Original Article

Recurrent laryngeal nerve injury after esophagectomy for esophageal cancer: incidence, management, and impact on short- and long-term outcomes

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Background: Recurrent laryngeal nerve (RLN) injury caused by esophagectomy may lead to postoperative morbidity, however data on long-term recovery are scarce. The aim of this study was to evaluate the consequences of RLN palsy (RLNP) in terms of pulmonary morbidity and long-term functional recovery.

Methods: Patients who underwent a 3-stage transthoracic (McKeown) or a transhiatal esophagectomy for esophageal carcinoma in the University Medical Center Utrecht (UMCU) between January 2004 and March 2016 were included from a prospective database. Multivariable analyses were conducted to assess the association between RLNP and pulmonary complications and hospital stay. Data regarding long-term recovery were summarized using descriptive statistics.

Results: Out of the 451 included patients, 47 (10%) were diagnosed with RLNP. Of the patients with RLNP, 34 (7%) had a unilateral lesion, 8 (2%) had a bilateral lesion, and in 5 (1%) the location of the lesion was unknown. The incidence of RLNP was 3/127 (2%) in the transhiatal group, and 44/324 (14%) in the McKeown group. RLNP after McKeown esophagectomy was associated with a higher incidence of pulmonary complications (OR 2.391; 95% CI 1.222–4.679; P=0.011), as well as a longer hospital stay (+4 days) (P=0.001). Of the RLNP patients with more than 6 months follow up almost half recovered fully {median follow-up of 17.5 [7–135] months}. Of the remainder, six required a surgical intervention and the others had residual symptoms.

Conclusions: RLNP after McKeown esophagectomy is associated with an increased pulmonary complication rate, longer hospital stay, and a moderate long-term recovery. Further studies are necessary that examine technologies, which may reduce RLNP incidence and contribute to the early detection and treatment of RLNP.

Keywords: Esophagectomy; recurrent laryngeal nerve (RLN); RLN injuries; vocal cord paralysis; pneumonia

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Introduction

Esophageal cancer is the eighth most common type of cancer worldwide, and its incidence is rising (1-3). The current standard of care for patients with a resectable locally advanced tumor is neoadjuvant chemo(radio) therapy, followed by surgical resection with a radical lymphadenectomy (4-6).

During esophagectomy, thermal injury, stretching, compression, or vascular compromise of the recurrent laryngeal nerve (RLN) may cause RLN palsy (RLNP) (7). The incidence of RLNP after esophagectomy varies, ranging from 0% to 59% (8-18). These disparities have been attributed to variation in extent of lymph node dissection, surgical technique (two- or three stage), the size and T-stage of the primary tumor, and the means of RLN injury diagnosis (8,19-21).

In addition to being the most important motor nerve of the larynx, the RLN innervates the cricopharyngeal muscle which form the upper esophageal sphincter, hereby playing a central role in swallowing (22). Patients with RLNP may present with symptoms ranging from hoarseness, dyspnea during speech, aspiration, difficulty with coughing, marked morbidity through pulmonary complications [pneumonia, acute respiratory distress syndrome (ARDS), atelectasis], and may even suffocate in case of bilateral damage. Only few retrospective studies have reported on the consequences of RLNP on the short term, particularly the incidence of pulmonary complications (8-10,19,23,24). Furthermore, information on the long term (i.e., recovery and possible surgical interventions) is lacking. Therefore, the current study aims to evaluate the consequences of RLNP in terms of (pulmonary) morbidity and long-term functional recovery.

Methods

Patients

This cohort study used a prospective database of the University Medical Center Utrecht (UMCU) to include patients who underwent a 3-stage transthoracic (McKeown) or transhiatal esophagectomy with a gastric conduit reconstruction for esophageal carcinoma between January 2004 and March 2016. Specific follow-up data regarding RLNP were supplemented from the electronic patient record. This study received ethical approval (Institutional Review Board number 13-061/C) from the Medical Ethics Review Committee of the UMCU, and informed consent was waived.

Outcomes

Primary outcome was the association of RLNP and postoperative pulmonary complications. To create a homogeneous cohort for analyzing the association between RLNP and postoperative pulmonary complications, only the McKeown esophagectomies were included. RLNP was defined as any kind of damage inflicted during surgery to the left, the right, or both of the RLN (s), resulting in paresis or paralysis. Paresis was defined as a partial interruption of laryngeal innervation, leading to hypomobility of the laryngeal muscles. Paralysis was defined as no motion of the affected muscle(s) (25). Pulmonary complications were defined as clinically proven pneumonia [in accordance with the revised Uniform Pneumonia Score (26)], pleural effusion leading to drainage, pleural empyema, ARDS, atelectasis, re-intubation, or the need for a tracheostomy.

Secondary outcomes were otolaryngological consultation for RLNP, clinical presentation of the RLNP (dysphonia and/or aspiration), means of RLNP diagnosis (clinical or laryngoscopic), and RLNP-specific therapy and functional recovery. For functional recovery, only people with a follow-up of at least 6 months at the time of data extraction were included, because RLNP recovery may not have occurred before that time (27). Complete recovery from RLNP symptoms, possibly with laryngoscopy showing full revival of vocal cord mobility, was seen as full recovery. Clinical improvement of RLNP symptoms, possibly with laryngoscopy showing some improvement of vocal cord mobility, was seen as partial recovery. No improvement of RLNP symptoms, possibly with laryngoscopy showing no improvement of vocal cord mobility, was seen as no recovery. Other secondary outcomes included re-intervention, 30-day postoperative or in-hospital mortality, intensive care unit (ICU) and hospital stay in days, readmission within 30 days, non-radical resection, and anastomotic leakage.

Statistical methods

All data were analyzed using IBM SPSS Statistics for Windows, version 22.0 (IBM corp., Armonk, New York, USA). All continuous data were presented as median (range) or mean [± standard deviation (SD)] based on their distribution; all categorical data were presented as a number (percentage). Baseline data were analyzed using either chi-

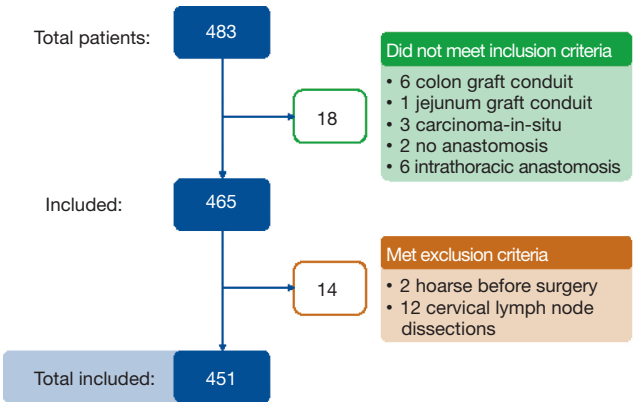

Figure 1 Inclusion flowchart.

square tests (categorical data), Mann-Whitney-U tests, or student's *t*-test (continuous data). Multivariable logistic and linear analyses were conducted to assess the association between RLNP and pulmonary complications and hospital stay, respectively. All variables with a P value <0.2 in univariable analysis were entered in the multivariable analyses and a P value of <0.05 was considered statistically significant.

Results

Patients

Between January 2004 and March 2016, 324 underwent a 3-stage transthoracic (McKeown) esophagectomy with a two-field lymphadenectomy and 127 patients underwent a transhiatal esophagectomy for esophageal carcinoma (*Figure 1*).

The baseline data showing patient and treatment-related characteristics for the McKeown group are provided in *Table 1*. The mean (SD) age was 65 (±8.53) years, 72% of the patients were male, most (61%) had an ASA II status and 51% were diagnosed with a pT3 tumor. The majority (82%) of patients underwent robot-assisted thoraco laparoscopic minimally invasive surgery (da Vinci Si System, Intuitive Surgical Inc., Sunnyvale, CA, USA), the other 58 (18%) underwent open surgery.

RLNP

In the McKeown group, 44 of the 324 patients (14%) were found to have a postoperative RLNP (the RLNP+ group). Interestingly, in the cohort of transhiatal esophagectomies RLNP occurred in only 3/127 (2%) patients.

In our study population of McKeown esophagectomies: 33/44 RLNPs were diagnosed through laryngoscopy, 11/44 RLNP patients were diagnosed by clinical examination (*Table 2*). Most patients (29/44) presented with a left RLNP, 3/44 had a right RLNP, 8/44 had bilateral palsy, and for 4/44 patients the location was unknown. The majority of patients were diagnosed with a paresis (27/44); the most common symptoms at presentation were dysphonia (43/44) and/or aspiration (25/44). Of all patients diagnosed with RLNP, the majority (36/44) received speech and language therapy (SLT), 21/44 were kept nil-per-os (NPO).

Lymph node yield was higher in the RLNP+ group {24.5 [7–57] versus 22 [6–53] in the RLNP– group, P<0.001}. There was also a significant difference in the pathological T-stage between the two groups (P=0.044), with more T3–T4 tumors in the RLNP+ group and more T0–T2 tumors in the RLNP– group, as is shown in *Table 1*.

Postoperative outcomes

In the univariable analysis, there were significantly more postoperative pulmonary complications in the RLNP+ group (61% versus 41% in the RLNP– group; P=0.013) (*Table 3*). Specifically, there was a significantly higher amount of atelectasis (34% versus 9%; P<0.001) and tracheostomies performed (16% versus 6%; P=0.014) in the RLNP+ group. The difference in length of hospital stay between the RLNP+ and RLNP– groups was not statistically significant (19 versus 15 days, respectively; P=0.084).

Results from the multivariable analyses are shown in *Tables 4* and 5. RLNP was associated with a higher incidence of pulmonary complications (*Table 4*) (OR 2.391; 95% CI 1.222–4.679; P=0.011). In addition, diabetic comorbidity was also associated with a higher incidence of pulmonary complications (OR 2.126; 95% CI 1.050–4.304; P=0.036). Moreover, RLNP was associated with a prolonged hospital stay (+4 days) (P=0.001, *Table 5*). Other factors associated with a longer hospital stay were older age (above 65 years) (P=0.039), pulmonary comorbidity (P=0.005), diabetes mellitus (P=0.008), anastomotic leakage (P<0.001), chylothorax (P<0.001). Factors associated with a shorter hospital stay were the ability to receive neoadjuvant chemotherapy (P=0.017) or chemoradiotherapy (P=0.002).

Table 1 Patient and treatment-related characteristics

Characteristics	Total (N=324, 100%)		RLNP+ (N=44, 13.6%)		RLNP– (N=280, 86.4%)		P value
	n	%	n	%	n	%	
Gender							0.817
Female	91	28.1%	13	29.5%	78	27.9%	
Male	233	71.9%	31	70.5%	202	72.1%	
Age (years)	64.5	±8.53	63.5	±8.93	65.0	±8.48	0.523
BMI (kg/m^2)	25.0	±4.42	25.1	±3.86	25.0	±4.50	0.864
ASA score							0.861
I	83	25.6%	13	29.5%	70	25.0%	
II	199	61.4%	24	54.5%	175	62.5%	
III	42	13.0%	7	15.9%	35	12.5%	
Pulmonary comorbidity							0.978
No	272	84.0%	37	84.1%	235	83.9%	
Yes	52	16.0%	7	15.9%	45	16.1%	
Cardiac comorbidity							0.018
No	259	79.9%	41	93.2%	218	77.9%	
Yes	65	20.1%	3	6.8%	62	22.1%	
Vascular comorbidity							0.090
No	247	76.2%	38	86.4%	209	74.6%	
Yes	77	23.8%	6	13.6%	71	25.4%	
Diabetes mellitus							0.480
No	284	87.7%	40	90.9%	244	87.1%	
Yes	40	12.3%	4	9.1%	36	12.9%	
Neoadjuvant treatment							0.328
No	95	29.3%	15	34.1%	80	28.6%	
Chemotherapy	85	26.2%	14	31.8%	71	25.4%	
Chemoradiotherapy	144	44.4%	15	34.1%	129	46.1%	
Approach							0.101
Open	58	17.9%	4	9.1%	54	19.3%	
Minimally invasive	266	82.1%	40	90.9%	226	80.7%	
Location of tumor							0.709
Proximal	12	3.7%	1	2.3%	11	3.9%	
Middle	53	16.4%	9	20.5%	44	15.7%	
Distal	122	37.8%	14	31.8%	108	38.6%	
GEJ	137	42.3%	20	45.5%	117	41.8%	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Total (N=324, 100%)		RLNP+ (N=44, 13.6%)		RLNP– (N=280, 86.4%)		P value
	n	%	n	%	n	%	
Histology							0.203
ADC	227	69.8%	33	75.0%	194	69.3%	
SCC	95	29.0%	10	22.7%	85	30.4%	
Other	2	0.6%	1	2.3%	1	0.3%	
pT stage							0.044
T0	59	18.2%	4	9.1%	55	19.6%	
T1	43	13.3%	5	11.4%	38	13.6%	
T2	45	13.9%	5	11.4%	40	14.3%	
T3	165	50.9%	28	63.6%	137	48.9%	
T4	12	3.7%	2	4.5%	10	3.6%	
pN stage							0.233
N0	154	47.6%	16	36.4%	137	48.9%	
N1	85	26.2%	16	36.4%	69	24.6%	
N2	58	17.9%	7	15.9%	51	18.2%	
N3	27	8.3%	5	11.4%	23	8.3%	
Lymph node yield*							<0.001
Median, range	22	6–57	24.5	7–57	22.0	6–53	
Radical resection							0.205
Yes	296	91.4%	38	86.4%	258	92.1%	
No	28	8.6%	6	13.6%	22	7.9%	

Data are n (%), median (range) and mean (± SD). *, skewed distribution, Mann-Whitney test applied. RLNP, recurrent laryngeal nerve palsy; BMI, body mass index; ASA score, American Society of Anesthesiologists Score; ADC, adenocarcinoma; SCC, squamous cell carcinoma.

Functional outcomes

The RLNP+ group is further characterized in *Table 2*. For functional outcome analysis only patients with a follow-up of at least 6 months were included (n=21). Median follow-up was 17.5 [7–135] months. During follow-up, almost half of patients made a full recovery (10/21), 5/21 patients recovered partially, and 6/21 patients did not recover. For 6/21 of these patients surgical intervention (medialization thyroplasty) was required. All treatment interventions for vocal cord paralysis were conducted after a median time of 16.5 [11–29] months after esophagectomy. Of all patients that underwent medialization thyreoplasty, 3/6 had no more RLNP symptoms afterwards 2/6 made a partial recovery from their RLNP, and 1/6 did not recover.

Discussion

The present study demonstrates that RLNP after esophagectomy was an independent predictor for both pulmonary complications and increased hospital stay. Moreover, it shows that over half of patients with RLNP after esophagectomy did not fully recover during follow-up, and a substantial part (14%) needed a surgical intervention to recover from RLNP.

These results stress the importance of preserving the RLN for both short- and long-term outcomes, since several studies have demonstrated that pulmonary complications significantly increase the ICU readmission rate, length of hospital stay and mortality rate, and permanent RLNP after esophagectomy deteriorates quality of life (15,28,29).

Table 2 RLNP characteristics and treatment

Characteristics	RLNP+ (N=44), n (%)
Location	
Left	29 (65.9)
Right	3 (6.8)
Bilateral	8 (18.2)
Unknown	4 (9.1)
Palsy	
Paresis	27 (61.4)
Paralysis	16 (36.4)
Unknown	1 (2.3)
ENT consultation	
Yes	30 (68.2)
No	14 (31.8)
Clinical presentation	
Dysphonia	43 (97.7)
Aspiration	25 (56.8)
Diagnostics	
Clinical	11 (25.0)
Laryngoscopy	33 (75.0)
Therapy	
NPO	21 (47.7)
SLT	36 (81.8)
Thyroplasty	6 (13.6)
Recovery	
Yes	10 (22.7)
No	5 (11.4)
Partially	6 (13.6)
Less than 6 months follow-up	23 (52.3)

Data are n (%), median (range) and mean (± SD). ENT, ear, nose, and throat (ENT) specialists; SLT, speech and language therapy; NPO, nil per os; RLNP, recurrent laryngeal nerve palsy.

Similar to other Western studies reporting on RLNP after McKeown esophagectomy with a two-field lymph node dissection and cervical anastomosis, this study found a RLNP incidence of 14%. Nevertheless, most RLNPs were temporary, indicating that injury of the RLN is rather caused by indirect actions like compression or traction of the nerve than direct damage. Asian studies report RLNP incidences up to 59% (8,9,13,16). This is mainly attributed to the extensive three-field lymph node dissection which is standard of care in Asia. Notably, our data also showed that patients with RLNP had a significantly higher lymph node yield, possibly indicating a more extensive lymph node dissection in these patients. Also, in this series, in the three stage procedures, a level 2 and 4 (paratracheal) lymph node dissection was always performed.

The results of this study regarding short-term complications after RLN injury during esophagectomy are in line with current literature (9,10,20,23,24). The first study published on this topic found higher rates of pulmonary complications after RLNP, leading to a higher reintubation rate, and consequently a prolonged ventilation time and longer ICU stay (23).

These findings were confirmed in more recent studies, all demonstrating an increase in pulmonary complications after esophagectomy complicated by RLNP (9,10,20,24). Similarly to our results, Koyanagi *et al.* (10) found an association between RLNP and prolonged hospital stay. No other studies could confirm this finding, though these studies were limited by their small sample sizes.

This study demonstrates that preventing RLNP during esophagectomy is not only pivotal for improving short-term, but also long-term surgical outcomes. The only study in which results regarding RLNP recovery after esophagectomy are published to date focused on quality of life 1 year after RLNP and found a significant deteriorated quality of life after permanent nerve paralysis due to esophagectomy (12). Hence, precautions to prevent RLNP can improve the outcomes after esophagectomy.

Considering its harmful consequences, it is important to find ways to prevent RLNP during esophagectomy. After transhiatal esophagectomy, the RLNP incidence was 2%, while this was 14% after McKeown esophagectomy. This indicates that the RLN is at risk during high mediastinal lymph node dissection. In accordance with current literature, the majority of patients in the present study were diagnosed with a left-sided palsy (10,20). The left RLN is longer than the right RLN and is situated close to lymph node stations 2L and 4L, consequently being more at risk for injury during lymph node dissection. Meticulous dissection of these stations is pivotal since there is a high frequency of lymph node metastasis (30-32). We experience robotic assistance of great value to perform a full paratracheal lymph node clearance, which was the standard of care for all these patients (33,34). Robotic assistance

Table 3 Postoperative complications

Outcomes	RLNP+ (N=44)		RLNP– (N=280)		P value
	n	%	n	%	
Pulmonary complications					
Total	27	61.4%	116	41.4%	0.013
Pneumonia	21	47.7%	106	37.9%	0.213
Atelectasis	15	34.1%	25	8.9%	<0.001
Tracheostoma	7	15.9%	16	5.7%	0.014
Reintervention	18	40.9%	93	33.2%	0.317
30-day postoperative mortality	0	0.0%	16	5.7%	0.104
ICU stay (days)*	1	1–43	1	1–155	0.620
Hospital stay (days)*	19	9–80	15	3–182	0.084
Readmission	5	11.4%	28	10.0%	0.787

Data are n (%), median (range) and mean (± SD). *, skewed distribution, Mann-Whitney test applied. RLNP, recurrent laryngeal nerve palsy.

Table 4 Pulmonary complications: univariable and multivariable analysis

Characteristics	Univariable			Multivariable		
	OR	95% CI	P value	OR	95% CI	P value
Female gender	0.771	0.471–1.261	0.301			
Age	0.993	0.968–1.019	0.614	0.991	0.964–1.019	0.525
BMI	1.020	0.970–1.072	0.441			
ASA score						
I	Ref	–	–			
II	1.065	0.635–1.788	0.811			
III	1.371	0.651–2.890	0.406			
Pulmonary comorbidity	1.325	0.731–2.400	0.354	1.462	0.786–2.718	0.230
Cardiac comorbidity	1.293	0.750–2.230	0.356			
Vascular comorbidity	0.871	0.519–1.462	0.602			
Diabetes mellitus	2.080	1.059–4.085	0.033	2.126	1.050–4.304	0.036
Neoadjuvant treatment						
None	Ref	–	–	Ref	–	–
Chemotherapy	0.787	0.437–1.417	0.425	0.738	0.401–1.356	0.327
Chemoradiotherapy	0.709	0.421–1.194	0.196	0.660	0.380–1.144	0.139
Minimally invasive surgery	0.966	0.546–1.711	0.907	0.853	0.463–1.572	0.611
Prox tumor location	0.747	0.428–1.303	0.304			
pT3–4 stage	1.157	0.744–1.798	0.518			
pN+ stage	0.977	0.629–1.515	0.916			
Lymph node yield	0.980	0.959–1.002	0.076	0.982	0.959–1.005	0.119
Irradical resection**	1.295	0.596–2.812	0.514			
Anastomotic leakage	0.842	0.494–1.436	0.528			
Chylothorax	1.241	0.717–2.148	0.440			
Recurrent nerve paresis	2.245	1.170–4.309	0.015	2.391	1.222–4.679	0.011

*, Tumor of the proximal or middle esophagus; **, R1 or R2 resection. BMI, body mass index; ASA score, American Society of Anesthesiologists Score.

Table 5 Hospital stay (no IHM): univariable and multivariable analysis

Characteristics	Multivariable			
	B*	95% CI	Additional days	P value
Female gender	0.059	–0.059–0.176	1	0.329
Age >65 years	0.114	0.006–0.222	2	0.039
BMI >25 kg/m^2	0.071	–0.037–0.180	1	0.198
ASA score				
I	Ref	–		–
II	0.043	–0.085–0.172	1	0.510
III	–0.017	–0.207–0.172	0	0.859
Pulmonary comorbidity	0.215	0.066–0.363	4	0.005
Cardiac comorbidity	0.078	–0.062–0.218	1	0.277
Vascular comorbidity	–0.008	–0.147–0.132	0	0.916
Diabetes mellitus	0.227	0.058–0.396	4	0.008
Neoadjuvant treatment				
None	Ref	–		–
Chemotherapy	–0.174	–0.317 to –0.110	–2	0.017
Chemoradiotherapy	–0.218	–0.354 to –0.083	–3	0.002
Minimally invasive surgery	–0.120	–0.261–0.021	–2	0.095
Anastomotic leakage	0.614	0.483–0.744	13	<0.001
Chylothorax	0.389	0.255–0.523	7	<0.001
Recurrent nerve paresis	0.250	0.096–0.403	4	0.001

*, Intercept = 2,708 (15 days). BMI, body mass index; ASA score, American Society of Anesthesiologists Score.

facilitates meticulous dissection along the left RLN and may reduce the incidence of RLNP (14,35).

Surgically induced RLNP is often not recognized during the procedure. Noninvasive intraoperative neurological monitoring (IONM) may enable surgeons to identify and preserve the RLN. IONM is already widely used in thyroid surgery, and although its effectiveness for esophagectomy is not well recognized, several studies report lower RLNP and consequently lower pulmonary complication rates (8,20,36-38). Therefore, the use of IONM may be considered for esophagectomy, particularly during high mediastinal lymph node dissection (10). A substantial part of RLNP is due to thermal injury. Electrocautery devices are used for hemostasis around the RLN during esophagectomy and may deliver heat at a single temperature or a range of temperatures, between 100 and 1,200 ℃. The use of alternatives to an electrocautery device, reducing maximum temperatures may be another measure to reduce RLNP rates (39). Additionally, the use of an intrathoracic anastomosis instead of a cervical anastomosis may also reduce the incidence of RLNP after esophagectomy (20,21), most probably because of the fact that the upper mediastinum is not fully dissected in these cases.

Besides avoiding unnecessary RLNP, early diagnosis might prevent complications secondary to RLNP. Over half of patients in the current study were diagnosed with RLNP after clinical presentation with symptoms of aspiration. In case of early diagnosis, one may decide to properly evaluate the swallowing process and potentially postpone oral intake, reducing aspiration pneumonia rates (20).

The majority of patients underwent SLT after hospital discharge, resulting in a satisfactory function of voice and

swallowing. However, due to persistent symptoms, 14% of all RLNP patients needed secondary surgery (medialization thyreoplasty), leading to a full or partial recovery in 5 out of 6 patients. All procedures were conducted in the absence of spontaneous recovery ≥10 months after esophagectomy. This suggests that these patients may have benefited from earlier intervention, since several studies on early versus late medialization show favorable outcomes for patients in early cohorts (40,41).

Strengths of this study include its large sample size from a prospective database of Western patients and the detailed information on both short- and long-term outcomes available from the database. Despite this, certain limitations apply to the current analysis. It was not possible to obtain data on recovery in all patients. All patients in which follow-up data was missing had early recurrent disease. This made complaints regarding RLNP of minor importance, resulting in poor registration. Lastly, an unexpected lower rate of cardiac comorbidity was found in the RLNP+ group. Although multivariable analysis corrected for all known confounders such as cardiac comorbidity, there may have been other unexpected, unknown confounders which were not included in the analysis, which may have led to bias.

The present study shows that RLNP after esophagectomy is associated with an increased pulmonary complication rate, longer hospital stay, and a moderate long-term recovery. This warrants further studies examining technologies that may reduce RLNP rates.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study received ethical approval (Institutional Review Board number 13-061/C) from the Medical Ethics Review Committee of the UMCU, and informed consent was waived.

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