Interactive CardioVascular and Thoracic Surgery 34 (2022) 393–401
https://doi.org/10.1093/icvts/ivab293 Advance Access publication 3 November 2021

ORIGINAL ARTICLE

Cite this article as: Pai C-P, Hsu P-K, Chien L-I, Huang C-S, Hsu H-S. Clinical outcome of patients after recurrent laryngeal nerve lymph node dissection for oesophageal squamous cell carcinoma. Interact CardioVasc Thorac Surg 2022;34:393–401.

THORACIC

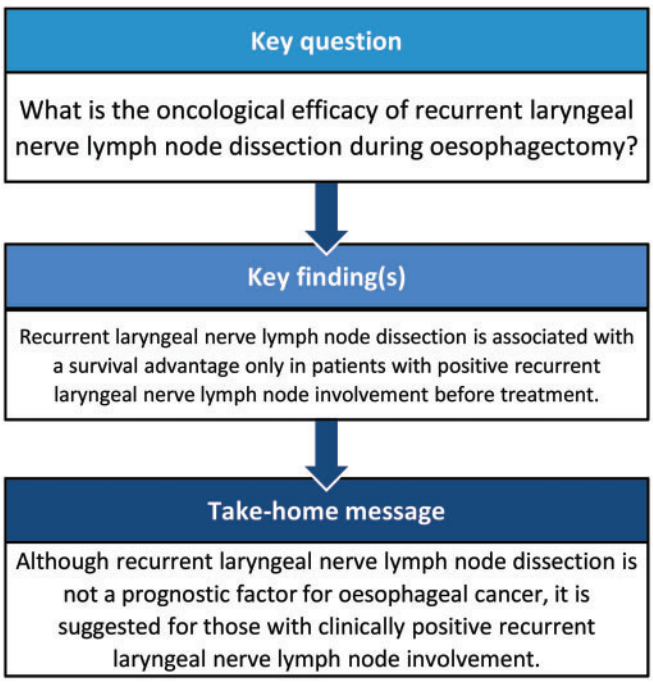
Clinical outcome of patients after recurrent laryngeal nerve lymph node dissection for oesophageal squamous cell carcinoma

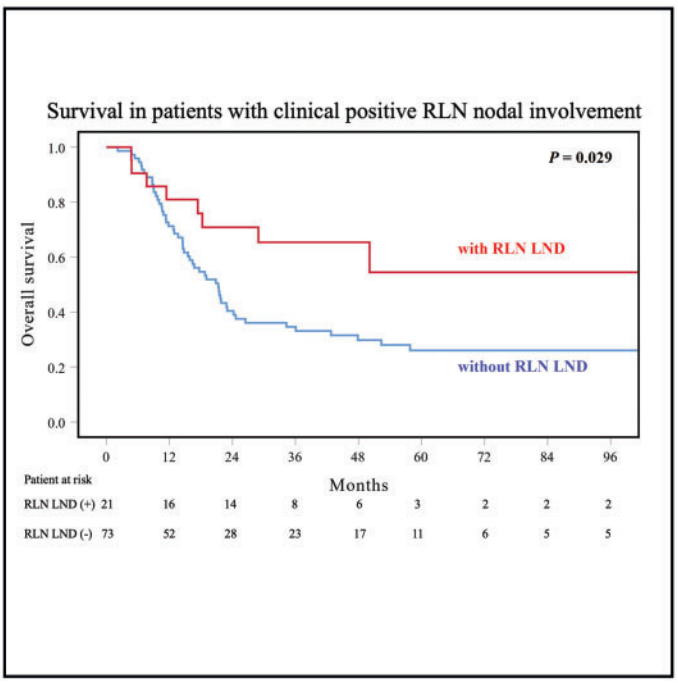
Chu-Pin Pai[a], Po-Kuei Hsu [a,b,*], Ling-I Chien[c], Chien-Sheng Huang [a,b] and Han-Shui Hsu[a,b]

[a] Division of Thoracic Surgery, Department of Surgery, Taipei Veterans General Hospital, Taipei, Taiwan
[b] School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan
[c] Department of Nursing, Taipei Veterans General Hospital, Taipei, Taiwan

* Corresponding author. Division of Thoracic Surgery, Department of Surgery, Taipei Veterans General Hospital, No. 201, Sec. 2, Shih-Pai Road, Taipei, Taiwan. Tel: 886-2-28757546; fax: 886-2-77232151; e-mail: hsupokuei@yahoo.com.tw (P.-K. Hsu).

Received 6 April 2021; received in revised form 26 August 2021; accepted 20 September 2021





Abstract

OBJECTIVES: Recurrent laryngeal nerve lymph node dissection (LND) has been incorporated into oesophagectomy for patients with oesophageal squamous cell carcinoma, but with uncertain oncological efficacy.

METHODS: The data of patients with oesophageal squamous cell carcinoma, including who underwent upfront surgery (surgery group) and those who received neoadjuvant therapy followed by surgery (neoadjuvant chemoradiotherapy group), were retrospectively examined. The overall survival (OS) and disease-free survival (DFS) were compared between patients with and without recurrent laryngeal nerve LND.

RESULTS: Among the 312 patients, no significant differences were found in 3-year OS and DFS between patients with and without recurrent laryngeal nerve LND in the entire cohort (OS: 57% vs 52%, $P = 0.33$; DFS: 47% vs 41%, $P = 0.186$), or the surgery group ($n = 173$, OS: 69% vs 58%, $P = 0.43$; DFS: 52% vs. 48%, $P = 0.30$) and the neoadjuvant chemoradiotherapy group ($n = 139$, OS: 44% vs 43%, $P = 0.44$; DFS: 39% vs

32%, $P = 0.27$). However, among patients with clinical positive recurrent laryngeal nerve lymph node involvement before treatment, there was significant OS and DFS differences between patients with and without recurrent laryngeal nerve LND (OS: 62% vs 33%, $P = 0.029$; DFS: 49% vs 26%, $P = 0.031$).

CONCLUSIONS: Recurrent laryngeal nerve LND is not a significant prognostic factor in patients with oesophageal squamous cell carcinoma; however, it is associated with better outcomes in patients with pre-treatment radiological evidence of recurrent laryngeal nerve lymph node involvement.

Keywords: Oesophageal cancer • Oesophageal surgery • Lymph nodes • Prognosis

ABBREVIATIONS

CT	Computed tomography
DFS	Disease-free survival
LND	Lymph node dissection
LVI	Lymphovascular invasion
NCRT	Neoadjuvant chemoradiation treatments
OS	Overall survival
OSCC	Oesophageal squamous cell carcinoma
PET	Positron emission tomography
PNI	Perineural invasion
RLN	Recurrent laryngeal nerves
SUV	Standard uptake value
TRG	Tumour regression grade

INTRODUCTION

Oesophageal squamous cell carcinoma (OSCC) is one of the most aggressive malignancies and has a high potential for lymphatic spread [1]. Although the scale of nodal metastasis has been reported to be associated with survival, the optimal extent of lymph node dissection (LND) has long been debated [1]. In patients who have undergone upfront surgery, aggressive LND has been reported to be associated with better outcomes [2–6]. However, its efficacy remains undetermined in patients who have received neoadjuvant chemoradiation treatments (NCRT) followed by surgery. Controversy remains as to whether a higher degree of LND improves long-term outcomes. For example, both Shridhar *et al.* and Koen Talsma *et al.* demonstrated that the number of resected nodes was not a prognostic factor in patients after NCRT [6, 7]. Moreover, more radical LND may increase the risk of postoperative complications. For example, as much as 41% of patients may experience recurrent laryngeal nerve palsy after dissection along the bilateral recurrent laryngeal nerves (RLN) [8–11].

To our knowledge, the question of the survival benefits of RLN LND in patients who have undergone upfront surgery remains unresolved. For instance, Park *et al.* reported superior survival in patients who received RLN LND for pT1 OSCC, whereas Yu *et al.* did not find any significant survival difference between patients with and without RLN LND for pT1/2 OSCC [12, 13]. Even fewer studies have focused on the efficacy of RLN LND in patients who have received NCRT followed by surgery. In view of this unsettled debate, we conducted the present study to assess the clinical outcome of patients after RLN LND for OSCC.

PATIENTS AND METHODS

Ethical statement

The study protocol was reviewed and approved by the Institutional Review Board of Taipei Veterans General Hospital (TPEVGH2020-08-014BC) and granted a waiver of the informed consent process.

Study design and selection criteria

We performed a retrospective study with the inclusion criteria of patients who underwent oesophagectomy for oesophageal malignancies between March 2009 and January 2018 in TPEVGH. The exclusion criteria included diagnoses other than squamous cell carcinoma (SCC), salvage surgery, and surgical mortality. After exclusion, data were analysed for the remaining patients who underwent upfront surgery (surgery group) and those who received NCRT followed by surgery (NCRT group).

Staging workup

The staging workup included a systemic physical examination, standard laboratory screening, oesophagogastroscopy, bronchoscopy for tumours in the upper or middle third of the oesophagus, computed tomography (CT) scanning from the neck to the upper abdomen, and whole-body fluorodeoxyglucose positron emission tomography/CT (PET/CT). Endoscopic ultrasound was recommended but not routinely performed. Tumour length was defined as longitudinal tumour length and was measured during initial diagnosis, either endoscopically or by imaging modality (PET/CT, chest CT). Pre-treatment lymph node involvement (clinical N stage), specifically at the bilateral upper paratracheal lymph node stations, according to the American Joint Committee on Cancer staging manual, or the bilateral recurrent laryngeal nerve, as adopted in the Japanese Classification [14], was determined based on fluorodeoxyglucose PET/CT and chest CT findings [lymph nodes with a short axis greater than 1 cm in chest CT or with a standard uptake value (SUV) higher than 2.5 in PET/CT were considered positive] and recorded as 'cRLN'. To illustrate, the superior boundary of RLN lymph node is drawn from the cephalic border of the subclavian arteries to the suprasternal notch, and the inferior boundary is the caudal border of the RLN curving upward on both sides. Lymph node involvement at bilateral RLN after neoadjuvant therapy and before surgery was recorded as 'ycRLN'. After surgery, pathological confirmation of lymph node metastasis at cRLN and ycRLN stations were documented as pRLN (surgery group) and ypRLN (NCRT group), respectively.

Treatment policies

Primary surgery or NCRT followed by surgery was chosen according to the National Comprehensive Cancer Network guidelines. The NCRT regimen, surgical methods and follow-up were performed as previously described [15]. In brief, the thoracic stage was performed using thoracotomy or video-assisted thoracoscopic surgery for oesophagectomy and mediastinal LND. In our hospital, RLN LND was not a standard and was only performed by a few surgeons (P.-K.H.). In patients who were planned for RLN LND, thoracoscopic oesophagectomy and LND were performed under single-lumen tracheal intubation with an artificial pneumothorax with a CO_2 insufflation pressure of 8 mmHg. The pleura on the dorsal side of the right vagus nerve was opened towards the right subclavian artery, where the right RLN could be exposed. The vessels which ran along the dorsal side of the right RLN were ligated using either clips or a vessel sealing system to prevent thermal injury. Lymphadenectomy was done along the right RLN towards the thoracic inlet, while the right inferior thyroid artery was the landmark for the cranial boundary. For left side RLN, the oesophagus traction towards the dorsal side and trachea compression to ventral side were necessary to expose the left side of the trachea. Dissection was done along the trachea and the left bronchus to delineate the ventral border of the dissection. The left RLN could be identified from the aortic arch and along the left side of the trachea. The tissue and lymph nodes surrounding the left RLN are released from the nerve and oesophagus. Lymphadenectomy is performed from the level of the aortic arch up to the thoracic inlet. Cervical LND would be performed only when metastasis to the neck lymph nodes was found preoperatively.

The abdominal stage consisted of gastric tube creation and dissection of pericardial and coeliac axis nodes by either laparotomy or laparoscopy. The oesophagogastric anastomosis was performed in the chest with the stapling method or at the neck with either the stapling or hand-sewn technique. For patients with cervical OSCC, a subtotal oesophagectomy was performed with intraoperative frozen section of the proximal cut end for confirming negative margin involvement. Postoperative complications were defined according to the guidelines of the oesophagectomy Complications Consensus Group [16].

Statistics

Continuous variables were summarized as medians and interquartile range. The normality of continuous variables was tested using Kolmogorov–Smirnov or Shapiro–Wilk method. A Student's *t*-test was used for assessing the differences between normally distributed continuous variables, while a non-parametric (Mann–Whitney *U*) test was utilized for comparing non-normally distributed continuous variables. Categorical variables were compared with the chi-squared test or Fisher's exact test if there were few observations (e.g. <5) for individual cells. Overall survival (OS) was defined as the time from the date of surgical resection until death or the last known follow-up, based on either medical records or a follow-up phone call. Disease-free survival (DFS) was defined as the time after treatment during which no sign of cancer was found and was measured from surgical resection to disease progression, death or the last known follow-up. Survival curves were plotted using the Kaplan–Meier method and compared using the log-rank test. In the subgroup analysis, pairwise comparisons between group, in which separate tests are computed for each pair of factor levels, were performed for linear trend using 'pairwise over strata' function in the software. Univariable and multivariable Cox regression modelling was used to identify factors associated to patient survival. To include factors for theoretical reasons, factors with a *P*-value <0.1 in univariable analysis were included in multivariable modelling. Enter procedure was used to select significant explanatory variables. All statistical analyses were conducted using the Statistical Product and Service Solutions (SPSS, version 25; IBM Corp, Armonk, NY, USA), and a two-sided *P*-value <0.05 was considered statistically significant.

RESULTS

Characteristics of the study patients

During the study period, a total of 386 patients met the criteria. After excluding patients with diagnoses other than SCC ($n = 43$), salvage surgery ($n = 24$) and surgical mortality ($n = 7$), the data of the remaining 312 patients were analysed. The clinical and pathological characteristics of the patients are summarized in Table 1. Among the 312 patients, 173 of them received upfront surgery (surgery group) and the remaining 139 underwent NCRT followed by surgery (NCRT group). In these 2 groups, no significant differences were found in the baseline factors between patients with and without RLN LND. The SUV of both the main tumour and the RLN LN in PET/CT decreased markedly after NCRT.

Recurrent laryngeal nerves lymph node metastasis

Among the 53 patients in the entire cohort who received RLN LND, the average number of RLN node was 2.9 and 8 (15.1%) patients exhibited positive RLN LN metastasis. Stratified by the RLN lymph node status during clinical staging workup, the positive rate was 11.1% (2/18) and 12.5% (1/8) in the cRLN (-) and cRLN (+) patients in the surgery group, respectively, whereas it was 14.3% (2/14) and 23.1% (3/13) in the cRLN (-) and cRLN (+) patients in the NCRT group, respectively. Moreover, the RLN LN was the only positive nodal station in 4 (50%) of the 8 patients with positive RLN LN metastasis after RLN LND, which if omitted would have resulted in a stage migration.

Survival after recurrent laryngeal nerves lymph node dissection

In the survival analysis, the median follow-up time for all patients was 33.5 (interquartile range: 21.5–48.6) months. The 3-year OS and DFS rates in the entire cohort were 54% and 43%, respectively. No significant differences were found in 3-year OS and DFS between patients with and without RLN LND (OS: 57% vs 52%, $P = 0.33$; DFS: 47% vs 41%, $P = 0.186$, Fig. 1A and B). In the surgery group, no significant differences were found in 3-year OS and DFS between patients with and without RLN LND (OS: 69% vs 58%, $P = 0.43$; DFS: 52% vs 48%, $P = 0.30$, Fig. 2A and B). In the NCRT group, no significant differences were found in 3-year OS and DFS between patients with and without RLN LND (OS: 44% vs 43%, $P = 0.44$; DFS: 39% vs 32%, $P = 0.27$, Fig. 2C and D).

A Cox proportional hazards regression model was used to analyse prognostic factors for OS (Supplementary Material, Table S1)

Table 1: Clinical characteristics of patients with and without RLN LND in the surgery and NCRT groups

	Total		Surgery group				NCRT group			
	N = 312		*N* = 173				*N* = 139			
		P^{*}	Total	RLN LND		P^{**}	Total	RLN LND		P^{***}
				(-) *N* = 147	(+) *N* = 26			(-) *N* = 112	(+) *N* = 27	
Age (years; median, IQR)	58.7 (51.0–66.0)	0.063	59.0 (51.0–67.0)	59.0 (51.0–67.0)	60.5 (55.8–67.3)	0.71	58.0 (51.0–64.0)	57.0 (50.0–63.0)	61.0 (52.0–71.0)	0.031
Sex (%)		0.284				0.190				0.038
Male	281 (90.1)		153 (88.4)	132 (89.8)	21 (80.8)		128 (92.1)	106 (94.6)	22 (81.5)	
Female	31 (9.9)		20 (11.6)	15 (10.2)	5 (19.2)		11 (7.9)	6 (5.4)	5 (18.5)	
Tumour location (%)		0.086				0.29				0.38
Cervical	5 (1.6)		4 (2.3)	4 (2.7)	0		1 (0.7)	0	1 (3.7)	
Upper	71 (22.8)		31 (17.9)	24 (16.3)	7 (26.9)		40 (28.8)	34 (30.4)	6 (22.2)	
Middle	136 (43.6)		75 (43.4)	63 (42.9)	12 (46.2)		61 (43.9)	46 (41.1)	15 (55.6)	
Lower	96 (30.8)		61 (35.3)	54 (36.7)	7 (26.9)		35 (25.2)	30 (26.8)	5 (18.5)	
OGJ	4 (1.3)		2 (1.2)	2 (1.4)	0		2 (1.4)	2 (1.8)	0	
Tumour length (cm; median, IQR)	5.0 (3.4–7.0)	0.004	5.0 (3.0–6.0)	5.0 (3.0–6.0)	4.0 (3.0–5.5)	0.31	5.0 (4.0–7.5)	5.0 (4.0–8.0)	6.0 (4.0–7.0)	0.69
cRLN (%)		<0.001				0.100				0.83
Negative	217 (69.6)		141 (81.5)	123 (83.7)	18 (69.2)		76 (54.7)	62 (55.4)	14 (51.9)	
Positive	95 (30.4)		32 (18.5)	24 (16.3)	8 (30.8)		63 (45.3)	50 (44.6)	13 (48.1)	
ycRLN (%)										0.72
Negative	126 (90.6)						126 (90.6)	102 (91.1)	24 (88.9)	
Positive	13 (9.4)						13 (9.4)	10 (8.9)	3 (11.1)	
p/yp T (%)		<0.001				0.124				0.57
0	59 (18.9)		1 (0.6)	1 (0.7)	0		58 (41.7)	49 (43.8)	9 (33.3)	
is/1/2	117 (37.5)		75 (43.3)	59 (40.1)	16 (61.6)		42 (30.3)	32 (28.6)	10 (37)	
3/4	136 (43.5)		97 (56.1)	87 (59.2)	10 (38.5)		39 (28.1)	31 (27.7)	8 (29.6)	
p/yp N (%)		0.246				0.131				0.27
0	199 (63.8)		102 (59.0)	84 (57.1)	18 (69.2)		97 (69.8)	81 (72.3)	16 (59.3)	
1	70 (22.4)		43 (24.9)	38 (25.9)	5 (19.2)		27 (19.4)	21 (18.8)	6 (22.2)	
2	36 (11.5)		23 (13.3)	22 (15.0)	1 (3.8)		13 (9.4)	9 (8.0)	4 (14.8)	
3	7 (2.2)		5 (2.9)	3 (2.0)	2 (7.7)		2 (1.4)	1 (0.9)	2 (3.7)	
TLN (median, IQR)	20 (14–27)	<0.001	22 (16–30)	22 (15–31)	26 (19–29)	0.23	17 (12–23)	17 (11–23)	18 (13–25)	0.42
Differentiation (%)		<0.001				0.95				0.52
No residual	68 (21.8)		4 (2.3)	4 (2.7)	0		64 (46.0)	54 (48.2)	10 (37.0)	
Well	6 (1.9)		4 (2.3)	4 (2.7)	0		2 (1.4)	2 (1.8)	0	
Moderately	187 (59.9)		128 (74)	107 (72.8)	21 (80.8)		59 (42.4)	46 (41.1)	13 (48.1)	
Poorly	49 (15.7)		37 (21.4)	32 (21.8)	5 (19.2)		12 (8.6)	9 (8.0)	3 (11.1)	
Unknown	2 (0.6)		0	0	0		2 (1.4)	1 (0.9)	1 (3.7)	
PNI (%)		0.001				0.82				0.75
Negative	244 (78.2)		123 (71.1)	104 (70.7)	19 (73.1)		121 (87.1)	98 (87.5)	23 (85.2)	
Positive	68 (21.8)		50 (28.9)	43 (29.3)	7 (26.9)		18 (12.9)	14 (12.5)	4 (14.8)	
LVI (%)		0.001				0.27				0.79
Negative	218 (69.9)		107 (61.8)	88 (59.9)	19 (73.1)		111 (79.9)	90 (80.4)	21 (77.8)	
Positive	94 (30.1)		66 (38.2)	59 (40.1)	7 (26.9)		28 (20.1)	22 (19.6)	6 (22.2)	

Continued

Table 1: Continued

	Total	Surgery group				NCRT group			
	$N = 312$	$N = 173$				$N = 139$			
	P^{*}	Total	RLN LND		P^{**}	Total	RLN LND		P^{***}
			(-) $N = 147$	(+) $N = 26$			(-) $N = 112$	(+) $N = 27$	
TRG (%)									0.081
0	55 (39.6)					55 (39.6)	46 (41.1)	9 (33.3)	
1	33 (23.7)					33 (23.7)	30 (26.8)	3 (11.1)	
2	31 (22.3)					31 (22.3)	20 (17.9)	11 (40.7)	
3	12 (8.6)					12 (8.6)	9 (8.0)	3 (11.1)	
Unknown	8 (5.8)					8 (5.8)	7 (6.3)	1 (3.7)	
Margin (%)					0.97				0.25
Free	287 (92.0)	160 (92.5)	136 (92.5)	24 (92.3)		127 (91.4)	104 (92.9)	23 (85.2)	
Not free	25 (8.0)	13 (7.5)	11 (7.5)	2 (7.7)		12 (8.6)	8 (7.1)	4 (14.8)	
Margin (%)					0.718				

*P-value comparing surgery group and NCRT group.
**P-value comparing RLN LND (+) and RLN LND (-) in the surgery group.
***P-value comparing RLN LND (+) and RLN LND (-) in the NCRT group.
OGJ: oesophagogastric junction; IQR: interquartile range; LND: lymph node dissection; LVI: lymphovascular invasion;NCRT: neoadjuvant chemoradiotherapy; PNI: perineural invasion; RLN: recurrent laryngeal nerve; TLN: total lymph node; TRG: tumour regression grade (0: complete response; 1: near-complete response; 2: partial response; 3: poor response).

and DFS (Supplementary Material, Table S2) in both groups. In the surgery group, the significant prognostic factors in univariable analysis for OS included sex, tumour length, cT stage, cRLN status, lymphovascular invasion (LVI), margin, pT stage and pN stage. Among these factors, tumour length and pN+ stage remained independent prognostic factors in the multivariable analysis. On the other hand, the significant prognostic factors in univariable analysis for DFS included sex, tumour location, tumour length, cT stage, cN stage, perineural invasion (PNI), LVI, margin, pT stage and pN stage. Among these factors, tumour location in the upper to middle third of the oesophagus and pN+ stage remained independent prognostic factors in the multivariable analysis. Notably, RLN LND was not a significant prognostic factor for OS or DFS in the surgery group.

In the NCRT group, the significant prognostic factors in univariable analysis for OS included tumour length, cRLN, SUV of RLN LN after NCRT, SUV of tumour after NCRT, PNI, LVI, tumour differentiation, margin, pT stage, pN stage and tumour regression grade (TRG). Among these factors, positive PNI and a TRG of 1/2/3 remained independent prognostic factors in the multivariable analysis. In addition, the significant prognostic factors in univariable analysis for DFS included tumour location, tumour length, cRLN, SUV of RLN LN after NCRT, SUV of tumour after NCRT, PNI, LVI, tumour differentiation, margin, ypT stage, ypN stage and TRG. Among these factors, a TRG of 1/2/3 remained an independent prognostic factor in the multivariable analysis. Notably, RLN LND was not a significant prognostic factor for OS or DFS in the NCRT group.

Subgroup analysis

Subgroup analysis was performed according to the cRLN and RLN LND status. As shown in Fig. 3, in the cRLN (+) subgroup, significant OS and DFS differences were found between patients with and without RLN LND (OS: 62% vs 33%, $P = 0.029$; DFS: 49% vs 26%, $P = 0.031$). By contrast, no survival significant differences were found between patients with and without RLN LND in the cRLN (-) subgroup (OS: 55% vs 59%, $P = 0.81$; DFS: 38% vs 48%, $P = 0.80$).

Subgroup analysis was also performed based on the cRLN, RLN LND and p/ypRLN status (Fig. 4). The median OS for the patients with negative metastasis at the RLN LN station confirmed by RLN LND was 67.6 months (95% confidence interval: 53.9–81.3), which was comparable to cRLN (-) patients who did not receive RLN LND (median OS: 78.6 months, 95% confidence interval: 69.9–87.4, $P = 0.59$). By contrast, the median OS of the patients with positive metastasis at the RLN LN station confirmed by RLN LND and those with cRLN (+) but did not receive RLN LND had the worst outcome.

Postoperative complications

The details of the perioperative course are listed in Table 2. No difference was found in the operation time between RLN LND (+) or (-). Regarding the postoperative course, higher rates of RLN paralysis and pneumonia were observed in RLN LND (+) patients, compared with RLN LND (-) patients. However, the difference was not statistically significant. Although vocal cord palsy was noted in 26.4% of patients who received RLN LND, more than half were transient type and recovered spontaneously. Type II vocal cord palsy could be noted in 11.3% of patients. Moreover, the

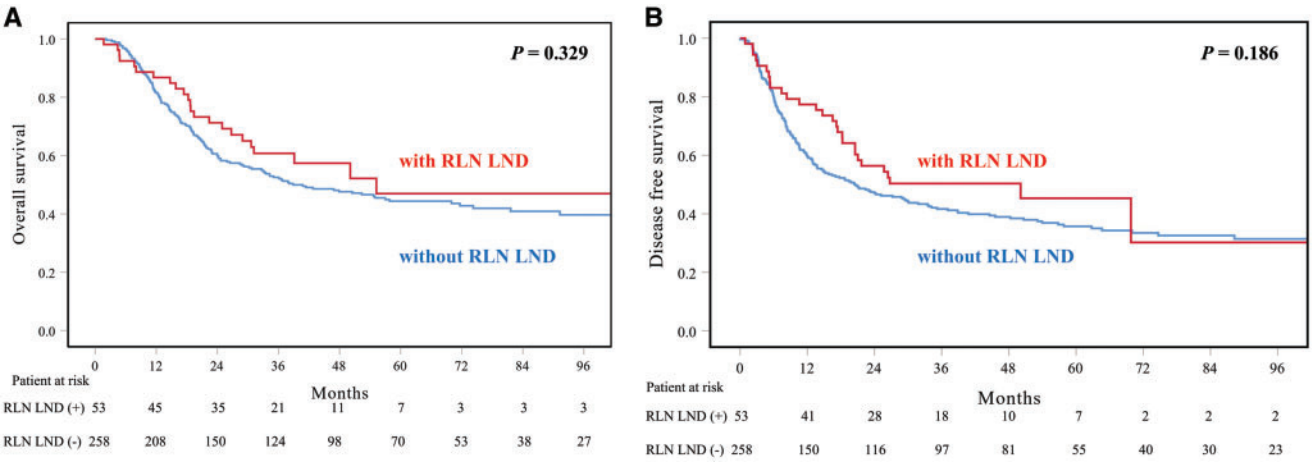


Figure 1: Survival curves of overall survival (**A**) and disease-free survival (**B**) categorized by recurrent laryngeal nerve lymph node dissection status [red: RLN LND (+); blue: RLN LND (-)] for the whole cohort. LND: lymph node dissection; RLN: recurrent laryngeal nerve.

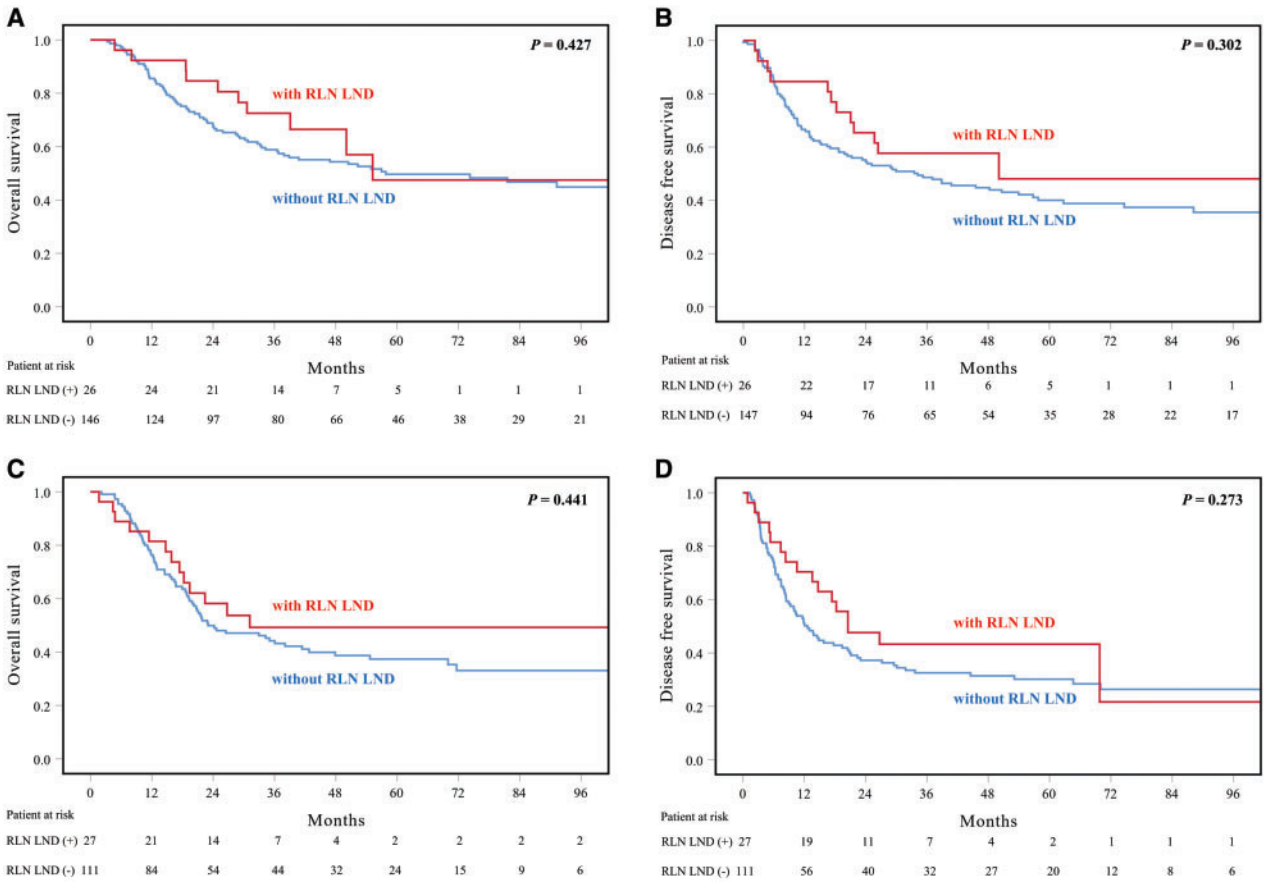


Figure 2: Survival curves of overall survival (**A**) and disease-free survival (**B**) for the surgery group, and of overall survival (**C**) and disease-free survival (**D**) for the NCRT group, categorized by recurrent laryngeal nerve lymph node dissection status [red: RLN LND (+); blue: RLN LND (-)]. LND: lymph node dissection; NCRT: neoadjuvant chemoradiotherapy; RLN: recurrent laryngeal nerve.

rates of chyle leaks, anastomotic leaks and the length of hospital stay were similar between RLN LND (+) and (-) groups.

In the NCRT group, we did not identify a statistically higher incidence of postoperative vocal cord palsy (29.6% vs 14.3%, $P = 0.085$), pneumonia (18.5% vs 6.3%, $P = 0.057$), chyle leaks (3.7% vs 7.1%, $P = 0.51$), anastomotic leaks (3.7% vs 7.1%, $P = 0.51$) and wound infection (0% vs 1.8%, $P = 0.48$) in patients who received an RLN LND, compared with those who did not.

Recurrence pattern

The pattern of recurrence was shown in Table 3. Tumour recurrence was observed in 164 (52.6%) patients. The recurrence rate was 41.5% and 54.8% in the RLN LND (+) and RLN LND (-) groups, respectively ($P = 0.077$). There was no difference in loco-regional, distant and within surgical field recurrences between RLN LND (+) and RLN LND (-) groups. However, there were

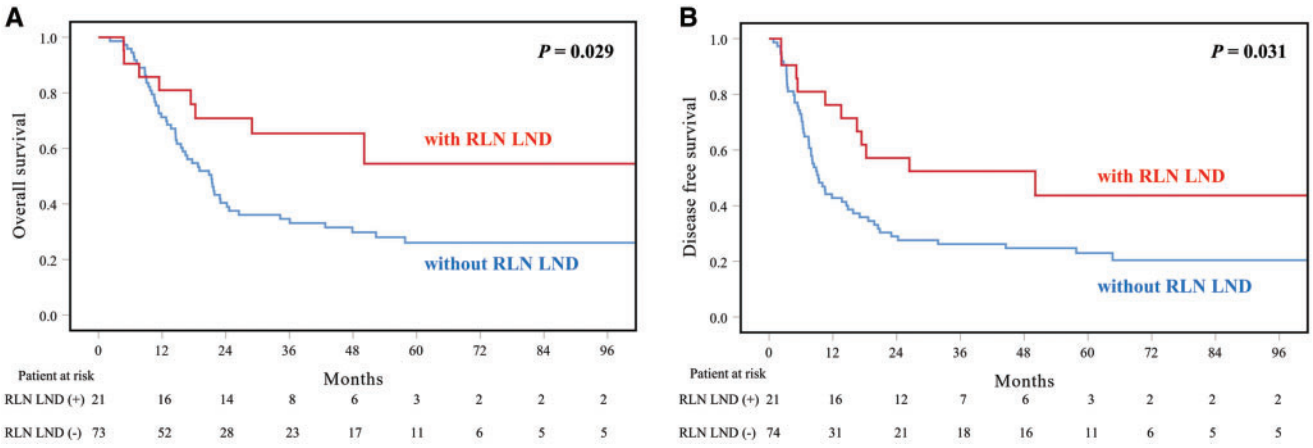


Figure 3: Survival curves of overall survival (**A**) and disease-free survival (**B**) categorized by recurrent laryngeal nerve lymph node dissection status [red: RLN LND (+); blue: RLN LND (-)] for the cRLN (+) group. LND: lymph node dissection; RLN: recurrent laryngeal nerve.

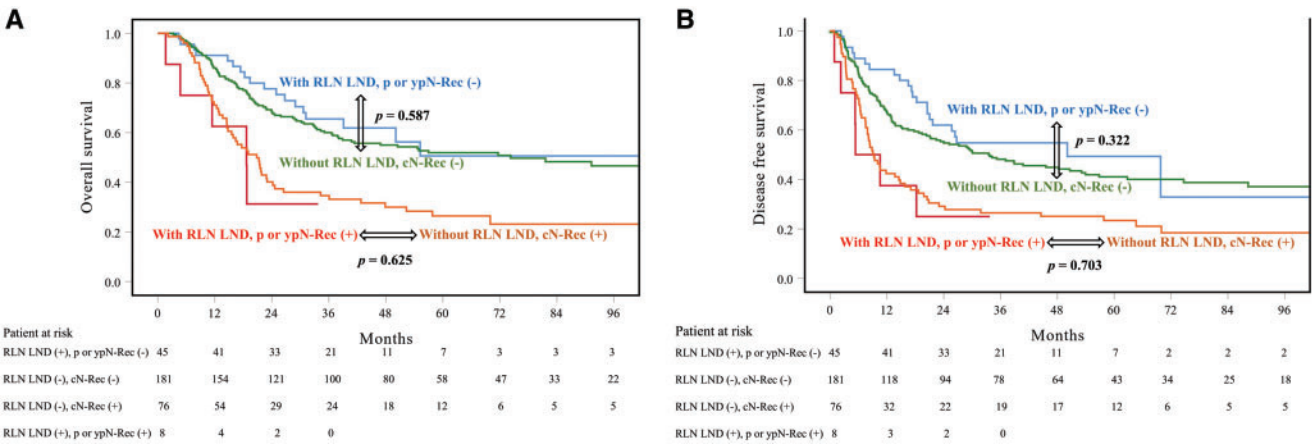


Figure 4: Survival curves of overall survival (**A**) and disease-free survival (**B**) according to RLN LND, p/ypN-RLN and cRLN status [blue: RLN LND (+)/p/ypRLN (-); green: RLN LND (-)/cRLN (-); yellow: RLN LND (-)/cRLN (+); red: RLN LND (+)/p/ypRLN (+)]. In (**A**), the *P*-value was 0.59, 0.001, 0.016, <0.001, 0.022 and 0.63, between blue and green, blue and yellow, blue and red, green and yellow, green and red, yellow and red curves, respectively. In (**B**), the *P*-value was 0.32, 0.001, 0.015, <0.001, 0.042 and 0.70, between blue and green, blue and yellow, blue and red, green and yellow, green and red, yellow and red curves, respectively. LND: lymph node dissection; RLN: recurrent laryngeal nerve.

more outside surgical field recurrences in the RLN LND (-) groups (50.2% vs 34.0%, $P = 0.031$). With regard to recurrence rates at the RLN LN station were 17.0% and 12.4% in the RLN LND (+) and RLN LND (-) groups, respectively ($P = 0.36$).

DISCUSSION

The incidence of RLN LN metastasis has been reported to range from 14.2% to 39.5% [12, 17–21]. Li *et al.* [19] have reported the advantage of providing complete staging information after RLN LND. In their study of patients who received NCRT followed by surgery, unsuspected RLN LN metastasis was recognized in 11 (19.6%) patients, among whom 8 exhibited further stage migration, among whom 7 had nodal metastasis solely at the RLN LN station. In another study, Chao *et al.* [21] reported RLN LN metastasis as the only positive station in 27.3% (3/11) of the ypN (+) patients in their cohort of patients who underwent NCRT followed by surgery. In the present study, 4 (50%) patients with RLN LN metastasis would have been erroneously classified as 'N0' if RLN LND had been omitted, leading to fallacious staging.

However, questions remain regarding the efficacy of loco-regional control of RLN LND, which is technically demanding and possibly results in considerable morbidity once RLN palsy has developed [11, 22, 23]. Park *et al.* [13] have demonstrated a better loco-regional control in their patients with superficial (i.e. pT1) OSCC, who received an RLN LND, compared with those who received a limited lower mediastinal lymphadenectomy. On the other hand, Chao *et al.* [21] reported similar overall recurrence and upper mediastinal lymph node recurrence rates between RLN LND (+) and RLN LND (-) groups in patients without preoperative radiological evidence of RLN LN involvement after NCRT (negative ycN-RLN). In our study, there were more outside surgical field recurrences in the RLN LND (-) groups (50.2% vs 34.0%, $P = 0.031$), whereas recurrences within the surgical field and around RLN area were similar between RLN LND (-) and RLN LND (+) groups. More studies are needed for elucidating whether RLN LND reduces the risk of loco-regional or distant recurrences. The survival impact of RLN LND was also controversial, especially in patients who have received NCRT followed by surgery [12, 13]. In Chao's study that focused specifically on patients with negative ycN-RLN status, there was no significant DFS difference between patients with and without RLN LND

Table 2: Perioperative outcomes of patients with and without RLN LND

	RLN LND (+) N = 53	RLN LND (-) N = 259	P-value
Operative time (min; median, IQR)	440 (393–570)	480 (410–590)	0.24
Chyle leaks, *n* (%)	3 (5.7)	11 (4.2)	0.72
Anastomotic leaks, *n* (%)	4 (7.5)	15 (5.8)	0.54
Vocal cord palsy, *n* (%)	14 (26.4)	47 (18.1)	0.167
Type I, *n* (%)	8 (15.1)	21 (8.2)	0.55
Type II, *n* (%)	6 (11.3)	24 (9.3)	
Pneumonia, *n* (%)	7 (13.2)	15 (5.8)	0.073
Wound infection, *n* (%)	0	6 (2.3)	0.59
LOS (days, median, IQR)	15 (13–23)	16 (13–25)	0.29

IQR: interquartile range; LND: lymph node dissection; LOS: length of stay; RLN: recurrent laryngeal nerve.

Table 3: Recurrence pattern in patients with and without RLN LND

	Total N = 312	RLN LND (+) N = 53	RLN LND (-) N = 259	P-value
Disease recurrence,[a] *n* (%)	164 (52.6)	22 (41.5)	142 (54.8)	0.077
Within surgical field, *n* (%)	105 (33.7)	18 (34.0)	87 (33.6)	0.96
Locoregional, *n* (%)	114 (36.5)	18 (34.0)	96 (37.1)	0.67
Anastomosis, *n* (%)	29 (9.3)	5 (9.4)	24 (9.3)	1.00
RLN LN, *n* (%)	9 (17.0)	9 (17.0)		0.36[b]
Mediastinum LN, *n* (%)	66 (21.2)	13 (24.5)	53 (20.5)	0.51
Cervical LN, *n* (%)	15 (4.8)	4 (7.5)	11 (4.2)	0.54
Abdominal LN, *n* (%)	28 (9.0)	2 (3.8)	26 (10.0)	0.114
Outside surgical field, *n* (%)	148 (47.4)	18 (34.0)	130 (50.2)	0.031
RLN LN, *n* (%)	32 (12.4)		32 (12.4)	0.36[b]
Distant site, *n* (%)	141 (45.2)	18 (34.0)	123 (47.5)	0.071
Lung, *n* (%)	71 (22.8)	7 (13.2)	64 (24.7)	0.069
Bone, *n* (%)	43 (13.8)	7 (13.2)	36 (13.9)	0.89
Distal LN, *n* (%)	35 (11.2)	5 (9.4)	30 (11.6)	0.65
Pleural seeding, *n* (%)	33 (10.6)	6 (11.3)	27 (10.4)	0.85
Liver, *n* (%)	33 (10.6)	2 (3.8)	31 (12.0)	0.077
Peritoneal seeding, *n* (%)	11 (3.5)	2 (3.8)	9 (3.5)	1.00
Brain, *n* (%)	8 (2.6)	1 (1.9)	7 (2.7)	1.00
Adrenal gland, *n* (%)	8 (2.6)	1 (1.9)	7 (2.7)	1.00

[a]Include both loco-regional recurrence and distant metastasis.
[b]Comparing recurrence at RLN LN between RLN LND (+) and RLN LND (-) groups.
LN: lymph node; LND: lymph node dissection; RLN: recurrent laryngeal nerve.

(60.7% vs 53.8%, $P = 0.439$) [21]. In the current study, we found no significant difference in the survival of patients for the surgery group, the NCRT group, or the entire study cohort, with and without RLN LND. However, in cRLN (+) patients, we observed a significant increase in survival among patients who received RLN LND compared with those who did not. Moreover, in subgroup analysis, patients with 'truly negative' RLN LN involvement confirmed by RLN LND exhibited the best survival. Although these findings may just reflect that current preoperative staging techniques are poor for proving if the RLN LN are really involved or not, our results suggest that, in terms of oncological efficacy, patients with pre-treatment radiological evidence of RLN LN involvement would benefit from RLN LND, and patients with 'truly negative' status of RLN LN confirmed by RLN LND exhibit the best survival. As for cRLN (-) patients, a prospective randomized study with a larger case number is mandatory to answer the question if a systematic RLN LND is clearly helpful and superior to its risk.

To identify predictors of RLN LN metastasis, Liu *et al.* [20] developed a nomogram model for patients with upfront surgery. In their study, tumour location, tumour size, subcarinal LN involvement and the diameter of RLN LN were independent risk factors. In another studies, RLN LN status before NCRT has been reported as the independent predictors of RLN LN metastasis [19]. On the other hand, Chao *et al.* [21] have reported that there was no significant risk factor associated with RLN LN metastasis in their study of patients with negative ycRLN status. In our study, LVI was the only clinicopathological factor that predicted RLN LN metastasis in the multivariable analysis (Supplementary Material, Table S3).

This study had some limitations that need to be addressed. First, because of its retrospective design, the decision to perform RLN LND was not randomized. Therefore, an inherent selection bias could not be totally excluded. Moreover, the technique was not standardized among all surgeons. The total lymph node number in our study was less than some series emphasizing radical nodal dissection [24]. Therefore, the role of RLN LND may be

under-estimated in our study. Second, small number of patients had confirmed initial RLN LN metastasis, it is statistically difficult to determine the actual significant predictors of RLN LN metastasis. Finally, a relatively small number of patients were included after dividing the cohort into surgery and NCRT groups.

In conclusion, RLN LND is not a significant prognostic factor in OSCC patients, regardless of whether they have undergone upfront surgery or received NCRT followed by surgery in the entire cohort. However, subgroup analysis demonstrated that RLN LND is associated with better survival in patients with pre-treatment radiological evidence of RLN LN involvement. A prospective randomized study with a larger case number is mandatory to answer the question if a systematic RLN LND is clearly helpful.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

Conflict of interest: none declared.

Data Availability Statement

All relevant data are within the manuscript and its supporting information files.

Author contributions

Chu-Pin Pai: Conceptualization; Formal analysis; Investigation; Writing—original draft. **Po-Kuei Hsu:** Conceptualization; Data curation; Investigation; Methodology; Project administration; Writing—review & editing. **Ling-I Chien:** Methodology; Resources. **Chien-Sheng Huang:** Conceptualization; Supervision. **Han-Shui Hsu:** Conceptualization; Supervision.

Reviewer information

Interactive CardioVascular and Thoracic Surgery thanks Mario Borin, Larry R Kaiser, Mohammad Behgam Shadmehr and the other anonymous reviewers for their contribution to the peer review process of this article.

REFERENCES

[1] Rice TW, Chen LQ, Hofstetter WL, Smithers BM, Rusch VW, Wijnhoven BP *et al.* Worldwide Esophageal Cancer Collaboration: pathologic staging data. Dis Esophagus 2016;29:724–33.

[2] Akiyama H, Tsurumaru M, Udagawa H, Kajiyama Y. Radical lymph node dissection for cancer of the thoracic esophagus. Ann Surg 1994;220:364–72.

[3] Fujita H, Sueyoshi S, Tanaka T, Fujii T, Toh U, Mine T *et al.* Optimal lymphadenectomy for squamous cell carcinoma in the thoracic esophagus: comparing the short- and long-term outcome among the four types of lymphadenectomy. World J Surg 2003;27:571–9.

[4] Kang CH, Kim YT, Jeon SH, Sung SW, Kim JH. Lymphadenectomy extent is closely related to long-term survival in esophageal cancer. Eur J Cardiothorac Surg 2007;31:154–60.

[5] Darling G. The role of lymphadenectomy in esophageal cancer. J Surg Oncol 2009;99:189–93.

[6] Koen Talsma A, Shapiro J, Looman CW, van Hagen P, Steyerberg EW, van der Gaast A *et al.*; CROSS Study Group. Lymph node retrieval during esophagectomy with and without neoadjuvant chemoradiotherapy: prognostic and therapeutic impact on survival. Ann Surg 2014;260:786–92.

[7] Shridhar R, Hoffe SE, Almhanna K, Weber JM, Chuong MD, Karl RC *et al.* Lymph node harvest in esophageal cancer after neoadjuvant chemoradiotherapy. Ann Surg Oncol 2013;20:3038–43.

[8] Ye T, Sun Y, Zhang Y, Zhang Y, Chen H. Three-field or two-field resection for thoracic esophageal cancer: a meta-analysis. Ann Thorac Surg 2013;96:1933–41.

[9] Koterazawa Y, Oshikiri T, Takiguchi G, Hasegawa H, Yamamoto M, Kanaji S *et al.* Prophylactic cervical lymph node dissection in thoracoscopic esophagectomy for esophageal cancer increases postoperative complications and does not improve survival. Ann Surg Oncol 2019;26:2899–904.

[10] Park SY, Kim DJ, Yu WS, Jung HS. Robot-assisted thoracoscopic esophagectomy with extensive mediastinal lymphadenectomy: experience with 114 consecutive patients with intrathoracic esophageal cancer. Dis Esophagus 2016;29:326–32.

[11] Taniyama Y, Miyata G, Kamei T, Nakano T, Abe S, Katsura K *et al.* Complications following recurrent laryngeal nerve lymph node dissection in oesophageal cancer surgery. Interact CardioVasc Thorac Surg 2015;20:41–6.

[12] Yu S, Lin J, Chen C, Lin J, Han Z, Lin W *et al.* Recurrent laryngeal nerve lymph node dissection may not be suitable for all early stage esophageal squamous cell carcinoma patients: an 8-year experience. J Thorac Dis 2016;8:2803–12.

[13] Park SY, Kim DJ, Son T, Lee YC, Lee CY, Lee JG *et al.* Extent of mediastinal lymphadenectomy and survival in superficial esophageal squamous cell carcinoma. J Gastrointest Surg 2017;21:1584–90.

[14] Japan Esophageal Society. Japanese Classification of Esophageal Cancer, 11th Edition: part I. Esophagus 2017;14:1–36.

[15] Lin CM, Tu CC, Yeh YC, Hsu PK, Chien LI, Huang CS *et al.* The prognostic impact of extracapsular lymph node involvement in esophageal squamous cell carcinoma. Ann Surg Oncol 2020;27:3071–82.

[16] Low DE, Alderson D, Cecconello I, Chang AC, Darling GE, D'journo XB *et al.* International Consensus on Standardization of Data Collection for Complications associated with esophagectomy: Esophagectomy Complications Consensus Group (ECCG). Ann Surg 2015;262:286–94.

[17] Kanemura T, Makino T, Miyazaki Y, Takahashi T, Kurokawa Y, Yamasaki M *et al.* Distribution patterns of metastases in recurrent laryngeal nerve lymph nodes in patients with squamous cell esophageal cancer. Dis Esophagus 2017;30:1–7.

[18] Park SY, Kim DJ, Do YW, Suh J, Lee S. The oncologic outcome of esophageal squamous cell carcinoma patients after robot-assisted thoracoscopic esophagectomy with total mediastinal lymphadenectomy. Ann Thorac Surg 2017;103:1151–7.

[19] Li ZG, Zhang XB, Wen YW, Liu YH, Chao YK. Incidence and predictors of unsuspected recurrent laryngeal nerve lymph node metastases after neoadjuvant chemoradiotherapy in patients with esophageal squamous cell carcinoma. World J Surg 2018;42:2485–92.

[20] Liu Y, Zou ZQ, Xiao J, Zhang M, Yuan L, Zhao XG. A nomogram prediction model for recurrent laryngeal nerve lymph node metastasis in thoracic oesophageal squamous cell carcinoma. J Thorac Dis 2019;11:2868–77.

[21] Chao YK, Chiu CH, Liu YH. Safety and oncological efficacy of bilateral recurrent laryngeal nerve lymph-node dissection after neoadjuvant chemoradiotherapy in esophageal squamous cell carcinoma: a propensity-matched analysis. Esophagus 2020;17:33–40.

[22] Koyanagi K, Igaki H, Iwabu J, Ochiai H, Tachimori Y. Recurrent laryngeal nerve paralysis after esophagectomy: respiratory complications and role of nerve reconstruction. Tohoku J Exp Med 2015;237:1–8.

[23] Oshikiri T, Takiguchi G, Hasegawa H, Yamamoto M, Kanaji S, Yamashita K *et al.* Postoperative recurrent laryngeal nerve palsy is associated with pneumonia in minimally invasive esophagectomy for esophageal cancer. Surg Endosc 2021;35:837–44.

[24] Otsuka K, Murakami M, Goto S, Ariyoshi T, Yamashita T, Saito A *et al.* Minimally invasive esophagectomy and radical lymph node dissection without recurrent laryngeal nerve paralysis. Surg Endosc 2020;34:2749–57.