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ORIGINAL ARTICLE

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Continuous vagal intraoperative neuromonitoring during video-assisted thoracoscopic surgery for left lung cancer: its efficacy in preventing permanent vocal cord paralysis

Yong Won Seong [a], Young Jun Chai [b], Jung-Man Lee [c], You Jung Ok [a], Se Jin Oh [a], Jae-Sung Choi [a] and Hyeon Jong Moon [a,*]

[a] Department of Thoracic and Cardiovascular Surgery, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul National University College of Medicine, Seoul, South Korea
[b] Department of Surgery, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul National University College of Medicine, Seoul, South Korea
[c] Department of Anesthesiology and Pain Medicine, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul National University College of Medicine, Seoul, South Korea

* Corresponding author. Department of Thoracic and Cardiovascular Surgery, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul National University College of Medicine, 20, Boramae-ro 5-gil, Dongjak-gu, Seoul 07061, South Korea. Tel: +82-010-3246-0299; e-mail: moon730@brmh.org (H. Jong Moon).

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Key question

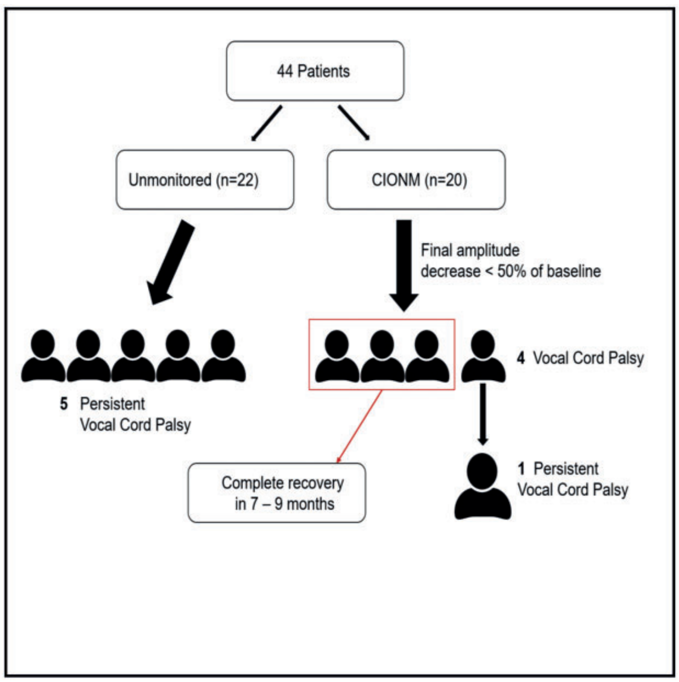
Can CIONM prevent permanent RLN injury during 4L LN dissection?

Key finding(s)

Three out of four RLN injury from CIONM group showed full recovery of vocal cord function.

Take-home message

CIONM may prevent permanent RLN injury during 4L LN dissection.



Abstract

OBJECTIVES: We investigated the safety and efficacy of continuous intraoperative neuromonitoring (CIONM) during video-assisted thoracoscopic lobectomy for left lung cancer in preventing recurrent laryngeal nerve injury.

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METHODS: From August 2015 to March 2020, 22 patients with left lung cancer without CIONM (unmonitored) and 20 patients with left lung cancer with CIONM underwent thoracoscopic lobectomy with complete mediastinal lymph node dissection including 4L dissection. Clinical outcomes from these 2 groups were compared.

RESULTS: The incidence of 4L metastasis was 7.14% (3 patients). There was no significant difference in the total number of dissected 4L lymph nodes between the 2 groups (3.23 ± 2.2 in the unmonitored group, 3.95 ± 2.0 in the CIONM group). CIONM was successful in all of the cases. There was no significant difference in the incidence of postoperative vocal cord palsy (22.7% in the unmonitored group, 20% in the CIONM group, $P = 1.000$). All of the 5 patients (100%) had permanent vocal cord palsy in the unmonitored group. Although statistically insignificant, 75% (3 patients) had total recovery of the vocal cord function, with only 1 patient remaining in permanent vocal cord palsy in the CIONM group.

CONCLUSIONS: CIONM was safe and efficient. CIONM might be helpful to avoid permanent vocal cord palsy by immediately warning the surgeon about impending nerve injury, so the surgeon can stop delivering further injury to the recurrent laryngeal nerve.

Keywords: Lung cancer • Thoracic surgery • Video-assisted • Lymph node excision • Vocal cord paralysis

ABBREVIATIONS

APS	Automated periodic stimulation
CIONM	Continuous intraoperative neuromonitoring
DL	Double lumen
ET	Endotracheal
IIONM	Intermittent intraoperative neuromonitoring
IONM	Intraoperative neuromonitoring
LLL	Left lower lobe
LN	Lymph node
MLND	Mediastinal lymph node dissection
NSCLC	Non-small-cell lung cancer
RLN	Recurrent laryngeal nerve
VATS	Video-assisted thoracoscopic surgery

INTRODUCTION

Lobectomy and mediastinal lymph node dissection (MLND) as surgical resection for primary lung cancer are considered the treatment of choice for non-small-cell lung cancer (NSCLC) [1]. Thoracoscopic lobectomy, also frequently referred to as video-assisted thoracoscopic surgery (VATS) lobectomy, has been gaining popularity and is currently considered one of the standard approaches for early-stage lung cancer with a shorter hospital stay, lesser morbidity and cost [2–5]. Recently, the clinical significance of left lower paratracheal (4L) lymph node (LN) dissection in left lung cancer has been emphasized by various reports [6–10]. However, thorough systematic LN dissection in radical surgery for primary lung cancer has been reported to frequently result in postoperative hoarseness due to recurrent laryngeal nerve (RLN) injury with the incidence varying from 6.0% to 31%, with notably worse outcomes with paralysis of the left RLN [11, 12]. Intraoperative neuromonitoring (IONM) is a technique of monitoring the RLN function at the vocal cord to detect and avoid intraoperative damage to RLN by detecting electromyography, which is generated and transferred from stimulating the RLN or the vagus nerve with a stimulating probe [13]. In the area of various head and neck surgeries, continuous IONM (CIONM) of the vagus nerve is reported to be superior to an intermittent IONM (IIONM) in real-time alerting and warning the surgeon of an impending nerve injury [14–16]. We analysed the safety and efficacy of the CIONM applied to left-side VATS lobectomy and MLND.

MATERIALS AND METHODS

Patients

From May 2018 to March 2020, a total of 20 patients were prospectively enrolled under written consent. This study was approved by the Institutional Review Board of Seoul Metropolitan Government-Seoul National University Boramae Medical Center (IRB No. 2017-43-083). These 20 patients were diagnosed with clinical stage I or II NSCLC by preoperative fine-needle aspiration/or transbronchial needle biopsy with routine lung cancer work-ups and then were planned to undergo a VATS lobectomy with MLND including complete dissection of 4L LN under CIONM (CIONM group). All the patients underwent preoperative work-ups for lung cancer, including positron emission tomography–computed tomography scan. Patients with the history of head and neck cancer or aortic disease were excluded. From August 2015 to February 2018, a total of 22 patients underwent VATS left-side lobectomy with MLND including complete dissection of 4L LN without monitoring (unmonitored group). The clinical outcomes of the unmonitored group and the CIONM group were statistically analysed.

Common surgical procedures in both groups

VATS lobectomy with MLND including complete dissection of 4L LN was performed under general anaesthesia with single-lung ventilation by a left-sided double-lumen (DL) endotracheal (ET) tube. All of the procedures were performed by a single surgeon who has enough experience in major thoracoscopic surgeries. The patient was placed in the right lateral decubitus position with mild lateral flexion. Three ports including one 4–5 cm utility incision at the 5th intercostal space were made. The utility incision was maintained with a wound protector (Alexis wound protector, Applied Medical, Inc.). We used a 10-mm 30° ultra-high definition thoracoscope (Synergy UHD4K™, Arthrex, Inc.). All of the vessels were individually dissected and divided using endoscopic staplers or hemoclips (Weck® Hem-o-lok®, Teleflex, Inc.). Bronchi were individually dissected and divided using endoscopic staplers as well. Complete systematic left LN dissection was performed using endoscopic Metzenbaum scissors and an energy device (HARMONIC ACE+®, ETHICON, Inc.). LN dissection was performed in an *en bloc* fashion, not to retrieve LNs in fragments as best as possible. Left lower paratracheal (4L) LN dissection started by initially identifying the vagus nerve at the posterior and upper hilum, then the left RLN was sharply dissected and identified. With the left main pulmonary artery gently pushed to the front with a peanut retractor, 4L LN was completely dissected from the left main pulmonary artery anteriorly, aortic arch and the left RLN superiorly, trachea medial inferiorly and descending aorta and oesophagus posteriorly. This dissection was performed mostly using the endoscopic Metzenbaum scissors and the energy device. This surgical principle did not change during the study period. A 24-Fr single soft chest tube drain was placed before the wound closure.

Concept of continuous intraoperative neuromonitoring

Anaesthesia. All the anaesthetic procedures were performed and supervised by a single expert anaesthesiologist. Initial intubation with a left-sided DL ET tube was followed by fibre-optic bronchoscopy to identify the proper place for the electrode. Then, the DL tube was retrieved out of the patient and cleansed, and then, an adhesive electrode was attached to the DL tube at a proper level. After attaching the electrode, the second intubation with the DL tube was performed, and the final location of the ET tube and the electrode was confirmed by the anaesthesiologist. Every intubation was performed under video-laryngoscopy in order not to give any damage to the vocal cords. Although there are single-lumen ET tubes with integrated electrodes commercially available, we decided to use our method in order to obtain the best location of the electrode and the DL tube for both adequate signal detection and single-lung ventilation. Rocuronium (10 mg) was hourly administered for muscle relaxation until the surgeon requested to stop the muscle relaxation at least 30 min before the CIONM.

Equipment settings and continuous intraoperative neuromonitoring procedures. We used the NIM Response 3.0 system (Medtronic, Jacksonville, FL, USA), 230 mm ball tip monopolar stimulating probe (Medtronic, Jacksonville, FL, USA) for IIONM and automated periodic stimulation (APS) probes (2 or 3 mm, Medtronic, Jacksonville, FL, USA) for CIONM. The event threshold was set at 100 mV and the stimulus current at 1 mA, with a frequency of 4 Hz for the IIONM. The stimulus frequency was only different, 1 Hz for the CIONM. In the first patient, 50% decrease in amplitude from baseline or 10% increase in latency from baseline.

After completion of lobectomy and retrieval of the specimen, the left vagus nerve overlying the lateral surface of the aortic arch (proximal to the bifurcation of the left RLN) was dissected circumferentially for 1–2 cm. A soft, rubber APS clipping probe was applied to the dissected vagus nerve using endoscopic forceps. The baseline amplitude of the CIONM was set before beginning the 4L LN dissection. When the left RLN was not easily identified after the beginning of the 4L LN dissection, the 230-mm ball tip monopolar stimulating probe was used to identify the location and the course of the left RLN. Complete dissection of the 4L LN was carefully performed after the identification of the left RLN as described above. The systematic dissection of stations 5, 6, 7, 9L, 10L, 11L and 12L was performed after completing the 4L dissection. When the alarm from the monitor was triggered, dissection of the 4L station was suspended for 20 min and during this suspension, dissection of stations 7, 9L, 10L, 11L and 12L was performed. Dissection of the 4L was restarted and continued when the amplitude recovered or did not recover after 20 min. The APS clipping probe was removed and the CIONM was stopped when the complete dissection of the 4L was completed. The APS probes and a schematic concept of the CIONM are shown in Fig. 1. A surgical view of the procedure of CIONM is shown in Fig. 2.

Intraoperative checklist and postoperative management and follow-up. During CIONM, we recorded events of haemodynamic instability, time spent for dissection of the vagus nerve and application of the APS (min), baseline amplitude (mV), number of adverse events, amplitude just before the removal of the APS (mV) and possible mechanism of the injury. Routine postoperative management for VATS lobectomy was applied to the patient. The chest tube was removed when the daily drainage amount was <200 ml, and then, the patient was discharged the next day. Indirect laryngoscopic evaluation by an experienced otolaryngologist was performed 1 week after discharge. For patients with identified vocal cord paralysis, vocal cord function was regularly monitored by laryngoscopic examination until full recovery was achieved. Vocal cord paralysis lasting longer than 1 year was defined as persistent vocal cord paralysis.

Statistical analysis

All statistical analysis was conducted using SPSS Statistics, version 20.0 (SPSS, Inc., Chicago, IL, USA). Data were expressed as a mean ± standard error. Assumption of normality in distribution of the continuous variables was assessed by *Q*–*Q* plots. Comparisons of the variables were performed using Pearson's Chi-square test, Fisher's exact test and Student's *t*-test. When minimum expected cell size was <5, Fisher's exact test was selected for comparing categorical variables.

RESULTS

CIONM was successfully done in every patient in the monitored group without any case of failure. All the intubations were carefully and meticulously performed by a single expert anaesthesiologist with the aid of the video-laryngoscope, and there were no cases of vocal cord damage during the anaesthesia, although there were 2 intubations for each patient. Patient characteristics and clinical outcomes are shown in Table 1. There were some cases of APS probe dislocation during monitoring, but it was easy to reattach the probe to the nerve. It took about 30–40 min for performing the CIONM during the 4L LN dissection. There was no significant difference between most of the clinical outcomes, but days of chest tube drainage were shorter in the monitored group and the average operation time was significantly longer in the monitored group, due to the additional procedure of CIONM. The incidence of metastatic 4L LN was 3 (7.1%) in all of the 42 patients. The incidence of immediate postoperative left vocal cord paralysis was not significantly different between the 2 groups.

In the monitored group, there were 4 patients with alarm events from decreased monitoring amplitude below 50% of the baseline. The cause of the amplitude decrease at the moment

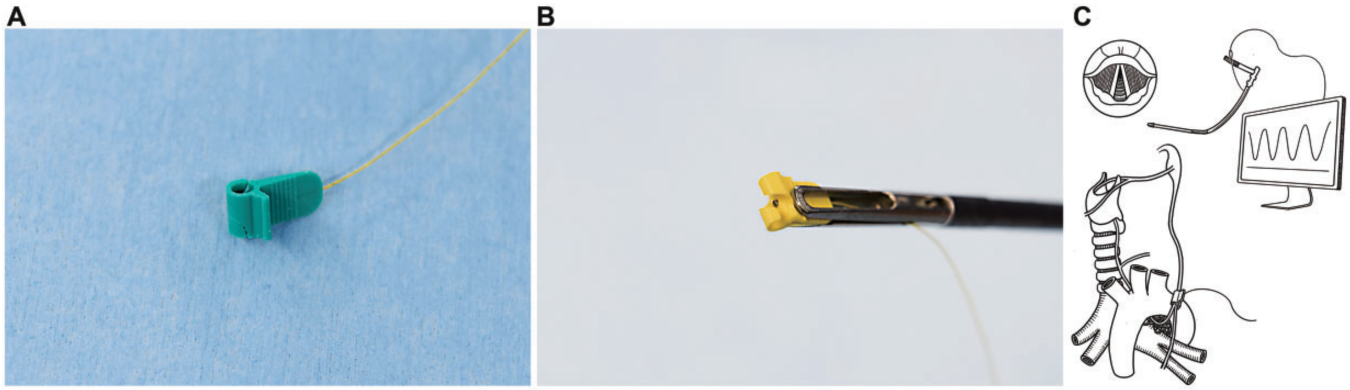

Figure 1: (**A**) A green 3-mm APS probe. (**B**) A yellow 2-mm APS probe opened by a 5-mm endoscopic atraumatic forceps. (**C**) A drawing of the schematic concept of continuous intraoperative neuromonitoring.

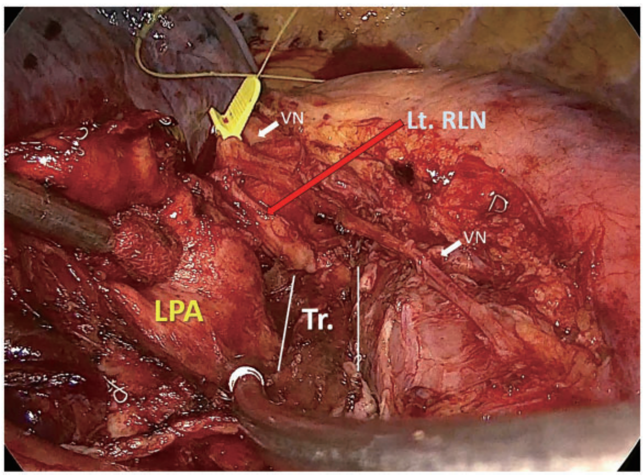

Figure 2: A surgical view of the continuous intraoperative neuromonitoring after finishing video-assisted thoracoscopic surgery left upper lobectomy and mediastinal lymph node dissection including 4L lymph nodes. A 2-mm yellow APS probe is properly placed at the left vagus nerve laterally to the aortic arch. LPA: left pulmonary artery; VN: vagus nerve (short arrows); Tr.: trachea; Lt. RLN: left recurrent laryngeal nerve (long arrow).

was a thermal injury from the ultrasonic energy device in all of the 4 cases. These 4 patients revealed left vocal cord paralysis from laryngoscopy postoperatively. However, 3 (15% of the monitored group) of these patients were able to obtain full recovery of the left vocal cord function during the follow-up period, and only 1 patient (5% of the monitored group) remained with persistent vocal cord paralysis. Although clinically insignificant, there was only 1 case of persistent palsy (5%) in the monitored group compared with 5 (22.7%) in the unmonitored group ($P = 0.060$).

Regarding the 4L LN metastases, all 3 cases were histologically adenocarcinoma with 2 cases of cancer located at the left lower lobe (LLL). There were 2 cases of multi-station N2 disease. However, there were no cases of LN metastasis at station 5 and station 6 from all of the 3 positive 4L cases.

Table 1: Patient characteristics and clinical outcomes

	Unmonitored ($n = 22$)	CIONM ($n = 20$)	*P*-Value
Age, mean ± SD	66.4 ± 7.4	61.0 ± 10.7	0.062
Male gender, *n* (%)	16 (72.7)	13 (65.0)	0.741
BMI, mean ± SD	24.9 ± 3.6	24.1 ± 4.2	0.446
Chest tube days, mean ± SD	6.32 ± 3.1	4.35 ± 1.8	0.019
24-h drain amount (ml), mean ± SD	579.3 ± 398.3	410.7 ± 183.2	0.091
Histology			0.744
Adenocarcinoma	12	13	
Squamous cell carcinoma	6	5	
Large cell carcinoma	1	0	
Others	3	2	
Operation time (min), mean ± SD	186.1 ± 54.7	237.5 ± 73.1	0.013
Tumour size (cm), mean ± SD	3.61 ± 1.9	2.66 ± 1.2	0.067
pN stage			0.625
pN0	17	13	
pN1	2	2	
pN2	3	5	
Number of dissected LNs, mean ± SD	27.9 ± 8.2	27.5 ± 8.7	0.878
Number of dissected 4L LNs, mean ± SD	3.23 ± 2.1	3.95 ± 2.0	0.264
4L metastasis, *n* (%)	2 (9.1)	1 (5.0)	>0.999
CIONM			
Success, *n* (%)		20 (100)	
Total CIONM time (min), mean ± SD		34.0 ± 12.1	
Time for vagus dissection (min), mean ± SD		6.30 ± 3.5	
Initial baseline amplitude (μV), mean ± SD		983.1 ± 531.2	
Final amplitude (μV), mean ± SD		771.4 ± 472.1	
Amp. decrease below 50%, *n* (%)		4 (20.0)	
Vocal cord injury			
Total number, *n* (%)	5 (22.7)	4 (20)	
Type of injury[a]	Unknown	All thermal[a]	
Transient (total recovery), *n* (%)	0	3 (15.0)	0.060
Persistent, *n* (%)	5 (22.7)	1 (5.0)	

[a]At the moment of the alarm sound provided the information of injury.
BMI: Body mass index; CIONM: continuous intraoperative neuromonitoring; LN: lymph node; SD: standard deviation.

DISCUSSION

Complete surgical resection is the preferred treatment of early-stage NSCLC. Prognosis after surgical resection is reported to be associated with the total number of dissected LNs [17, 18]. Guidelines from the National Comprehensive Cancer Network (NCCN) and the European Society of Thoracic Surgeons (ESTS) both have recommended complete systematic LN dissection with at least 3 N2 LN stations dissected [19, 20]. However, there still are no rigid specifications on the LN stations that should be dissected, and surgical practice still somewhat depends on the surgeons' experience.

Regarding the left side lung, Riquet [21] reported in his study of the pulmonary lymphatic system that the left lower paratracheal (4L) LNs played an essential role in the left bronchial-recurrent LN chain, an important lymphatic pathway of the left lung. Recently, the clinical significance of 4L LN dissection in left lung cancer has been getting more attention from many investigators with better prognosis after dissection of 4L LNs [6–10]. Wang *et al.* [10] reported that 4L dissection group had significantly better survival than the 4L undissected group (5-year disease-free survival (DFS), 54.8% vs 42.7%, $P = 0.0376$). Fang *et al.* [9] reported that 4L metastasis was the independent risk factor for poor prognosis in left side NSCLC. Recently, Yang *et al.* [6] reported that patients with 4L LN dissection revealed a significantly better 5-year overall survival rate than those without (72.9% vs 62.3%, $P = 0.002$), and 4L LN dissection was an independent risk factor for overall survival ($HR = 0.678$, $P = 0.006$). However, Zhao *et al.* [6] reported that 4L LN dissection could only bring survival benefit to patients with stage II or above, indicating that 4L LN dissection may be unnecessary for early-stage left-sided NSCLC. Deng *et al.* [7] investigated the pattern of LN metastasis in patients with clinical IA peripheral NSCLC, revealing that for NSCLC $\leq$2 cm in the LLL, there was no LN metastasis in the upper LN stations (stations 4L, 5 and 6), indicating that dissection of these upper LN stations may be unnecessary in these tumours. Outcomes from our data also follow these results from previous studies. Three cases with 4L metastasis all had tumour size $\geq$3.0 cm (8.5-cm LLL and 4.8-cm left upper lobe in the unmonitored group and 3.4 cm LLL in the CIONM group). Regarding the incidence of 4L metastasis, it varied from 11.9% to 20.9% from the previous studies [6, 8–10]. Our data revealed an incidence of 7.1% (3 cases).

Station 4L LN dissection for left lung cancer is more difficult than right paratracheal LN dissection for right lung cancer. This difficulty originates from the anatomic difference of the Left lower paratracheal area caused by the aortic arch and especially the left RLN routing nearby [10]. The proportion of VATS approaches varied from 20.7% to 62.8% in previous studies [6, 8]. Filaire *et al.* [12] reported postoperative vocal cord dysfunction with an incidence of 31% after left lung resection for cancer, which can lead to dramatic pulmonary complications. Zumtobel *et al.* [22] reported reduced quality of life in patients with unilateral vocal cord paralysis after thoracic surgery.

In the area of the head and neck surgery, there has been old controversy about whether to routinely dissect and identify the RLN or not during thyroidectomy. Chiang *et al.* reported excellent clinical results with the overall incidence of temporary/permanent vocal cord palsy 5.1% and 0.9% respectively, recommending routine identification of RLN during thyroid surgery. To prevent injury to the RLN during thyroidectomy, the IONM technique was developed and applied. The earliest IONM technique was the IIONM technique by intermittently stimulating the proximal vagus or proximal RLN [23, 24]. This IIONM provided information on the functional integrity of the RLN which contributed to the protection of the RLN. However, IIONM had crucial limitations. First, the information of the RLN was able to be obtained only during the direct stimulation of the nerve. Second, the direct stimulation applied distal to the injury site of the RLN can result in a 'normal' IONM signal, which is a false negative result [16]. To overcome these limitations, the technique of CIONM using APS of the proximal vagus nerve was introduced [25, 26]. Ulmer *et al.* [26] first introduced this technique using a flexible cuff, but this earlier cuff was opened by pulling two 4-0 monocryl sutures, which was relatively not easy to handle and almost impossible to be used in minimally invasive surgery. Schneider *et al.* [15] later introduced a refined and detailed technique of CIONM with excellent clinical outcomes using commercially available equipment, which we also used in our study. This commercially available APS probe had a line long enough to be put in the thoracic cavity through various port sites. One of the 2 clamping handles of the flexible APS probe was very short as shown in Fig. 1A, which was actually not ideal for endoscopic manipulation, but we managed to handle it without difficulty as shown in Fig. 1B.

Regarding IONM for surgery for lung cancer, Zhao *et al.* reported a technique of IONM for surgery for left lung cancer. The technique was IIONM, and they reported that IIONM of RLN to be a safe and effective method for identifying the Lt. RLN [27]. However, there had been no reports regarding CIONM for surgery for lung cancer.

We established a technique of VATS CIONM of the left vagus nerve for surgery for lung cancer. The time needed for dissection of the left vagus was around 6 min from our series, <10 min. Total CIONM time in our series was around 34 min, and during this period, we mainly dissected 4L and 5 LNs around the Lt. RNL. Dislocation of the APS probe from the Lt. vagus nerve sometimes happened, but we did not record this dislocation as events because the relocation of the APS probe could be very easily done.

Limitations

There are some limitations in our study. This is a single-centre retrospective study with a small number of patients. This study is also not a randomized trial, not free from selection bias. Further prospective, randomized study with a larger number of cases would be helpful in clarifying and validating our clinical outcomes.

CONCLUSION

CIONM of the Lt. vagus nerve was a safe and effective procedure that can provide real-time information of imminent RLN injury during 4L LN dissection. This real-time information can enable surgeons to immediately stop delivering further damage to the RLN, which may prevent persistent RLN injury.

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Conflict of interest: none declared.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Author contributions

Yong Won Seong: Conceptualization; Data curation; Formal analysis; Methodology; Visualization; Writing—original draft; Writing—review & editing. **Young Jun Chai:** Conceptualization; Data curation; Methodology. **Jung-Man Lee:** Conceptualization; Investigation; Methodology. **You Jung Ok:** Data curation; Formal analysis; Investigation; Methodology. **Se Jin Oh:** Conceptualization; Investigation; Methodology. **Jae-Sung Choi:** Formal analysis; Investigation; Methodology. **Hyeon Jong Moon:** Conceptualization; Data curation; Funding acquisition; Methodology; Supervision; Writing—review & editing.

Reviewer information

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