

ORIGINAL RESEARCH

Intraoperative neuromonitoring of the recurrent laryngeal nerve is indispensable during complete endoscopic radical resection of thyroid cancer: A retrospective study

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Abstract

Objective: Complete endoscopic radical resection of thyroid cancer, especially through the areolar approach, can achieve curative and acceptable cosmetic effects in patients with differentiated thyroid carcinoma. However, some inherent characteristics of endoscopic procedures hamper functional protection of the recurrent laryngeal nerve (RLN). Intraoperative neuromonitoring (IONM) is considered the most important accessory to protect the nerves during conventional radical thyroidectomy. This study aimed to evaluate the feasibility and necessity of IONM during complete endoscopic radical resection of thyroid cancer.

Methods: A total of 106 patients with differentiated thyroid carcinoma were enrolled in the study between February 2013 and April 2018. Based on the use of the IONM technique, all patients were divided into the IONM ($n = 54$) and non-IONM groups ($n = 52$). Overall, 66 RLNs were involved in the IONM group, and 61 RLNs were involved in the non-IONM group. The time and ratio of RLN identification and the number of transient and permanent RLN injuries between both groups were compared.

Results: Compared to the non-IONM group, the IONM group required less time for RLN identification (3.05 ± 1.58 vs. 9.36 ± 4.82 min, $p < .01$). The ratio of RLN identification in the IONM group was much higher than that in the non-IONM group (100.00% vs. 88.52%, $p = .01$). A significant difference was observed in RLN transient injury between the two groups (one case accounting for 1.51% in the IONM group vs. eight cases accounting for 13.11% in the non-IONM group; $p = .03$).

Conclusion: IONM significantly improved RLN identification and reduced transient RLN injuries during complete endoscopic radical resection.

Level of Evidence: 3b.

KEYWORDS

complete endoscopic radical resection of thyroid cancer, intraoperative neuromonitoring, recurrent laryngeal nerve, thyroid carcinoma

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1 | INTRODUCTION

The morbidity of thyroid carcinoma has been growing rapidly in the last 30 years.¹ Approximately, 95% of thyroid carcinomas are well differentiated; therefore, 90% of patients commonly have a favorable prognosis with more than 10-year survival.² Young female individuals between 15 and 24 years of age are susceptible, accounting for 7.5%–10% of patients with thyroid carcinoma.³ Therefore, in addition to eradicating the disease, surgeons should pay attention to postoperative cosmetic outcomes when treating thyroid carcinoma, especially in young female patients.⁴

By gaining access to the thyroid gland through a remote non-cervical approach to avoid an unattractive scar in the neck, complete endoscopic radical resection of thyroid cancer could satisfy the demands of cosmetic outcomes and eradicating the disease in female patients who are concerned about their physical appearance. Various non-cervical approaches have been proposed by surgeons worldwide, such as the chest–breast, complete areola, axilla, axilla–breast, and oral approaches. Of these, the complete areola approach has significant advantages in terms of cosmetic effects because areola pigmentation can conceal skin scars.^{5,6} Moreover, with the appropriate visual direction similar to conventional operations, the complete areola approach allows surgeons to handle bilateral thyroid lobes easily and eradicate the inherent optic angle limitation of the axillary approach. Furthermore, this approach could eliminate wound contamination that could occur in the transoral approach and erase the possible scar hyperplasia in the sternum area associated with the chest–breast approach.⁷

Avoiding recurrent laryngeal nerve (RLN) injury in conventional thyroidectomy remains a challenge due to the anatomical complexity of the nerve. The incidence of RLN injuries ranges from 2% to 14%.⁸ Endoscopic high-definition and magnified visualizations may facilitate RLN identification, whereas unilateral fluoroscopy may lead to limitations. Since the 1970s, scholars have explored ways to reduce RLN injuries. In 1966, Shedd et al. first described techniques that could identify electrical stimulation of the RLN using endolaryngeal balloon spirometry in an experimental thyroid surgery.⁹ Intraoperative neuromonitoring (IONM) using endotracheal tube-based surface electrodes was described in 1996.^{10,11} Owing to their ease of use and installation, suitability for purpose, convenience, non-invasiveness, and capacity for larger areas of contact with target muscles, endotracheal tube-based surface electrodes have become the commonly used standard technique for IONM.^{10,12} IONM plays a role in RLN protection in many ways, such as initial nerve identification and separation, course mapping, bifurcation distinction, injury detection, repair support, and functional prognosis evaluation. However, few convincing comments on this promising technique for the complete endoscopic radical resection of thyroid cancer have been reported. There is continuing debate over its capability to protect the RLN. Initial meta-analyses and prospective or retrospective studies have reported that it failed to reduce the rate of persistent or transient paralysis of the RLN.^{13,14} However, two recent meta-analyses supported the application of IONM in reducing both transient and permanent RLN injuries during

thyroidectomy, particularly in bilateral operations and reoperative cases.^{15,16} Generally, there is no need to dissect the central lymph node and expose the RLN during surgery in cases of benign thyroid tumors. Thus, IONM is not typically implemented in patients with benign thyroid tumors. Therefore, we chose patients with differentiated thyroid carcinoma to evaluate the feasibility and necessity of IONM administration for complete endoscopic radical resection of thyroid cancer.

2 | MATERIALS AND METHODS

2.1 | Patients

This retrospective study was performed based on the clinical data of 106 patients with differentiated thyroid carcinoma confirmed using preoperative fine-needle cytology (104 patients with papillary carcinomas and 2 patients with follicular carcinomas) from February 2013 to April 2018. The inclusion criteria were as follows: (1) age ≤ 45 years; (2) patients with confirmed differentiated thyroid carcinoma; and (3) patients who were able to provide written informed consent. The exclusion criteria were as follows: (1) the maximum diameter of the lesion >2 cm or the central group lymph nodes were apparently fused and fixed; (2) patients with concomitant hyperthyroidism; (3) previous history of neck surgery or irradiation; (4) obesity or coexisting brevicollis; and (5) patients with benign thyroid disease. All 106 patients underwent radical thyroidectomy (85 unilateral and 21 bilateral resections). They were divided into the IONM group ($n = 54$) and the non-IONM group ($n = 52$) according to their voluntary choice based on their financial situation. A total of 66 RLNs were involved in the IONM group, and 61 RLNs were involved in the non-IONM group. The study was approved by the Ethics Committee of the Fourth Medical Center of the Chinese PLA General Hospital (No. 2020023), and all patients provided written informed consent.

2.2 | Operative and IONM technique

The function of the vocal cords was evaluated and recorded preoperatively using fiberoptic laryngoscopic examination. The patient was placed in a supine position, with the legs separated and the neck hyperextended. A special endotracheal tube integrated with surface electrodes for general anesthesia and gaining electromyographic signals was accurately inserted between the vocal cords under direct vision (NIM TriVantage[®] EMG Tube, Medtronic, Jacksonville, FL, USA). The NIM-Neuro[™] 2.0 system (Medtronic) was used. A monopolar electrode and the interrupted stimulation technique at 1 mA, a 100 ms impulse duration, and 4 Hz frequency to stimulate the nerves. Mid- or short-effect non-depolarizing muscle relaxants at insufficient doses were adopted for anesthetic induction to ensure that the generation of electromyographic signals was not affected.

One 12-mm trocar and two 5-mm trocars were inserted for a 30° endoscope and dissecting instruments through three tiny incisions in the mammary areolas bilaterally, following a working space beneath

the superficial fascia with the outer edges of the bilateral sternocleidomastoid. The upper edge of the thyroid cartilage was developed using a blunt-tipped dilator with or without the aid of inflation fluid. The maintenance of the working space depended on CO₂ insufflation at 6–7 mmHg. After separation of the linea alba cervicalis and exposure of the thyroid lobe, the standard steps of IONM recommended by the International Neural Monitoring Study Group (INMSG) were started. A special endoscopic clamp was used as a nerve stimulator, covered by an insulating layer, except for its blunt tips, and integrated with IONM wires.

Four standardized steps were mandatory according to the guidelines of INMSG.^{17–19} The standard four-step method for IONM signal detection using a special stimulating clamp is presented in Figure 1. (1) V1 signal: the electromyographic signal was obtained by stimulating the carotid sheath with a 3 mA stimulating current before dissecting the RLN,²⁰ to detect the existence of a non-RLN, as well as to verify the efficacy of the equipment. (2) R1 signal: the electromyographic signal was obtained by stimulating the exposed RLN with a 1 mA current following mapping the nerve with a cross method of a 2 mA stimulating current at the level of the lower pole of the affected thyroid lobe. The waveform, amplitude, and latency of the electromyography (EMG) were identified and recorded as the baseline for further comparison. (3) R2 signal: the electromyographic signal was obtained by stimulating the most proximal portion of the RLN following the entire course of the nerve in the neck dissected through a 2 mA stimulating current mapping the course. Simultaneously, the affected thyroid lobe and central group of lymph nodes were removed. Dissection of the area adjacent to the entry point of the nerve was precautionary for nerve injury due to the involvement of Berry's ligament and possible bifurcation of the nerve. (4) V2 signal: the electromyographic signal was obtained by stimulating the

ipsilateral vagus with a 3 mA current after all the specimens were removed, and hemostasis in the surgical field was completed. The intact function of the RLN was indicated by the intensity of R2, and V2 signals were not significantly weakened compared to R1 and V1. However, the loss of R2 and V2 signals, or >50% attenuation of signal intensity, indicates nerve injury, and the injury point needs to be detected and identified with the aid of IONM followed by appropriate solutions. IONM systems are generally divided into the following categories¹²: (1) the recording side involves the endotracheal tube recording electrodes, its recording ground electrode, and associated connections at the interface-connector box and monitor; and (2) the stimulation side includes the stimulation neural probe, its grounding electrode, and associated connections to the interface box connector and stimulation current pulse generator within the monitor. The loss of signals (LOSs) were defined as the following¹²: (1) EMG changes from the initial satisfactory EMG; (2) no or low response (i.e., 100 μ V or less) with stimulation at 1–2 mA, dry field; and (3) no laryngeal twitch and/or observed glottic twitch.

2.3 | Observational indexes

The RLN identification time was measured from the initiation of the RLN search to the confirmation of RNL identification. The ratio of RLN identification was defined as the ratio of the amount of definite identification of the RLN to the total number of LNs. Transient RLN injury was defined as vocal cord immobility on the affected side that recovered 4 weeks postoperatively, which was confirmed by fiberoptic laryngoscopy. Permanent RLN injury was defined as constant vocal cord palsy on the affected side for 3 months, as confirmed by a laryngoscope.

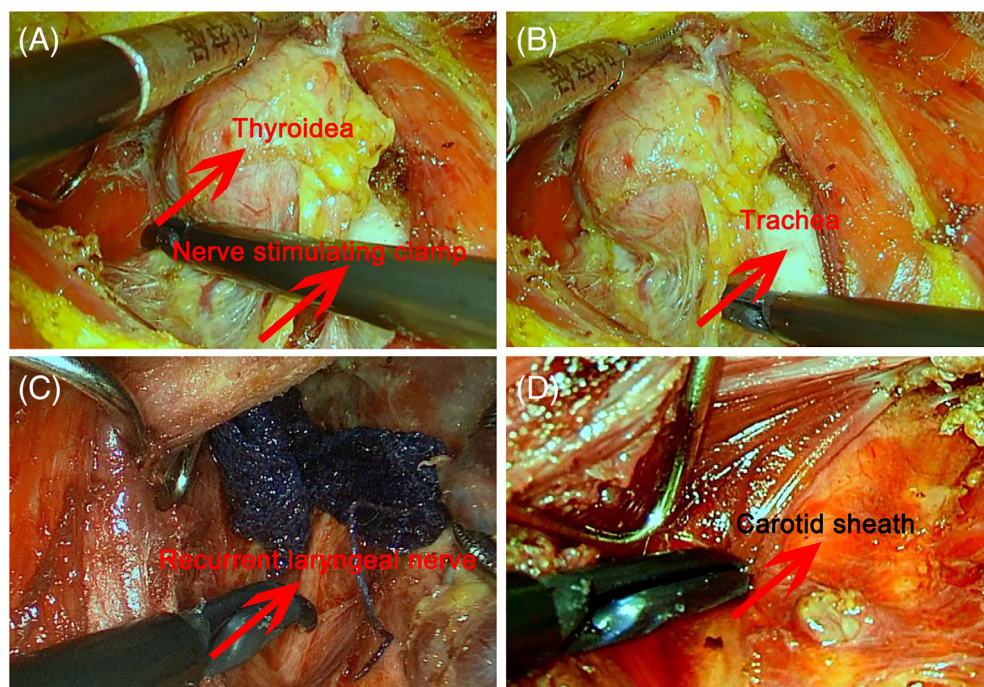


FIGURE 1 Standard four-step method for intraoperative neuromonitoring (IONM) signals detection using a special stimulating clamp. (A) V1 signal; (B) R1 signal; (C) R2 signal; (D). V2 signal

	The IONM group (54)	The non-IONM group (52)	<i>p</i> -value
Age (years)	31.54 ± 5.82	33.61 ± 7.85	.12
Pathologic types (n, %)			
Papillary	52 (96.30)	52 (100.00)	.49
Follicular	2 (3.70)	0 (0)	
Lesions (n, %)			
Single lesion	44 (81.48)	43 (82.69)	.93
Multiple lesions	10 (18.52)	9 (17.31)	
Lymph nodes (n, %)			
N0	46 (85.19)	47 (90.38)	.94
N1a	8 (14.81)	5 (9.62)	
Resection (n, %)			
Unilateral resection	42 (77.78)	43 (82.69)	.70
Bilateral resection	12 (22.23)	9 (17.31)	

Abbreviation: IONM, intraoperative neuromonitoring.

TABLE 1 Baseline characteristics between the IONM and non-IONM groups

Indexes	The IONM group	The non-IONM group	<i>p</i> -value
No. of RLNs	66	61	—
Time of RLN identification (min)	3.05 ± 1.58	9.36 ± 4.82	<.01
RLN identification (n, %)	66 (100.00)	54 (88.52)	.01
Transient RLN injuries (n, %)	1 (1.51)	8 (13.11)	.03
Permanent RLN injuries	0 (0)	1 (1.64)	.92

Abbreviations: IONM, intraoperative neuromonitoring; RLN, recurrent laryngeal nerve.

TABLE 2 Comparison of intraoperative and postoperative RLN function indexes

2.4 | Statistical analysis

Data were analyzed using the SPSS software (version 19.0; IBM, Armonk, NY, USA). Continuous variables are presented as mean ± SD if normally distributed, or as median (quartiles) if non-normally distributed. Categorical variables were expressed as numbers (percentages). The chi-square test or Fisher's exact test was used to analyze categorical variables. Student's *t*-test was used to analyze continuous variables. *p* < .05 was considered to indicate a statistically significant.

3 | RESULTS

All 106 patients who underwent complete endoscopic radical resection of thyroid cancer, with no conversion to an open procedure, were ultimately enrolled in the study. The baseline characteristics of the IONM and non-IONM groups are shown in Table 1. The baseline characteristics were comparable between the two groups (all *p* > .05). Furthermore, 66 RLNs were involved in the IONM group and 61 RLNs were involved in the non-IONM group. Compared with the non-IONM group, the IONM group required less time to for RLN identification (3.05 ± 1.58 vs. 9.36 ± 4.82 min, *p* < .01). The ratio of RLN identification in the IONM group was much higher than that in the non-IONM group (100.00% vs. 88.52%, *p* = .01).

Three LOSs were found in the IONM group, including one caused by deep intubation and two resulting from a muscle relaxant overdose. All three LOSs were excluded during the operation. A case of transient RLN injury occurred in a patient who underwent IONM; however, the patient recovered 2 weeks postoperatively. In contrast, a total of eight transient RLN injuries were detected in the Non-IONM group; six of these patients recovered within 2 weeks, and the remaining two patients with RLNs recovered within 4 weeks. There was a statistically significant difference between the two groups (*p* = .03). Regarding permanent RLN injury, patients who received IONM did not show statistically significant superiority over those did not receive IONM. The characteristics of RLNs in the two groups are summarized in Table 2.

4 | DISCUSSION

RLN injury is a well-known and severe complication that may lead to hoarseness, aphonia, and dyspnea in radical thyroidectomy.^{8,21} RLN injury has been reported to occur in nearly 6% of patients who undergo thyroid surgery within ≤30 days.²² Preservation of RLN function during surgery is controversial and challenging. Since its initiation, thyroidectomy has experienced three states of development: RLN not exposed (regional protection), RLN exposure, and RLN functional monitoring using the IONM technique. With the protective strategy

of nerve exposure without IONM, the morbidity of transient and permanent injuries of the RLN was 6.3% and 2.4% after traditional thyroidectomy; comparatively, the morbidity was reduced to 2.6% and 1.4% in the IONM group, respectively.²³ IONM is associated with a lower risk of RLN injury.²⁴ The significant anatomical diversity and intraoperative characteristics of the RLN may influence the risk of neural injury.²⁵ From the point of the RLN crossing the lower pole of the thyroid to the point of entry to the larynx, there is an area where the RLN can be easily damaged because of the presence of many confounding blood vessels and its superficial course.

With the prerequisite of eradicating tumors, complete endoscopic radical resection of thyroid cancer is a novel technique that can satisfy the esthetic demands of female patients.²⁶ Owing to the merits of high definition and magnifying visualization, the endoscope will be helpful in identifying the RLN. The RLN appears as a silvery refractive cord located in the tracheoesophageal groove on endoscopy. The main difference between the vessels is the absence of waxing and waning signs when pulled. However, the fixed visual angle, absence of assistance, and mandatory use of harmonics are inherent characteristics of complete endoscopic radical resection of thyroid cancer, which hampers the functional protection of the RLN. The prevalence of RLN transient injury was 13.11% in the current study, which was higher than the previously reported 2%–11%.²⁷ This may be caused by a lack of experience when starting IONM.

Before introducing IONM, functional protection of the RLN mainly depends on the total intraoperative exposure of the course of the RLN. However, visual structural integrity does not indicate functional health.²⁸ A prospective study by Lo et al.²⁹ documented that 5.6% (28/500) of patients with seeming healthy RLN progressed into postoperative RLN paralysis as confirmed by laryngoscopic examination. In recent years, IONM has gradually been recognized by many surgeons as an adjunct to complicated thyroidectomy (eradication, huge goiter, and reoperation). It has been reported that standardized monitoring of endoscopic thyroidectomy via the bilateral areolar approach is feasible.³⁰ Moreover, IONM also helps overcome the limitations of the endoscopic procedure and reduces the risk of RLN injury in complete endoscopic radical resection of thyroid cancer.^{31,32} In the present study, we found that IONM could improve RLN identification and significantly reduce transient RLN injuries, which is consistent with the findings of the previous studies mentioned above. Meanwhile, IONM shortens the time required for RLN identification during the complete endoscopic radical resection of thyroid cancer. The time for RLN identification in the present study was similar to that reported by Prachy et al. (3.05 vs. 3.70 min).²⁸

The operative sequence of complete endoscopic radical resection of thyroid cancer is stereotyped as an inferior pole to a superior pole owing to the fixed visual angle. According to the standardized four-step method of IONM, the V1 signal should be detected initially to confirm the validity of the equipment connection, followed by an R1 signal to identify the RLN at the level of the inferior pole. Subsequently, the entire course of the RLN was dissected using harmonics

with the assistance of intermittent or continuous IONM. However, harmonic waves can cause heat damage to the RLN. The operating temperature can reach 100°C even if the triggered time is less than 10 s, which causes lateral heat damage to the adjacent nerve.³³ Therefore, it is necessary to maintain a safe distance (>3 mm) between the harmonic working pole and RLN. A moist liver may also play an important role in isolating and protecting the nerve. In the process of dissection, when there is a significant reduction or LOSs, surgeons should suspend the procedure to locate the injury and explore the cause with the assistance of IONM.³³ Traction and heat are often the primary factors that contribute to RLN injury. Most of the signal reduction could be restored within a few minutes, so that the procedure can be continued. However, if the lost signal cannot be restored, the planned contralateral thyroidectomy should be postponed to a second surgical intervention to avoid the catastrophic risk of bilateral RLN damage. In addition to routine RLN identification, the utmost benefit of IONM administration is the provision of decision-making alterations in cases of unilateral RLN damage.

RLN is the leading major complication of thyroid surgery and may also result in complications, such as hoarseness, dysphagia, and dyspnea. Although IONM is not a standard practice, it has been used widely to identify and evaluate the RLN to avoid injury. IONM not only assesses RLN function but also contributes to the detection of anatomical variations during surgery and anticipation of postoperative vocal cord function. It enables surgeons to diagnose RLN injury intraoperatively, estimate postoperative nerve function, and modify the surgical strategy to avoid vocal cord paralysis. Although there is a continuing debate over the effects of IONM on RLN protection, two recent meta-analyses supported the application of IONM in reducing both transient and permanent RLN injury during thyroidectomy, particularly in bilateral operations and reoperative cases.^{15,16}

This study has some limitations. First, this was a single-center, retrospective study. Although consecutive patients were screened for eligibility, selection bias could not be excluded, and the patients' choices regarding IONM may have been based on their financial status, and this may have caused selection bias. Second, the current sample size was limited, and the results need to be confirmed by a larger prospective study. Third, the surgeries were performed by two different surgeons. However, to minimize observer bias, all surgeons involved in the present study had comparable background experience both in complete endoscopic radical resection of thyroid cancer and the utilization of IONM.

5 | CONCLUSIONS

In complete endoscopic radical resection of thyroid cancer, the advantages of IONM administration for RLN protection could be as follows: (1) assisting RLN identification at the level of the inferior pole of the thyroid lobe; (2) functional monitoring in the process of nerve dissection; and (3) reduction of the risk of transient RLN

injuries. Therefore, we recommend IONM as an indispensable component in complete endoscopic radical resection of thyroid cancer to protect the RLN function, especially for novice surgeons.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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