#### RESEARCH



# Effectiveness of recurrent laryngeal nerve monitoring on nerve paralysis during open McKeown esophagectomy: a prospective, cohort study

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Received: 29 October 2024 / Accepted: 6 May 2025 © The Author(s) 2025

#### **Abstract**

**Background** Recurrent laryngeal nerve paralysis (RLNP) is a critical postoperative complication in esophagectomy. Intraoperative nerve monitoring (IONM) is a technique that can be used in high-risk surgeries to prevent, identify, and mitigate nerve damage. In this prospective study, we evaluated the feasibility and effectiveness of IONM in open McKeown esophagectomy for esophageal cancer.

**Methods** From December 2020 to September 2023, 88 patients diagnosed with esophageal cancer were enrolled to receive IONM for open McKeown esophagectomy at Cancer Center, Sun Yat-sen University. The primary outcome was the incidence of RLNP after extubation. The secondary outcomes were postoperative complications, number of dissected lymph nodes, length of hospital stay, ICU duration and number of deaths.

**Results** A total of 83 patients were included in the final analysis. The incidence of RLNP after extubation was 30.1%. The occurrence of postoperative pulmonary complications was 20.5%. The median hospital stays were 13 days. The incidence of anastomotic leakage was 13.3%. No in-hospital deaths were reported. Postoperative RLNP prolonged the length of hospital stay (P = 0.042).

**Conclusion** Our findings indicated that IONM could potentially be associated with a possible reduction in RLNP incidence following open McKeown esophagectomy for esophageal cancer. However, future research including well-designed randomized controlled trials may be beneficial to clarify these preliminary results.

Trial registration number ChiCTR2000029687

https://www.chictr.org.cn/showproj.html?proj=49103

 $\textbf{Keywords} \ \ Intraoperative \ nerve \ monitoring \cdot Recurrent \ laryngeal \ nerve \ paralysis \cdot Open \ McKeown \ esophagectomy \cdot Esophageal \ cancer$ 

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Published online: 14 May 2025

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#### Introduction

The lymph nodes along the bilateral recurrent laryngeal nerves (RLN) are considered nodal stations in esophageal cancer, with an incidence rate of 3.6% to 31.9% [1–3]. The high incidence rate of lymph node spread determines that total mediastinal lymphadenectomy must be carried out when esophagectomy is performed to improve prognosis and survival rate.

Recurrent laryngeal nerve paralysis (RLNP) is a complication that often occurs after RLN lymphadenectomy. The incidence of RLNP during esophagectomy for cancer varies depending on surgical approaches and expertise. The frequency of RLNP in conventional thoracotomy for esophageal cancer surgery was reported to range from 15 to 50%, while in thoracoscopic surgery, it ranged from 36 to 43% [4, 5]. A study [6] reported that the rate of RLNP was as high as 60% by laryngoscopy after esophageal cancer surgery, and most of them could recover within 12 months after surgery. RLNP may result in a motility disorder of the vocal cord muscles, causing hoarseness, aspiration, pneumonia, and sometimes life-threatening conditions [7, 8]. RLNP hindered recovery from surgery and negatively influenced postoperative survival [9].

The application of IONM technology in thyroid surgery has been widely recognized [10]. It is mainly used to monitor the integrity of laryngeal nerve function during operation to reduce the risk of RLNP. In recent years, IONM has also been applied in mediastinal lymphadenectomy in minimally invasive esophagectomy and has been found to improve the efficiency of mediastinal lymphadenectomy and reduce RLNP [11–15]. Among them, Zhao et al. showed that IONM could reduce RLNP (8.6% vs 21.3%, P = 0.032) and increase the number of lymph node dissection in minimally invasive Mckeown esophagectomy [15]. However, these studies had drawbacks such as small sample sizes, a predominance of minimally invasive surgical methods, and retrospective study designs. There may be differences in the incidence of RLNP between open esophagectomy and minimally invasive esophageal cancer surgery. Taniyama Y's study [5] showed that the probability of RLNP was different after minimally invasive esophagectomy and open esophagectomy. There is currently no prospective study on the use of IONM in monitoring RLNP during open McKeown esophagectomy for esophageal cancer.

We conducted a prospective, cohort study with a large sample size to evaluate the effectiveness of IONM in reducing the incidence of RLNP during open McKeown esophagectomy for esophageal cancer.

#### Methods

#### Study design

This prospective, single-center cohort study was conducted in compliance with the Declaration of Helsinki. Between December 2020 and September 2023, 83 patients in our center scheduled to undergo open McKeown esophagectomy for esophageal cancer under general anesthesia were enrolled. All surgeries were performed by the same surgical team. Although our study was a prospective cohort study, retrospective data from the same group of surgeons were collected and analyzed to support the current findings. The inclusion criteria were as follows: (I) patients aged from 18 to 70 years old with American Society of Anesthesiologists (ASA) I to III; (II) patients who were diagnosed with esophagus cancer scheduled to undergo open McKeown esophagectomy for esophageal cancer under general anesthesia. Exclusion criteria were: (I) patients who had a preoperative diagnosis of vocal cord paralysis; (II) refusal to sign the consent form; (III) patients with a history of myocardial infarction, severe/unstable angina, coronary artery bypass grafting, congestive heart failure, cerebrovascular accident (including transient ischemic attack), pulmonary embolism, or ongoing arrhythmia within the preceding 12 months of the study. All patients underwent the vocal cord function before the operation.

# **Anesthetic management**

After entering the operating room, the patients were monitored by an electrocardiogram, noninvasive blood pressure, pulse oximeter, TOF-watchSX muscle relaxant monitor and Narcotrend index. Before anesthesia induction, all patients received ultrasound-guided 7/8 or 8/9 thoracic epidural catheterization as postoperative analgesia to reduce postoperative pain's effect on cough and sputum excretion.

All patients received anesthesia induction with dexmedetomidine 0.5 ug/kg, target-controlled plasma infusion (TCI) propofol 4 ug/mL, sufentanil 0.3—0.5 μg/kg, and rocuronium 0.6 mg/kg. TCI propofol 2.5—4.5 ug/mL and remifentanil 0.05—0.5 ug/kg/min were used to maintain anesthesia during the operation. Anesthesia depth was kept at the Narcotrend index D2—E0 level. TOF-watchSX muscle relaxant monitor was used to control the amount of muscle relaxant and ensure that there was no influence of muscle relaxant during IONM. Sugammadex 2—4 mg/kg, a specific antagonist of rocuronium, was administered before RLN monitoring. After completing the IONM of thoracic surgery, intermittent rocuronium was resumed.



Patients were intubated with 8.0 mm ID, a Medtronic Nerve Integrity Monitor (NIM) TriVantage electromyography (EMG) (Jacksonville, FL, USA) with two probe electrodes above the airbag. The anesthesiologists confirmed by video laryngoscopy that the probe electrode was placed on the vocal cord. The right lung was isolated by blocking the right main bronchus with a 9.0 mm endobronchial blocker for one-lung ventilation (OLV). The correct position of the endobronchial blocker was confirmed with fiberoptic bronchoscopy.

#### **IONM** equipment and operation

When performing thoracotomy, surgeons needed sufficient muscle relaxants to reduce the chance of muscle bleeding and rib fracture. Sugammadex was used to antagonize the neuromuscular blockade before IONM to ensure that IONM was not affected by muscle relaxants. Before the IONM was performed, the T1% of muscle relaxation monitoring was returned to 50% or preoperative values to ensure that sugammadex had taken effect. IONM was performed with the NIM Response System 3.0 (Medtronic Inc., Jacksonville, FL, USA). As a neurostimulator, the NIM-eclipse monopolar bulb tip stimulator probe (Medtronic) was used. Before the RLN entered direct vision, the nerve stimulator was calibrated to 1.0 to 2.0 mA. After visual recognition of the RLN, the current was reduced to 0.3 to 0.5 mA and used for confirmation of the nerves' location and integrity.

IONM protocols were implemented in three sequential surgical phases: (1) initial RLN tracking during esophageal mobilization and tracheoesophageal groove lymphadenectomy, (2) continuous monitoring during high-risk dissection of the aortic arch and laryngeal RLN entry points, and (3) revalidation was performed after lymph node dissection. Targeted neural structures included the right RLN and the corners and distal ends of the left RLN. Post-lymphadenectomy reassessment confirmed preserved signal conduction in bilateral RLN pathways. Real-time EMG feedback served as the primary monitoring modality, with predetermined intervention thresholds: signal amplitude reductions > 50% prompted immediate surgical protocol adjustments, including traction force minimization, dissection plane modification and reduction of electrotome power. IONM was performed by senior surgeons, and it was thoroughly checked by anesthesiologists.

#### Surgical technique

Surgeons carefully separated the lower thoracic esophagus and surrounding tissues from the esophageal hiatus

using electrocautery of 60 mV and electrocoagulation of 60 mV, and cleaned the supradiaphragmatic lymph nodes. Then they lifted the lower thoracic segment of the esophagus, freed it from below to the level of the carina, and cut open the mediastinal pleura in front of the esophagus to clean the lymph nodes below the carina. They continued to separate the esophagus upwards to the level of the top of the chest. Next, they used electrocautery of 30 mV and electrocoagulation of 30 mV to complete the dissection of lymph nodes in the left corner area. The surrounding lymphoid adipose tissue (i.e., lymph nodes adjacent to the left recurrent laryngeal nerve) was swept up along the left RLN to the thoracic inlet, and the right RLN lymph nodes were swept at the level of the right subclavian artery. Finally, they cut open the pleura of the tracheal septum and cleaned the lymph nodes in front of the trachea. The surgery was completed by placing a closed drainage bottle through a chest tube in the sixth intercostal space at the front of the right rib and the ninth auxiliary space at the midaxillary line and then closing the chest.

## Postoperative management and outcomes

All patients received patients controlled epidural analgesia for three days. The postoperative epidural analgesic regimen consisted of a mixture of 0.15% ropivacaine 250 mL and 0.3—0.4 ug/mL sufentanil. The background was set to 2 mL/h with a bolus dose of 5 mL and a locking time of 15 min. RLNP was determined by observing the vocal cord activity of the patients with fiberoptic bronchoscopy in the recovery room within 30 min after extubation, and we videotaped the vocal cord activity of each patient. If the patient had abnormal vocal cord movement or hoarseness in the recovery room, fiberoptic bronchoscopy was performed again by the designated anesthesiologist on the first, third, and seventh postoperative days.

The primary outcome was the incidence of RLNP after extubation. The secondary outcomes were postoperative cardiopulmonary complications, anastomotic leak, number of dissected lymph nodes, length of hospital stay, ICU duration and number of deaths.

#### Definition

RLNP was defined as a diagnosis made within 30 min after extubation by an anesthesiologist with over 5 years of experience, which included vocal cord fixation and movement disorders. The affected side was carefully recorded, and the entire procedure was closely supervised by experienced endoscopists. Postoperative pulmonary complications were usually presented as a composite,



which then included possible fatal and nonfatal respiratory events of new-onset occurring in the postoperative period, including pneumonia, respiratory failure, second intubation and pulmonary atelectasis [16]. Pneumonia was defined as the attenuation of permeability on chest radiography with infection by any microorganism. Anastomotic leakage was defined as a clinical sign, such as the discharge of saliva or food from the cervical wound or drain and fistula formation at the anastomotic site, as observed by esophagography [5]. The effectiveness of IONM was defined and calculated according to Chan and Lo [17]: loss of IONM signal was defined as true positive (TP) when postoperative laryngoscopy confirmed RLNP and as false positive (FP) when vocal cord activity was good. When RLNP was diagnosed by postoperative laryngoscopy, an intact IONM signal was interpreted as a false negative (FN), whereas it was interpreted as a true negative (TN) when postoperative laryngoscopy results were normal. Sensitivity was calculated as TP/(TP + FN). The specificity was calculated as TN/(FP+TN). Positive predictive value (PPV) was calculated as TP/(TP + FP). The negative predictive value (NPV) was calculated as TN/(FN + TN).

#### Sample size

The incidence of RLNP after open McKeown esophagectomy without IONM was approximately 50% in other previous studies and data from the thoracic team at our hospital [6, 18, 19] and the incidence of RLNP after open McKeown esophagectomy was expected to decrease by 15% through IONM. This expectation was supported by our previous study involving 15 patients, where 5 patients experienced RLNP despite the use of IONM. The power was 0.8, and level  $\alpha$  was 0.05. Dropout was calculated as 10%, and the final required sample size was 83.

#### **Statistical analysis**

For continuous variables, data were presented as mean  $\pm$  SD or median (IQR [range]) depending on the distribution of the data, with between-group comparisons performed using independent t-tests or the Wilcoxon rank-sum test. For categorical variables, frequency/percentage was calculated, with group comparisons conducted via chi-square test or the Mann–Whitney U test. All statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). All statistical analyses were performed independently by the research group statisticians.

**Fig. 1** Flow of participants in the study

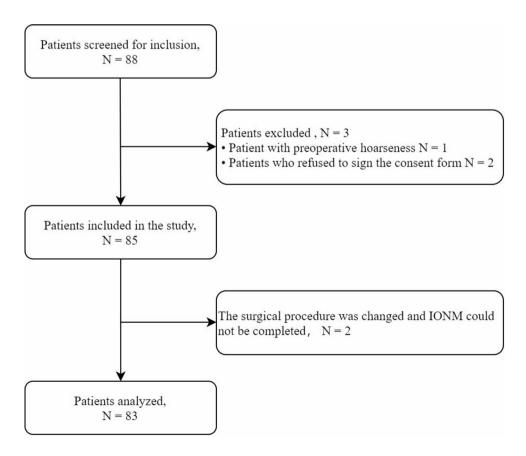




Table 1 Patient characteristics

	Total (N = 83)
Sex ratio (M: F)	70:13
Age, mean (SD), y	60.5 (6.5)
BMI, mean (SD), kg/m <sup>2</sup>	22.7 (3.1)
Smoking	61 (73.5)
Comorbidities	
Hypertension	27 (32.5)
History of pulmonary disease	9 (10.8)
Coronary heart disease	6 (7.2)
Diabetes	12 (14.5)
Preoperative Treatment	
No	63 (76.0)
Chemoradiotherapy	20 (24.0)
Location of neoplasm	
Upper	2 (2.4)
Middle	42 (50.1)
Lower	25 (30.1)
Middle and upper segments	2 (2.4)
Middle and lower segments	12 (14.5)
Tumor length, mean (SD), mm	33.2 (16.4)
Pathological	
SC	82 (98.8)
AC	0 (0.0)
Other	1 (1.2)
Tumor staging	
T-stage	
Tis	1 (1.2)
pT0	9 (10.8)
pT1	11 (13.3)
pT2	11 (13.3)
pT3	50 (60.2)
pT4	1 (1.2)
N-stage	
pN0	38 (45.8)
pN1	23 (27.7)
pN2	14 (16.7)
pN3	8 (9.6)

Note: Values were n (%) unless otherwise indicated

Abbreviation: AC adenocarcinoma, BMI body mass index, IQR interquartile range, SC squamous carcinoma, SD standard deviation

## Result

#### **Patients**

88 patients were evaluated for study participation. 85 patients who met the inclusion criteria were enlisted in the study. 2 out of 85 patients were excluded because the surgical procedure was changed and RLN monitoring could not be completed. The recruitment pathway was presented

Table 2 Operation characteristics

Value
110.0 (26.8)
276.8 (36.6)
233.3 (37.3)
96.0 (26.8)
17.0 (5.8)
100 (100—200)
400 (300—800)
14 (16.9)
2500 (2000—2500)
2025 (1550—2950)
23.5 (9.1)

Note: Values were n (%) unless otherwise indicated

Abbreviation: IQR interquartile range, SD standard deviation, OLV one-lung ventilation, IONM intraoperative nerve monitoring

Table 3 Postoperative outcome

	N = 83
	1v = 65
Cases with RLNP	
Right side	1 (1.2)
Left side	24 (28.9)
Both sides	0 (0)
No	58 (69.9)
Pulmonary complications	17 (20.5)
Respiratory failure	3 (3.6)
Second intubation	4 (4.8)
Pulmonary infection	4 (4.8)
Pulmonary atelectasis	9 (10.8)
Anastomosis leak	11 (13.3)
Cardiac complications	4 (4.8)
Chylothorax	1 (1.2)
Death	0 (0)
Other Complications	1 (1.2)
Length of ICU stay, median (IQR), day	1 (1—2)
Postoperative hospital stays, median (IQR), day	13 (10—19)

Note: Values were n (%) unless otherwise indicated

Abbreviation: ICU intensive care unit, IQR interquartile range, RLNP recurrent laryngeal nerve paralysis

in Fig. 1. The demographic characteristics of the patients were shown in Table 1.

## The surgical outcomes

The intraoperative characteristics of the patients were shown in Table 2. Duration of thoracotomy, anesthesia, operation, and OLV were  $110.0 \pm 26.8 \text{ min}, 276.8 \pm 36.6 \text{ min}$ 



min,  $233.3 \pm 37.3$  min and  $96.0 \pm 26.8$  min, respectively. After the antagonistic effect of sugammadex on muscle relaxation, nerve monitoring signals were successfully detected in all patients. The duration of IOMN was 17.0  $\pm 5.8$  min. No hypoxemia occurred during OLV.

# Results of postoperative RLNP and other complications

Data of postoperative outcomes for this study were shown in Table 3. The incidence of RLNP after extubation was 30.1%. It was worth noting that compared with the paralysis on the right side, the paralysis on the left side was more pronounced, accounting for 28.9%. There was only one case of right RLNP, which was mild (postoperative laryngoscopy showed that the right vocal cord activity was slightly worse), and no patient had bilateral RLNP. The vocal cord activity situation on the first day and seventh day after the operation was the same as after the operation. Postoperative pulmonary complications occurred in 17 patients, and the incidence was 20.5%. Among them were 3 cases of respiratory failure, 4 cases of second intubation, 4 cases of pulmonary

Table 4 Comparison of outcome between RLNP and non-RLNP

Outcomes	RLNP (n = 25)	Non-RLNP $(n = 58)$	P value
Pulmonary complica- tions	8 (32)	9 (15.5)	0.088
Anastomosis leak	4 (16)	7 (12.1)	0.628
Postoperative hospital stays, median (IQR), day	13 (12—23.5)	11.5 (9—17)	0.042*

Note: Values were n (%) unless otherwise indicated

Abbreviation: RLNP recurrent laryngeal nerve paralysis, IQR interquartile range

**Table 5** Comparison of postoperative outcomes with historical retrospective data

M Group Non-IONM Group $(n = 101)$	P value
0.1) 51 (50.5)	0.005*
18(14—24)	< 0.001*
2) 1(1—2)	0.946
3 (2.97)	0.795
5 (4.95)	0.982
11 (10.9)	0.140
8) 15 (14.9)	0.440
11 (10.9)	

Note: Values were n (%) unless otherwise indicated

Abbreviation: *IONM* intraoperative nerve monitoring, *RLNP* recurrent laryngeal nerve paralysis, *IQR* interquartile range, *ICU* intensive care unit

infection, and 9 cases of pulmonary atelectasis. 4 patients had postoperative cardiac complications (atrial fibrillation and abnormal elevation of myocardial enzymes), and 11 patients had an anastomotic leak, there was one other complication, referring to a tracheoesophageal fistula. The median duration of ICU stay was 1 day, and the median length of hospital stay was 13 days. Postoperative RLNP prolonged the length of hospital stay (P = 0.042), while it had no effects on postoperative pulmonary complications and postoperative anastomotic leakage (Table 4). No patient died during hospitalization.

# Intraoperative lymph node dissection and the results of IONM

Lymph node dissection was shown in Supplemental Table 1. All patients underwent bilateral lymph node dissection. The average number of bilateral harvested was 2.2 on the left, 2.7 on the right sides, and 4.2 on the left corner. The average number of total thoracic lymph nodes harvested was 28.4, The mean number of total lymph nodes harvested was 37.7. The sensitivity and specificity of IONM after lymph node dissection were shown in Supplemental Table 2.

# Comparison of postoperative outcomes with historical retrospective data.

We retrospectively collected data from 101 patients who underwent esophagectomy without IONM by the same surgical team between 2018 and 2020. The mean age of these patients was  $60.2 \pm 7.4$  years, with a male-to-female ratio of 76: 25, and the mean BMI was  $22.0 \pm 2.92$  kg/m². Detailed data were provided in Supplementary Table 3. A comparison of the main postoperative outcomes with historical retrospective data was presented in Table 5. The IONM group exhibited significantly lower RLNP rates (30.1% vs. 50.5%, P = 0.005) and shorter median hospital stays (13 [IQR



<sup>\*</sup>P value was significant

<sup>\*</sup>P value was significant

10–19] vs. 18 [14–24] days, P < 0.001). No significant differences were observed in ICU stay duration (median 1 [IQR 1–2] day, in both groups), respiratory failure, reintubation, pulmonary infection, or atelectasis (all P > 0.05).

## **Discussion**

This study was designed to explore the feasibility and efficacy of IONM in open esophagectomy. The core research results demonstrated that the incidence of RLNP was 30.1%, and the incidence of postoperative pulmonary complications was 20.5%. The median length of hospital stay was 13 days. When comparing patients with RLNP and those without RLNP, the incidence of pulmonary complications in the paralysis group was higher than that in the non-paralysis group (32% vs 15.5%), although it did not reach statistical significance. Meanwhile, postoperative RLNP prolonged the length of hospital stay (P = 0.042).

Previous studies had shown that open esophagectomy procedures may have a RLNP rate ranging from 15 to 50%, while minimally invasive surgeries, such as thoracoscopic or laparoscopic approaches, may see rates between 36 and 43% [4, 5]. Hence, the implementation of IONM held significant importance. In our study, we showed that the incidence of postoperative RLNP was 30.1% with intraoperative IONM. Yu sato's study reported that the incidence of RLNP under laryngoscopy after esophageal cancer surgery was as high as 60% in cases without IONM [6]. Meanwhile, we collected data from the same group of surgeons performing open McKeown esophagectomy for esophageal cancer without the use of IONM. Compared with data from these studies without IONM, the results of our study seemed substantial. However, in contrast to Zhong et al. study [20], we still had a higher paralysis rate after using IONM. To this, we made the following several explanations. Firstly, we defined RLNP as abnormal vocal cord activity observed in the recovery room after surgery. It was possible that other studies' RLNP rates were underestimated because the only indication for laryngoscopy was postoperative hoarseness, and many patients presenting with RLNP did not present with hoarseness. Therefore, RLNP may be missed when using clinical manifestations alone [6]. Secondly, our total number of chest lymph nodes harvested was more than theirs (number of total dissected lymph nodes:  $30.39 \pm 8.41$ ) [20], which may be more likely to lead to injury. Lastly, our surgeon had a high electric knife power (30 watts), which may have elevated the chance of RLNP.

Moreover, our study found that postoperative paralysis of the left vocal cord (28.9%) was greater than that of the right (1.2%), which indicated that the left RLN was more vulnerable to paralysis during surgery. Similar results were shown in Yu sato's study, in which 163 out of 178 patients (54.5%)

had left RLNP and 74 out of 178 patients (24.7%) had right RLNP [15, 21–23]. Possible explanations for this might be that when the right transthoracic approach was used, the anatomical relationship around the left RLN was complex, including the aortic arch, the main pulmonary artery, the left main bronchus, the thoracic duct, and the blood supply was rich. The anatomy of the left RLN outside the narrow gap between the trachea and the vertebrae was technically tricky. Another factor was that the left RLN was longer than the right RLN and was easily compromised by the dissection of the LN surrounding this nerve.

In our study, patients with RLNP had a higher incidence of pulmonary complications than those without RLNP (32% vs 15.5%), although it did not reach statistical significance. We believed that postoperative RLNP could lead to incomplete closure of the vocal cord, inability to effectively isolate the respiratory tract and digestive tract, and an inability to form negative pressure when coughing. This could result in cough weakness. Additionally, ineffective coughing could cause sputum accumulation, which significantly increased the risk of pulmonary infection. Previous studies had also shown that RLNP was a risk factor for aspiration pneumonia. Gockel I et al. study found that 33 (52.4%) of 63 patients with RLNP developed postoperative pneumonia compared with 90 (26.4%) of 341 patients without RLNP (P = 0.027), indicating that RLNP was significantly associated with an increased risk of postoperative pneumonia [7]. In one study, Hulscher JB found patients with RLNP had a higher rate of pulmonary complications (38.7% vs. 23.9%), resulting in a significantly higher rate of reintubation and a significantly longer duration of mechanical ventilation and ICU stay [24]. In the case of bilateral RLNP, asphyxia may even cause death. Fortunately, no patient in our study had bilateral RLNP.

Although we showed the feasibility and efficacy of IONM in open McKeown esophagectomy for esophageal cancer in this study, there were some limitations. First, this study was a single-arm, single-center clinical trial without a clinical control group, and the results could not be well evaluated. To address this, we supplemented our study with retrospective historical data as a control. Second, we did not perform long-term follow-up, so we could not further assess recovery from RLNP or distinguish whether the paralysis was temporary or permanent. Lastly, we did not perform IONM in the cervical lymph node dissection because repeated muscle relaxation and antagonism might lead to delayed postoperative recovery. Therefore, these results need to be verified by further randomized controlled trials.

Notwithstanding the limitations previously discussed, our findings demonstrated that the use of IONM in open McK-eown esophagectomy was a safe and beneficial approach for patients undergoing this procedure for esophageal carcinoma. This may provide valuable insights and hold potential



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significance for the design of future randomized controlled trials.

#### **Conclusions**

Our findings indicated that IONM could potentially be associated with a possible reduction in RLNP incidence following open McKeown esophagectomy for esophageal cancer. However, future research including well-designed randomized controlled trials may be beneficial to clarify these preliminary results.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s00423-025-03732-6.

Author contributions The authors declare no conflicts of interest.

Funding This work and the article processing fees were funded by the Sun Yat-Sen University Cancer Center Clinical Research 308 Program (2019-FXY-046), the Natural Science Foundation of Guangdong Province (2022 A1515012543), Guangdong Esophageal Cancer Institute Science and Technology Program (M202314), Science and Technology Projects in Guangzhou (202201010792) and the Lanzhou Science and Technology Development Guiding Plan Project (2020-ZD-48).

**Data availability** No datasets were generated or analysed during the current study.

#### **Declarations**

**Ethics and dissemination** Ethics approval was granted by the Clinical Research Ethics Committee of the Sun Yat-sen University Cancer Center. All participants will be required to provide written informed consent.

**Competing interests** The authors declare no competing interests.

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