*Laryngoscope Investigative Otolaryngology*
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# Continuous Intraoperative Neuromonitoring for Thyroid Cancer Surgery: A Prospective Study

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**Objective:** We evaluated the utility of continuous intraoperative neuromonitoring (CIONM) during surgery for thyroid cancer (TC) in an educational university hospital.

**Study Design:** Prospective observational study.

**Methods:** During the period April 2016 to March 2017, 43 patients who underwent standardized surgery with CIONM were prospectively included: 5 men and 38 women, 24–87 years old (median 52 years); 23 lobectomies and 20 total thyroidectomies with node dissection were conducted. Thirty-six operations were performed by a supervising surgeon, and seven were performed by trainees.

**Results:** Temporal vocal cord paresis (VCP) was identified in 9 of 63 nerves at risk (14.3%) by postoperative laryngoscopy. VCP was not related to clinical factors including the surgeon's experience or the severe nerve stress demonstrated by CIONM. A significant relation only between VCP and loss of signal (LOS) was demonstrated ($P = .002$). The recovery of VCP was rapid (<1 month) in patients with global injury even when LOS was demonstrated, but was prolonged in patients demonstrating obvious segmental nerve injury and LOS.

**Conclusion:** The present standard protocol of CIONM was useful to some extent to protect prolonged VCP, but not enough to detect every nerve stress causing VCP during TC surgery. On the other hand, CIONM is a promising method that could contribute surgical education at training hospitals enabling the instant confirmation of the procedure safely.

**Key Words:** Continuous intraoperative neuromonitoring, recurrent laryngeal nerve injury, thyroid cancer surgery, surgical education.

**Levels of Evidence:** 3b

## INTRODUCTION

According to the National Cancer Registry, 19,000 people in Japan are suffering from thyroid cancer (TC).[1] The number of patients with TC has been increasing due to the improvement of diagnostic methods as well as the widespread use of mass screening.[2] The pathological form of >90% of TC tumors is differentiated TC, which usually has a favorable prognosis after treatment. The 10-year survival rate for TC exceeds 90% in patients with localized disease. Radioisotope iodine therapy after a total thyroidectomy could also contribute extending the survival of TC patients with advanced disease. A safe and effective surgery is thus the most important initial step to treat patients with TC.

The standard surgery for TC is not a highly invasive procedure, and most patients are able to return to daily life soon after the operation. However, one of the main complications of thyroid surgery is recurrent laryngeal nerve (RLN) palsy, which impairs the quality of patients' lives largely with hoarseness and incidental aspiration. The reported frequency of RLN palsy after thyroid surgery for TC is <3%, but the patients' awareness of subjective symptoms was as often as 6%–10% of the examined cases,[3,4] and the reported rates of vocal cord paresis (VCP) were in the same range when a postoperative laryngeal examination was routinely conducted.[5,6] The rate of VCP might be higher after TC surgery with the dissection of any node(s) involved.

Intraoperative neuromonitoring (IONM) is used to detect the motion of vocal cords by a sensor attached to the endotracheal tube when the RLN is appropriately stimulated in the operative field. The use of IONM was recommended to avoid unaware nerve injury.[7,8] Continuous IONM (CIONM) enables the real-time monitoring of the RLN by placing a probe on the vagus nerve. With the CIONM technique, surgeons may be able to detect nerve stress before injury.[9,10] We conducted the present study to prospectively evaluate the objective clinical utility of CIONM for avoiding RLN injury during surgery for TC at an educational university hospital. Our study's primary

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Editor's Note: This Manuscript was accepted for publication 24 June 2019.

Funding and Conflict of Interest: None declared.

Meeting information: Part of this study was presented in the 51st Annual Meeting of Japan Association of Thyroid Surgeons (October 25, 2018 in Yokohama, Japan) and the 80th Congress of the Japan Surgical Association (November 24, 2018 in Tokyo, Japan).

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**DOI: 10.1002/lio2.290**

end point was the objective VCP observed by postoperative laryngoscopy. We determined the correlations between VCP and the nerve stress observed by CIONM, the surgeon's experience, and the patients' clinical factors.

## PATIENTS AND METHODS

### *Patients*

During the period from April 2016 to March 2017, consecutive patients who underwent initial surgery for primary TC were prospectively included in this study. Patients with a tumor <4 cm and with sufficient organ functions for surgery were included. The following patients were excluded: those <20 years of age; with a tumor with gross extrathyroidal extension; showing RLN paresis preoperatively; with clinical disease in the central nervous system; with arrhythmia; or with a history of neck surgery.

### *Thyroid Surgery*

The standardized surgical procedures were as follows. Under general anesthesia with an endotracheal tube (NIM TriVantage, Medtronic Japan, Tokyo), a 5–10 cm collar incision was made and strap muscles were divided in the middle to approach the thyroid gland. After the ipsilateral vagus nerve was identified between the carotid artery and internal jugular vein, the vocal cord movement response (more than 500 μV) was confirmed with an IONM system (NIM response 2.0/3.0 system: Medtronic Japan) by stimulating the nerve via a handheld probe with 1 mA.[11] An automatic periodic stimulation (APS) electrode for CIONM (APS probe: Medtronic Japan) was then placed on the vagus nerve and the patient's baseline amplitude and latency values were determined, and the waveforms were continuously monitored during the surgery with 1 mA stimulation per a second.[12] In case baseline amplitude showed less than 500 μV, electrode was replaced and the endotracheal tube was readjusted until confirming the baseline amplitude of more than 500 μV.

RLN was identified with the assistance of the handheld probe by mobilizing the thyroid lobe. Operative procedure was temporarily paused and all retracted organs in the operative field were returned to the original position when the surgeon was alerted to severe nerve stress by the CIONM system as described below section, until the waveform returned to baseline. After the APS electrode was detached and operative field was washed with warm saline and hemostasis was confirmed, the final reaction of the vocal cord(s) was determined by stimulating both the vagus nerve and the RLN(s).

### *Assessment of Nerve Function during Operation*

During the surgery, the CIONM system alerted the surgeon about nerve stress when the signal reached a >50% reduction in the amplitude and/or a >10% increase in the latency from the baseline. We defined "severe combined event (sCE)" as when a >50% reduction in the amplitude and a >10% increase in the latency were simultaneously observed as described previously.[12] The term "loss of signal (LOS)" denoted the total loss of nerve stimulation response.[13] The point of nerve injury was determined by using handheld probe in case LOS was identified. When the point of injury was obviously identified, it was classified as a "segmental" nerve injury. A "global" nerve injury was judged when no clear point of nerve injury was found.

### *Assessment of Postoperative Vocal Cord(s) Function*

Objective hoarseness on the second day after the surgery was evaluated by the patient's physician. A laryngeal fiberscope examination was conducted at 3–6 days postsurgery. When the vocal cord movement was abnormal, the degree of abnormality was recorded either as the vocal cord was "fixed (no movement)" or "unfixed (move weakly than the other side)." Repeated examinations were performed at 2 weeks later and then monthly thereafter.

### *Statistical Analyses*

The correlations between the clinical factors and objective VCP were analyzed by Fishers' exact test. Statistical significance was set at $P < .05$.

### *Ethics*

This study was approved by the Ethics Committee of Osaka City University Hospital (#3717).

## RESULTS

Of the 54 patients who met the inclusion criteria, one patient was excluded due to age <20 years, one patient due to congestive heart failure, and two patients due to nonavailability of the IONM system. Among the 50 patients who underwent surgery with IONM, the CIONM system was not available in three, and a postoperative laryngeal examination was not performed in four patients. We thus analyzed a final total of 43 patients. Overall, 63 nerves at risk in the 43 patients were successfully identified and monitored by CIONM. No patient with aberrant RLN anatomy was identified. No patient needed a change in the surgical strategy.

The 43 patients were 5 men and 38 women, aged 24–87 (median 52) years old. Forty-one papillary thyroid carcinomas, one follicular carcinoma, and one medullary carcinoma were treated. The patients' clinical characteristics and pathological TNM classification are shown in Table I. Thirty-six of the surgeries were performed by a supervising surgeons (N.O., S.N., or S.K.), and the other seven surgeries were performed by trainees supervised by N.O. Eleven left lobectomies, 12 right lobectomies, and 20 total thyroidectomies were performed with 19 ipsilateral central, 21 ipsilateral central + lateral, and three bilateral central + lateral zone node dissections. The operation times were 77–313 minutes (median 143 minutes, average 151.3 ± 48.5 minutes) with blood loss of 5–130 g (median 20 g, average 25.7 ± 25.6 g). One patient required reoperation on the same day as the initial operation, due to postoperative bleeding.

TABLE I.
Patient Characteristics.

| Characteristic | Category | No. | Vocal Cord Paresis | *P* Value |
| --- | --- | --- | --- | --- |
| Age (yr) | 24–87 (median 52) | | | |
| | <55 | 20 | 3 | .467 |
| | ≥55 | 23 | 6 | |
| Gender | | | | |
| | Men | 5 | 2 | .277 |
| | Women | 38 | 7 | |
| BMI (kg/m$^2$) | 18–34 (median 23) | | | |
| | <25 | 36 | 6 | .147 |
| | ≥25 | 7 | 3 | |
| Tumor histology | | | | |
| | Papillary | 41 | 8 | .379 |
| | Follicular | 1 | 0 | |
| | Medullary | 1 | 1 | |
| T-category* | | | | |
| | cT0-2 (pT0-2) | 27 (26) | 3 (3) | .058 |
| | cT3-4 (pT3-4) | 16 (17) | 6 (6) | (.122) |
| Extrathyroidal invasion | | | | |
| | No | 27 | 4 | .257 |
| | Yes | 16 | 5 | |
| Multiple lesions | | | | |
| | No | 36 | 7 | .624 |
| | Yes | 7 | 2 | |
| N-category* | | | | |
| | cN0 (pN0) | 28 (15) | 5 (2) | .696 |
| | cN1 (pN1) | 15 (28) | 4 (7) | (.723) |
| M-category* | | | | |
| | M0 | 39 | 7 | .188 |
| | M1 | 4 | 2 | |
| Operation | | | | |
| | Lobectomy | 23 | 3 | .263 |
| | Total thyroidectomy | 20 | 6 | |
| Node dissection† | | | | |
| | D1-hemi | 19 | 1 | 1.000 |
| | D2 | 21 | 8 | |
| | D3 | 3 | 0 | |
| Surgeon | | | | |
| | Supervisor | 36 | 8 | 1.000 |
| | Trainee | 7 | 1 | |
| sCE | | | | |
| | No | 40 | 7 | .106 |
| | Yes | 3 | 2 | |
| LOS | | | | |
| | No | 36 | 4 | .002 |
| | Yes | 7 | 5 | |

*TNM classification: based on UICC 7th edition.

†D1-hemi: ipsilateral central node dissection, D2: ipsilateral central and lateral node dissection, D3: bilateral central and lateral node dissection.

BMI = body mass index; LOS = loss of signal; sCE = severe combined event.

Objective VCP was observed in nine sides (14.3%) in nine different patients (20.9%). No significant correlation between VCP and any of the clinical factors was revealed. An sCE was recorded in three sides (4.8%) in three different patients (7.0%). In one of the patients with an sCE, transition to LOS was avoided by allowing a temporary pause in the procedure. In the other two patients, sCE progressed to LOS during the procedure; one patient needed shaving of the nerve (patient 5) and the other needed a sharp dissection with scissors (patient 63) to remove the primary tumor from the affected RLN. Both case demonstrated segmental nerve injury at the site of nerve dissection. In total, LOS was identified in seven sides (11.1%) in seven different patients (16.3%), and a significant correlation between LOS and VCP was demonstrated ($P = .002$).

In five patients, sCE did not precede LOS, including a patient (patient 9) with the thermal injury of a vagus nerve due to the vascular sealing device during node dissection. Point of nerve injury could not be identified in other four nerves with LOS, and were classified as global nerve injury. Objective VCP was confirmed by laryngoscopy in five patients with LOS, but it was also observed in four patients without any abnormal findings by CIONM. Recovery from VCP was confirmed within 1 month in these four patients who did not demonstrate LOS. In two other patients with LOS who showed global nerve injury, VCP also resolved rapidly (within 2 weeks). However, recovery was prolonged from 3 to 12 months in three patients with segmental nerve injury with LOS (patients 5, 9, and 63) (Table II).

## DISCUSSION

In this prospective study, the rate of VCP (9 of 63 nerves; 14.2%) observed was far more frequent than we had expected. There was no correlation between the incidence of VCP and any of the patients' characteristics or the surgeon/trainee experience level. It is possible that the rather high frequency of VCP might have been due to our aggressive procedure with over-reliance on the CIONM system. We had expected that each instance of nerve stress that did not reach an sCE would recover without causing VCP. However, LOS and VCP were not preceded by sCE in five and seven patients, respectively. We thus could not identify every instance of nerve stress before injury with the use of the CIONM system according to the recommended criteria during TC surgery.[11]

The reported causative events for RLN injury were most commonly traction of the RLN rather than with thermal or mechanical stress.[14] Nerve injuries showed graded severity before falling into complete LOS.[15] Our present observations indicated that the VCP that occurred in the present patient series was due mostly to the mild traction of an RLN during the operation. Procedures that are performed to rotate and retract the thyroid gland or to dissect lymph nodes around the nerve are unavoidable during TC surgery, and these procedures may repeatedly stretch the RLN. It is, thus, often difficult to recognize every RLN injury ahead of time by CIONM in TC surgery.[16] These mild RLN injuries may be prevented by taking stricter care of nerve stress demonstrated by CIONM, even when the nerve stress does not reach the point of an sCE. In addition, VCP was avoided in a case when normal APS

TABLE II.
Patients with Any Findings.

| # | sEX | sCE | LOS | Type of Nerve Injury | Vocal Cord Paresis (Month Persisted) | Hoarseness at Second Postoperative Day |
|---|---|---|---|---|---|---|
| 48 | 0 | – | + | Global | — | – |
| 13 | 0 | + | – | — | — | – |
| 72 | 0 | – | – | — | — | + |
| 3 | 2 | – | + | Global | — | + |
| 29 | 0 | – | – | — | Unfixed (1) | – |
| 66 | 1 | – | – | — | Unfixed (1) | – |
| 37 | 0 | – | + | Global | Unfixed (0.5) | – |
| 47 | 0 | – | + | Global | Fixed (0.5) | – |
| 41 | 2 | – | – | — | Fixed (1) | + |
| 68 | 1 | – | – | — | Unfixed (0.5) | + |
| 9 | 0* | – | + | Segmental | Fixed (3) | + |
| 5 | 2[†] | + | + | Segmental | Fixed (4) | + |
| 63 | 1[‡] | + | + | Segmental | Fixed (12) | + |

0 = no, 1 = minimal, 2 = gross.
*Thermal injury of the vagus nerve.
[†]Needed shaving.
[‡]Needed sharp dissection.
LOS = loss of signal; sCE = severe combined event; sEX = extrathyroidal extension at surgery.

signals could be obtained after sCE alert. In contrast, all three cases with prolonged VCP in the present study demonstrated both LOS and segmental nerve injury by unavoidable surgical maneuvers. LOS by segmental injury should be a strong indicator of serious nerve injury to cause prolonged VCP. These observations suggested the necessity of additional criteria besides amplitude and latency, for example, time length or number of time of the nerve stress, to prevent VCP during TC surgery.

In the present series, LOS was not found in four cases with VCP. All these VCP recovered within a month, suggesting minimal injury of the nerve caused partial paresis. Contrary, VCP was not found in two cases with LOS. In one case, LOS was due to the size mismatch of the endotracheal tube[11] after releasing compression of the thyroid mass. Another LOS without VCP was found after bilateral lateral node dissection, indicating the possible involvement of edema of the vagus nerve by long operation.[11]

CIONM was reported as a safe procedure.[10,17,18] Although the usefulness of IONM for decreasing the rate RLN palsy rate has not been established in prior studies, this was due mostly to the low incidence of RLN palsy.[19] IONM may have other advantages, including 1) minimizing the time to identify the RLN, 2) protecting against bilateral VCP,[20] 3) confirming the absence of RLN palsy immediately after the operation,[21] and 4) contributing to the decision-making regarding staged surgery for contralateral dissections.[22] We additionally observed that the rate of VCP was not different according to the surgeons' experience, suggesting the use of CIONM was useful for the instant confirmation of the procedure during the educational training of surgeons, benefiting both new surgeons and their supervising surgeons. Furthermore, demonstrations of the RLN-protection procedure with the assistance of CIONM are informative for new surgeons and medical students to understand surgical anatomy.

The use of IONM during TC surgery has been covered by public insurance in Japan, but the insurance coverage is not enough to cover all of the devices needed for IONM (ie, the handheld probe, endotracheal tube, and APS electrode). A limited use of this technique may be considered by the selection of appropriate patients, for example, those needing a bilateral procedure, a repeat operation, or surgery for a patient who already had RLN palsy in one side.[20] We recommend the routine use of CIONM in TC surgery training, not only to protect against RLN injury but also to establish safe procedures with objective measurements.

Our study has several limitations. First, the number of patients (n = 43) was limited and resulted in a number of abnormal events revealed by CIONM that was too small to analyze the correlation between sCEs and nerve injury. Second, we could not clearly demonstrate any potential benefits or harm of CIONM in contrast to IONM, due to the nonrandomized single-arm study design. Last, postoperative laryngoscopy was done on day 3–6 postop, which might have resulted in underestimation of shorter-lasting transient nerve events. A study of a larger number of patients and the accumulation of more precise data are necessary to establish the clinical utility of CIONM.

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