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ORIGINAL ARTICLE

Usefulness of intraoperative nerve monitoring in esophageal cancer surgery in predicting recurrent laryngeal nerve palsy and its severity

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Abstract

Background Recurrent laryngeal nerve (RLN) palsy is a critical postoperative complication in esophageal cancer surgery. However, intraoperative prediction of its occurrence and severity is difficult. In this prospective study, we evaluated the usefulness of intraoperative nerve monitoring (IONM) in predicting RLN palsy and its severity.

Methods Twenty patients who underwent subtotal esophagectomy with 3-field lymph node dissection were enrolled. Intraoperative electromyography (EMG) amplitudes of the vocal cords were measured by IONM at RLN and vagus nerve (VN) stimulation. Comparison was made between the vocal cords with RLN palsy and those without palsy and additionally between the vocal cords with transient RLN palsy and those with persistent palsy.

Results Among 40 vocal cords in 20 patients, 26 were intact and 14 were paralyzed. Seven had transient, six had permanent palsy. The mean EMG amplitude of intact vocal cords was significantly larger than that of paralyzed ones at VN (506 ± 498 μV vs. 258 ± 226 μV, $p = 0.022$) and RLN stimulation (642 ± 530 μV vs. 400 ± 308 μV, $p = 0.038$). The cut-off value for postoperative palsy were 419 μV [positive predictive value (PPV): 48.0%, negative predictive value (NPV): 84.6%] at VN and 673 μV (PPV: 44.8%, NPV: 90.9%) at RLN stimulation. The mean EMG amplitude of persistently paralyzed vocal cords tended to be small, compared with that of recovered ones at both VN (168 ± 173 μV vs. 336 ± 266 μV, $p = 0.11$) and RLN (244 ± 223 μV vs. 536 ± 344 μV, $p = 0.051$) stimulation.

Conclusion The absolute EMG amplitude of IONM might be helpful to predict the occurrence and severity of RLN palsy after esophageal surgery although the predictive value is low.

Keywords Esophageal cancer · Recurrent laryngeal nerve · Vagus nerve · Intraoperative nerve monitor · Palsy

Introduction

Recurrent laryngeal nerve (RLN) palsy which is mainly caused by RLN lymph node dissection is one of the most frequent postoperative complications in esophageal cancer surgery [1]. The occurrence is reported as high as 14–24% [1–3]. Although most paresis recovers in several months, some remain permanently [4] and can be a cause of aspiration, potentially resulting in pulmonary complications such as aspiration pneumonitis [1]. If the paresis, especially severe ones were predicted in early stage, subsequent diseases could be prevented by careful postoperative treatment. However, since the palsy can occur even when the nerves were preserved carefully, it is difficult to foresee its occurrence and severity intraoperatively [5].

Intraoperative nerve monitor (IONM) is used to detect activities of the muscles by stimulating the corresponding nerves during the operation. This system has mostly been used to detect RLN in thyroid surgery which also might cause the paresis after dissection. Some researchers advocate that the use of IONM enabled easier detection of RLNs and decreased the risks of their paresis [6–9]. IONM could be

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also useful in confirming the integrity of the nerves or the severity of their paresis.

In esophageal cancer surgery, although the incidence of RLN palsy is more common due to the thorough dissection of RLN lymph nodes from the neck to the thorax [1], the usefulness of IONM has not been established. Thus, we conducted this prospective study to investigate the usefulness of IONM in detecting the integrity of RLNs and predicting the severity of the paresis in esophageal cancer surgery.

Materials and methods

Patients

From March 2013 and April 2015, 150 patients underwent esophagectomy for thoracic esophageal cancer in our hospital. During this study period, this prospective study enrolled 20 patients who were indicated for subtotal esophagectomy with 3-field lymph node dissection and matched the following criteria; (1) under age 80, (2) with clinical tumor depth T1b or more, any clinical lymph node stage and without clinical distant metastasis except for metastasis in cervical, common hepatic or splenic lymph nodes, (3) without major organ dysfunction, (4) without preoperative vocal cord paresis. In our hospital, 3- field lymphadenectomy is planned for patients with the upper thoracic esophageal cancer or patients with the middle or lower thoracic esophageal cancer with cervical or RLN lymph node metastasis [10].

Preoperative chemotherapy was performed for patients with clinical stage IB, II, III or IV without distant organ metastasis. Preoperative chemoradiotherapy was provided to patients with deeply invading thoracic esophageal cancers without distant organ metastasis or to those with tumors in the upper third of the thoracic esophagus with infiltration into the cervical esophagus [11, 12].

This prospective study was approved by the appropriate institutional review boards of Osaka University Hospital. The registered UMIN code is 000022706.

Surgical procedure

Our surgical treatment strategy was described previously [13, 14]. Three-field lymph node dissection is consisted of cervical, thoracic and abdominal lymph node dissection. First, mediastinal lymph node dissection is performed in left lateral position through right thoracotomy or prone position through video-assisted thoracotomy. Subsequently, neck and abdominal lymph node dissection is performed in supine position. The right and left RLNs were revealed from the levels of the right subclavian artery and the aortic arch, respectively. The nodal chains along the nerves were dissected up to the level of inferior thyroidal artery. The anastomosis was performed through neck incision.

Intraoperative neuromonitoring

After the thoracic procedure, the patients were intubated with dedicated electrode embedded tracheal tube (NIM3.0® EMG tube; Medtronic, Minneapolis, Minnesota, USA) in supine position. An airway scope was used to make sure the electrodes were in contact with the vocal codes. The electrode impedance and impedance balance were confirmed to be less than 5 kΩ and 1 kΩ, respectively. After lymph node dissection was completed, RLNs and vagus nerves (VNs) were monitored with NIM3.0® (Medtronic). The VNs, proximal RLNs close to the branching from the VN, were stimulated with dedicated monopolar electrode with 1.0 mA of intensity which is considered safe and adequate suprathreshold stimulation [15]. Stimulation at distal RLNs close to the larynx was also conducted in 12 patients. Constant 4 stimulations per second, with the duration of 100 μS for each, were administered. The amplitude of electromyogram (EMG) of the vocal cords, which is defined as the deflection of EMG wave between the lowest and highest points, was used as a quantitative parameter of the muscle response. When the nerves were stimulated, the effect of muscle relaxant is reversed with Rocuronium Bromide.

Postoperative evaluation

One day after the extubation, the motility of the vocal cords was evaluated with laryngoscope. When the vocal cord palsy was diagnosed, regular observation was made 3 weeks, 2, 4 and 6 months after the operation.

Statistical analysis

One-sided parametric statistical test (t test) was employed to compare the EMG amplitudes of the two groups. To determine the threshold values which predict the postoperative paralysis, receiver operating characteristics (ROC) curve analysis was performed [16]. A p value of <0.05 was considered statistically significant. JMP software, version 11 (SAS Institute, Inc., Cary, NC, USA) was used for all statistical analyses.

Results

Patient characteristics

The mean age of the patients was 65.3 ± 7.3. 16 were male and 4 were female. The tumors were located in upper, middle and lower thoracic esophagus in 7, 8 and 5 patients,

respectively. Clinical Stages I, II, III and IV were diagnosed in 2, 1, 16 and 1 patients, respectively. All patients underwent three-field lymphadenectomy. RLN lymph node metastasis was suspected in 14 patients preoperatively. Preoperative chemotherapy and chemoradiotherapy were introduced in 14 and three patients, respectively. Open and video-assisted thoracotomy were performed in 16 and 4 patients, respectively.

Table 1 Intraoperative nerve monitor (IONM) findings and postoperative outcomes

IONM and postoperative findings	
Mean potential amplitudes of the vagus nerves (VNs) (μV)	
Right	581 ± 534
Left	247 ± 209
Mean potential amplitudes of the proximal RLNs (μV)	
Right	680 ± 577
Left	434 ± 314
Postoperative vocal cord paresis (number of patients)	
Non	7
Right side paresis alone	1
Left side paresis alone	11
Bilateral side paresis	1
Postoperative vocal cord paresis (number of nerves)	
Without paresis	26
With paresis	14
Severity of the paresis (number of patients)	
Transient	7
Persistent	5
Severity of the paresis (number of nerves)	
Transient	7
Persistent	6
Mean duration of the paresis (month)	3.9 ± 1.8

Postoperative outcomes and intraoperative EMG data

The RLN palsy was diagnosed in 13 patients after surgery. Among them, left, right and bilateral palsy were found in 11, 1 and 1 patients, respectively (Table 1). The mean EMG amplitude on the right side in response to the VN stimulation was larger than that on the left side (581 ± 534 μV vs. 247 ± 209 μV). Similarly, the mean amplitudes on the right after stimulating proximal RLNs was larger than those on the left (680 ± 577 μV vs. 434 ± 314 μV). The postoperative laryngoscopy revealed 26 intact and 14 paralytic vocal cords (Table 1). The mean EMG amplitude of intact vocal cords was significantly larger than that of paralyzed vocal cords at VN stimulation (506 ± 498 μV vs. 258 ± 226 μV, $p = 0.022$, Fig. 1a). Similarly, the mean amplitude of intact vocal cords was also significantly larger than that of paralyzed vocal cords at proximal RLN stimulation (642 ± 530 μV vs. 400 ± 308 μV, $p = 0.038$, Fig. 1b). On the other hand, there was no significant difference in EMG values between intact and paralyzed vocal cords at distal RLN stimulation (639 ± 540 μV vs. 568 ± 370 μV, $p = 0.36$, Fig. 1c).

The threshold values to predict postoperative palsy

The cut-off value of EMG amplitude to predict RLN palsy at VN stimulation was 419 μV [positive predictive value (PPV): 48.0%, negative predictive value (NPV) 84.6%, sensitivity 85.7%, specificity 45.8% and accuracy 68.8%] with area under the curve (AUC) 0.63 (Fig. 2a). The cutoff value at proximal RLNs stimulation was 673 μV (PPV 44.8%,

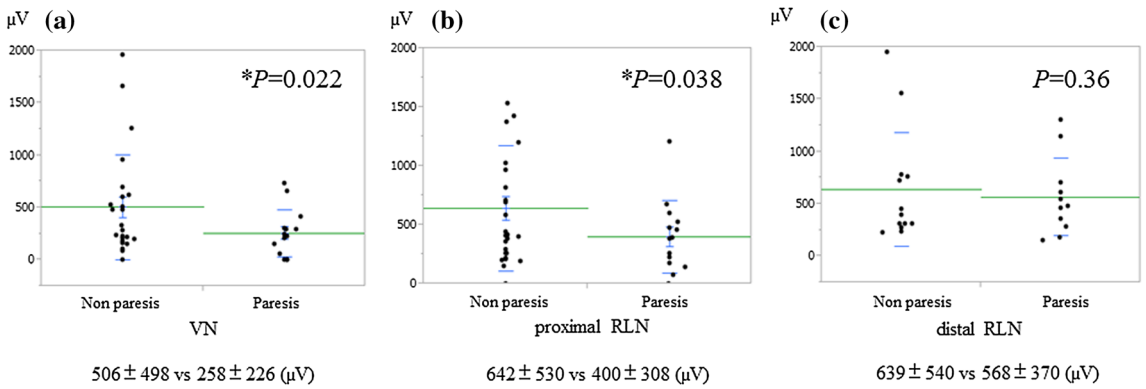

Fig. 1 Comparison of intraoperative potential amplitudes of electromyography (EMG) between vocal cords with paresis and without paresis. **a** Vagus nerve (VN) stimulation. **b** Proximal recurrent laryngeal nerve (RLN) stimulation. **c** Distal recurrent laryngeal nerve (RLN) stimulation. The mean EMG amplitude of paralyzed vocal cords were significantly lower than that of non-paralyzed ones at VN and at proximal RLN stimulation. No significant difference was shown between vocal cords without paresis and with paresis at distal RLN stimulation

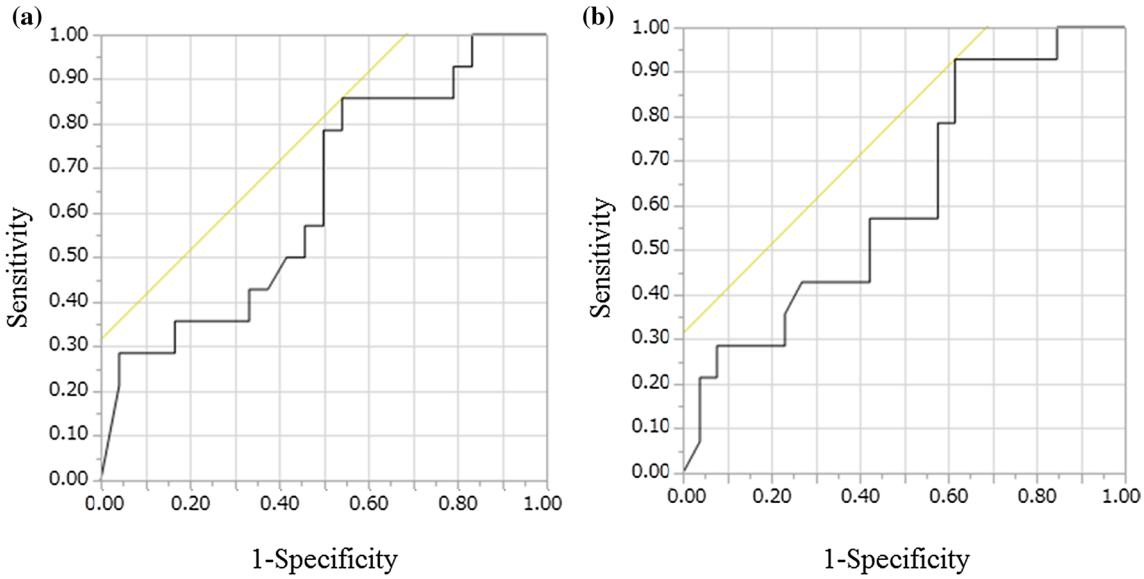

Fig. 2 Receiver operating characteristics (ROC) curve analysis in predicting postoperative vocal cord palsy. **a** The threshold: 419 μV at VN stimulation. **b** The threshold: 673 μV at proximal RLN stimulation

NPV 90.9%, sensitivity 92.9%, specificity 38.5% and accuracy 57.5%) with AUC 0.62 (Fig. 2b).

The relationship between intraoperative EMG values and the duration of the postoperative laryngeal palsy

Among 13 patients with postoperative vocal cord palsy, 7 patients restored the vocal cord motility, 5 patients had persistent palsy and 1 patient was lost due to death caused by pneumonia during the 6 months of follow-up period. Among 13 paralyzed vocal cords of 12 patients, 7 vocal cords had transient paresis and 6 vocal cords had persistent paresis (Table 1). The mean intraoperative amplitude at VN stimulation tended to be smaller in vocal cords with persistent paresis than vocal cords with transient paresis, although the difference was not statistically significant (168 ± 173 μV vs. 336 ± 266 μV, $p = 0.11$, Fig. 3a). Similarly, the mean EMG amplitude at proximal RLN stimulation also tended to be smaller in vocal cords with persistent paresis than vocal cords with transient paresis (244 ± 223 μV vs. 536 ± 344 μV, $p = 0.051$, Fig. 3b).

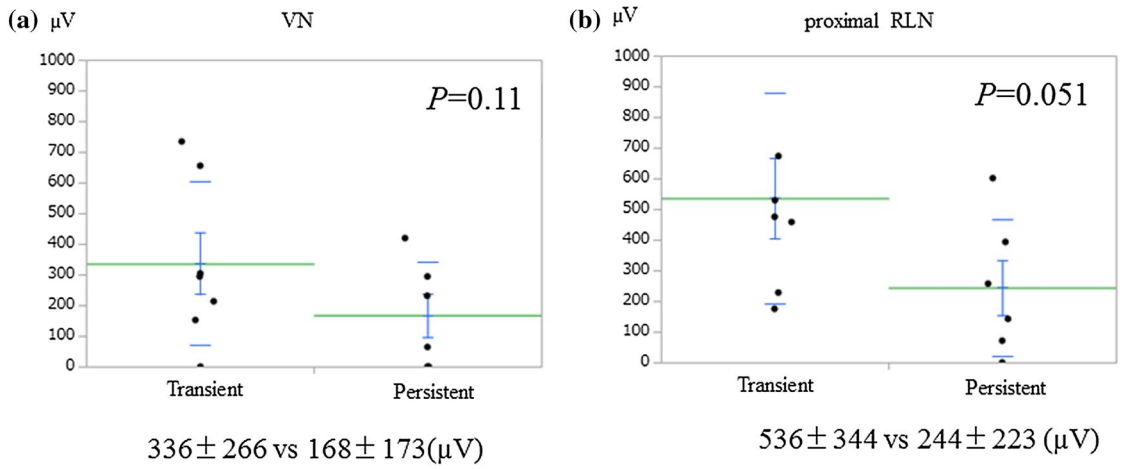

Fig. 3 Comparison of intraoperative potential amplitudes of electromyography (EMG) between vocal cords with transient paresis and permanent paresis. **a** VN stimulation. **b** Proximal RLN stimulation. The mean EMG amplitude of the vocal cords with persistent paresis tended to be lower than that of the vocal cords with transient paresis at VN and at proximal RLN stimulation

Evaluation of EMG difference between proximal RLN and distal RLN

In 12 patients, EMG amplitude at proximal and distal RLN stimulation were measured. The mean amplitude difference (distal RLN-proximal RLN) of vocal cords without paresis, with transient paresis and with persistent paresis were 2 ± 101 μV, 99 ± 376 μV and 240 ± 219 μV, respectively (Fig. 4). The RLN amplitude difference was significantly larger in vocal cords with persistent paresis than those without paresis ($p = 0.022$).

Discussion

There are several researches which suggested the usefulness of IONM in detecting the RLNs in esophageal surgery [17–20]. The RLN detection with IONM is expected to decrease the occurrence of nerve injury [17, 18, 20]. On the other hand, diagnostic value of IONM on nerve paralysis is not fully evaluated. In this study, we focused on the usefulness of intraoperative EMG amplitude in predicting postoperative RLN paralysis or its severity.

In our results, the paralyzed vocal cords showed significantly smaller mean EMG amplitude than non-paralyzed ones at VN or proximal RLN stimulation. This is consistent with past reports of thyroid surgery [4, 21–23]. However, the thresholds predicting the paresis presented low

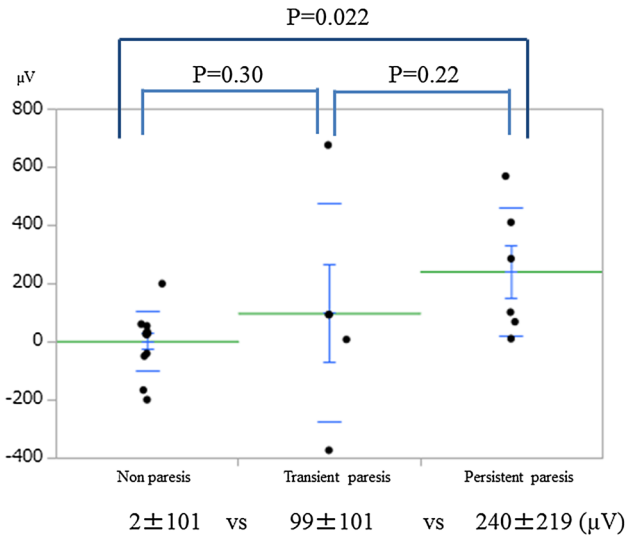

Fig. 4 Comparison of EMG amplitude difference (distal RLN-proximal RLN) between vocal cords without paresis, with transient paresis and with permanent paresis. The difference was significantly larger in vocal cords with persistent paresis than those without paresis ($p = 0.022$). There was no significant difference between those without paresis and with transient paresis ($p = 0.30$), nor between those with transient paresis and persistent paresis ($p = 0.22$)

PPV (48.0% at VN stimulation and 44.8% at proximal RLN stimulation), although NPV were high (84.6% at VN stimulation and 90.9% at proximal RLN stimulation) in this study. The low PPV reported in previous studies of thyroid surgery (12–48%) [4, 22, 24] is suggested as the cause of a large number of false positive cases [22]. It means that even if the nerves are tested positive to have palsy intraoperatively, nearly half of the vocal cords are found to be intact.

This low PPV for RLN palsy can be due to early recovery of the palsy [23] or disposition of the tracheal tube. However, the main reason is suggested to be the considerable difference of EMG amplitude between individuals [23, 25]. Caragacianu et al. reported that the EMG value of vocal cord with postoperative normal function ranged from 247 to 3607 μV in 125 patients who underwent thyroid surgery [25]. Our data also showed wide range of EMG amplitude of normal vocal cord (506 ± 498 μV at VN stimulation and 642 ± 530 μV at RLN stimulation). The difference of baseline EMG amplitude might make the palsy prediction difficult.

To reduce the influence of the baseline diversity, the difference or ratio of individual EMG amplitude might be useful. Wu et al. presented preferable PPV (100%) for RLN palsy using EMG amplitude reduction rate (a percentage of reduced EMG amplitude of proximal RLN in relation to that of distal RLN) [23]. In our study, we evaluated the difference of EMG amplitude between distal and proximal RLN. The vocal cords with permanent paresis showed significantly larger distal-proximal EMG difference compared with those without paresis. In terms of predicting RLN palsy, these parameters such as the difference or the reduction rate may be useful rather than the absolute value of EMG. Further studies are needed to establish a more reliable parameter for predicting RLN palsy.

In the subgroup analysis, vocal cords with permanent palsy tended to show smaller EMG amplitude and larger EMG difference than those with transient palsy. This result is similar to that of a previous study in thyroid surgery, which showed greater reduction rate of EMG amplitude in cases with permanent palsy [21]. It implies that when the nerve damage is more critical, the decrease in EMG amplitude becomes greater. Intraoperative EMG finding might be helpful to discriminate permanent palsy from transient palsy.

There is no agreement about whether VN or RLN stimulation is the better predictor of RLN palsy. Several studies in thyroid surgery suggest that VN stimulation better predicts RLN palsy than RLN stimulation due to less possibilities of false negative reaction [4, 21]. In our study, at the both VN and proximal RLN stimulation, paralyzed vocal cords showed significantly lower mean EMG amplitude than intact ones. Since proximal RLN close to the VN bifurcation was stimulated, there might have been fewer chances to cause false negative reaction. Further investigation is needed to

decide which nerve to be stimulated for accurate prediction of the palsy.

There are several limitations in this study. First, the sample size is small in single institute. Second, IONM was performed in the supine position only at the end of the operation. In esophageal cancer, IONM is generally used during thoracic procedure to identify RLN and prevent RLN palsy during thoracic procedure. However, the main purpose of this study was to investigate whether the EMG data by IONM is associated with the occurrence and severity of RLN palsy. Thus, we performed IONM at the end of the operation, because RLN palsy seems to occur not only during thoracic procedure but also during cervical lymphadenectomy.

In conclusion, IONM might be helpful to predict the occurrence and severity of RLN palsy in esophageal cancer surgery. However, PPV was not very high using absolute EMG amplitude. Further studies are needed to establish ideal parameters in predicting occurrence and severity of RLN palsy.

Compliance with ethical standards

Conflict of interest There is no conflict of interest to disclose.

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