
60
50
40
30
20
10
0
Palsy rate
Total
≥ C-D Grade II
2011
2012
2013
2014
2015
2016
2017
2018
Year

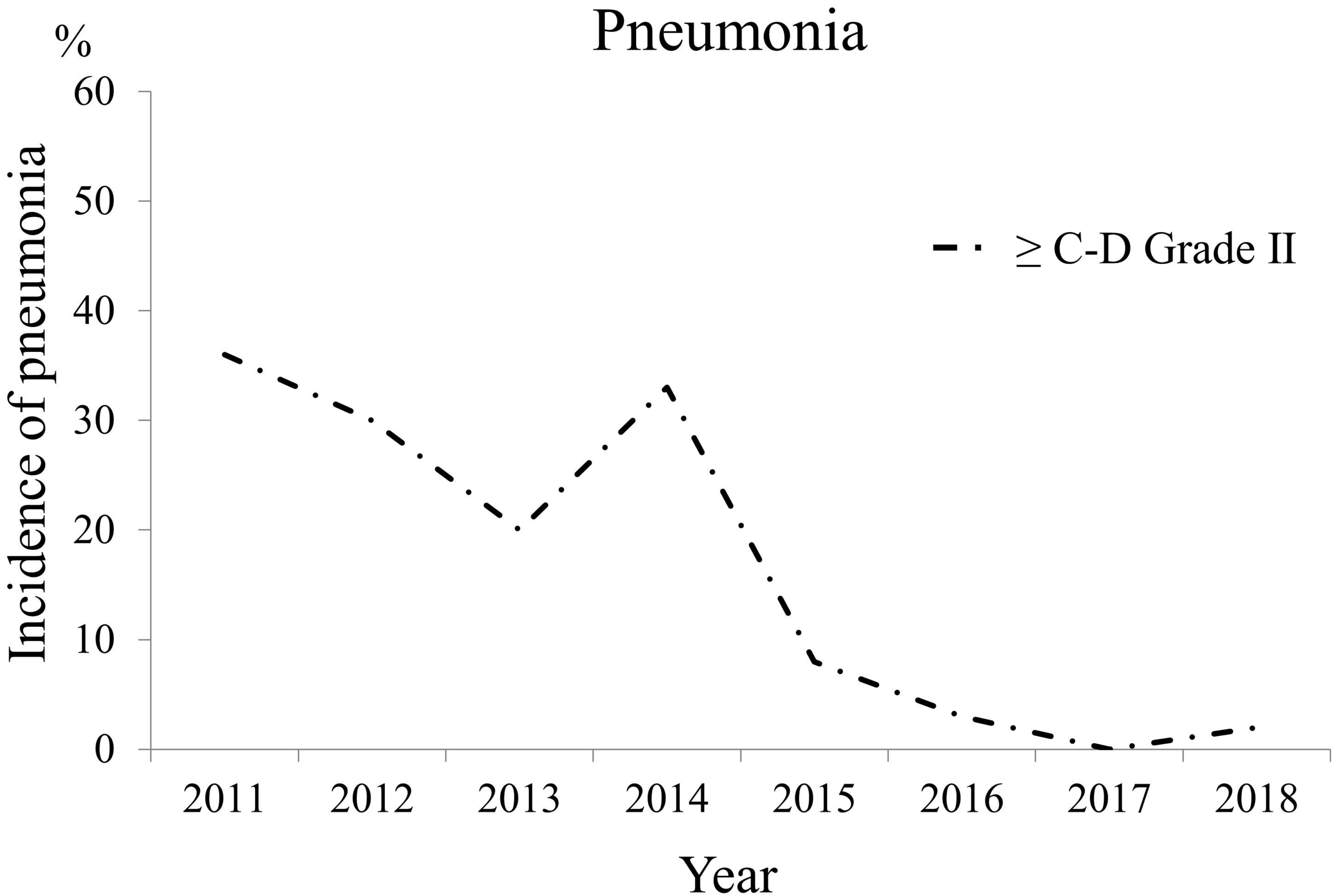

Pneumonia
%
60
50
40
30
20
10
0
Incidence of pneumonia
≥ C-D Grade II
2011
2012
2013
2014
2015
2016
2017
2018
Year

Table 1. Patient characteristics

	Total n = 209	Pneumonia[b] (+) n = 44	Pneumonia[b] (-) n = 165	*P*
	n (%)	n (%)	n	
Age, years	65.6 ± 8.5	67.9 ± 7.5	64.9 ± 8.6	0.036
Sex				0.206
Male / female	178 (85%) / 31 (15%)	40 (91%) / 4 (9%)	138 (84%) / 27 (16%)	
Sarcopenia				0.827
Yes / No	59 (28%) / 150 (72%)	13 (30%) /31 (70%)	46 (28%) / 119 (72%)	
Tumor location				0.244
Ut	38 (18%)	8 (18%)	30 (18%)	
Mt	98 (47%)	25 (57%)	73 (44%)	
Lt	73 (35%)	11 (25%)	62 (38%)	
Depth of tumor invasion				0.883
T1	84 (40%)	19 (43%)	65 (39%)	
T2	32 (15%)	6 (14%)	26 (16%)	
T3	93 (45%)	19 (43%)	74 (45%)	
Lymph node metastasis				0.943
cN+ / cN-	113 (54%) / 96 (46%)	24 (55%) / 20 (45%)	89 (54%) / 76 (46%)	
UICC c-stage[a]				0.742
III or IV / I or II	81 (39%) / 128 (61%)	18 (41%) / 26 (59%)	63 (38%) / 102 (62%)	
Histology				0..701
Scc / other	197 (94%) / 12 (6%)	42 (95%) / 2 (5%)	155 (94%) / 10 (6%)	

Preoperative chemotherapy				0.925
Yes / no	139 (67%) / 70 (33%)	29 (66%) / 15 (34%)	110 (67%) / 55 (33%)	

[a] UICC, Union for International Cancer Control

[b] Clavien-Dindo classification grade ≥II was recognized as postoperative morbidity.

Table 2. Treatment-related characteristics and outcomes

		Total	Pneumonia[b] (+)	Pneumonia[b] (-)	
		n = 209	n = 44	n = 165	*P*
		n (%)	n (%)	n	
Abdominal procedure					0.645
Laparoscopy / open		153 (73%) / 56 (27%)	31 (70%) / 13 (30%)	122 (74%) / 43 (26%)	
Conduit[a]					0.190
Gastric / pedicled jejunum		195 (93%) / 14 (7%)	39 (89%) / 5 (11%)	156 (95%) / 9 (5%)	
Reconstruction route					0.877
Posterior mediastinum		183 (88%)	38 (87%)	145 (88%)	
Retrosternal		6 (3%)	1 (2%)	5 (3%)	
Presternal		20 (9%)	5 (11%)	15 (9%)	
Lymph node dissection					0.014
3-field / 2-field		94 (45%) / 115 (55%)	27 (61%) / 17 (39%)	67 (41%) / 98 (59%)	
Operative time, minutes					
Entire procedure		701 ± 115	729 ± 130	693 ± 110	0.067
Thoracic procedure		318 ± 66	320 ± 74	318 ± 64	0.800
Blood loss		266 (30-11000)	338 (30-11000)	240 (30-2605)	0.064
Transfusion					0.009
Yes / no		61 (29%) / 148 (71%)	20 (45%) / 24 (55%)	41 (25%) / 124 (75%)	
Recurrent laryngeal nerve palsy[b]					
Left	Yes / no	37 (18%) / 172 (82%)	19 (43%) / 25 (57%)	18 (11%) / 147 (89%)	<0.0001
Right	Yes / no	12 (6%) / 197 (94%)	4 (9%) / 40 (91%)	8 (5%) / 157 (95%)	0.308

Any	Yes / no	38 (18%) / 171 (82%)	20 (45%) / 24 (55%)	18 (11%) / 147 (89%)	<0.0001
Anastomotic leakage[b]					0.408
Yes / no		34 (16%) / 175 (84%)	9 (20%) / 35 (80%)	25 (15%) / 140 (85%)	

[a] Colon reconstruction was not performed.

[b] Clavien-Dindo classification grade >II was recognized as postoperative morbidity.

Table 3. Pulmonary complications: univariate and multivariate analysis

Factor	n	Pneumonia[b]			
		Univariate analysis		Multivariate analysis	
		OR (95% CI)	*P*	OR (95% CI)	*P*
Age	209	1.047 (1.004–1.095)	0.031	1.049 (1.001–1.103)	0.046
Sex					
Male / female	178/31	1.957 (0.712–6.905)	0.206		
Sarcopenia					
Yes / No	150/59	1.085 (0.509-2.219)	0.827		
Tumor location					
Lt	73	1.000			
Mt	98	1.930 (0.898–4.378)	0.093	1.529 (0.625–3.873)	0.354
Ut	38	1.503 (0.532–4.108)	0.433		
Depth of tumor invasion					
T1	84	1.000			
T2	32	0.789 (0.263–2.108)	0.647		
T3	93	0.878 (0.427–1.807)	0.723		
Lymph node metastasis					
cN+ / cN-	113/96	1.025 (0.526–2.012)	0.943		
UICC c-stage[a]					
III or IV / I or II	81/128	1.121 (0.563–2.200)	0.742		
Histology					
Scc / other	197/12	1.355 (0.340–9.033)	0.694		

Preoperative therapy					
Yes / no	139/70	0.967 (0.484–1.989)	0.925		
Abdominal procedure					
Laparoscopy / open	153/56	0.840 (0.409–1.798)	0.645		
Conduit					
Stomach / pedicled jejunum	195/14	0.45 (0.147–1.533)	0.190		
Reconstruction route					
Posterior mediastinum	183	1.000			
Retrosternal	6	1.31. (0.203–25.485)	0.802		
Presternal	20	0.786 (0.284–2.538)	0.666		
Lymph node dissection					
3-field / 2-field	94/115	2.323 (1.185–4.664)	0.014	1.650 (0.775–3.535)	0.193
Operative time					
Entire procedure	209	1.003 (0.999–1.005)	0.072	1.001 (0.997–1.005)	0.657
Thoracic procedure	209	1.001 (0.995–1.006)	0.800		
Blood loss	209	1.000 (0.999–1.001)	0.082	1.000 (0.999–1.001)	0.422
Transfusion					
Yes / no	61/148	2.520 (1.258–5.036)	0.009	1.532 (0.664–3.434)	0.311
Recurrent laryngeal nerve palsy[b]					
Yes / no	38/171	6.806 (3.172–14.879)	<0.0001	6.210 (2.728–14.480)	<0.0001
Anastomotic leakage[b]					
Yes / no	34/175	1.44 (0.591–3.272)	0.408		

[a] UICC, Union for International Cancer Control

[b] Clavien-Dindo classification grade >II was recognized as postoperative morbidity.