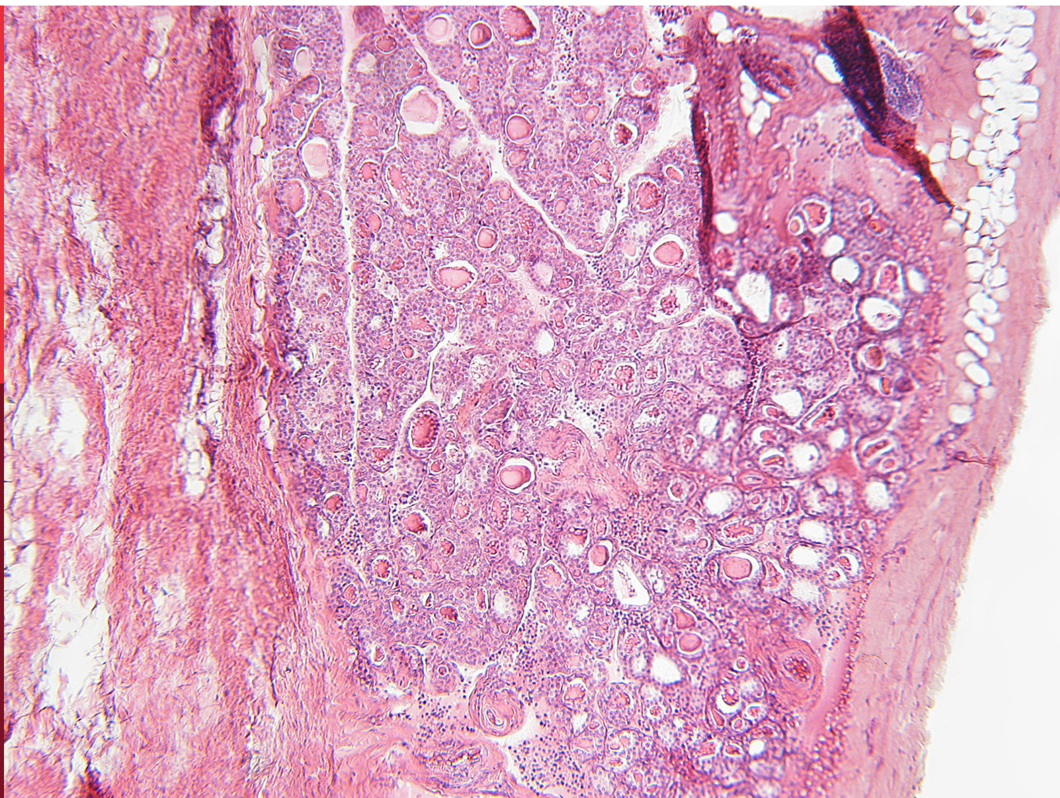
frontiers | Research Topics

# Improving voice outcomes after thyroid surgery and ultrasound-guided ablation procedures

**Edited by**
Che-Wei Wu, Gianlorenzo Dionigi and Kyung Tae

**Published in**
Frontiers in Endocrinology
Frontiers in Surgery



ISSN 1664-8714
ISBN 978-2-83251-139-8
DOI 10.3389/978-2-83251-139-8

## About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

## Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

## Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

## What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

# Improving voice outcomes after thyroid surgery and ultrasound-guided ablation procedures

**Topic editors**
Che-Wei Wu — Kaohsiung Medical University, Taiwan
Gianlorenzo Dionigi — University of Milan, Italy
Kyung Tae — Hanyang University, Republic of Korea

**Citation**
Wu, C.-W., Dionigi, G., Tae, K., eds. (2023). *Improving voice outcomes after thyroid surgery and ultrasound-guided ablation procedures*. Lausanne: Frontiers Media SA.
doi: 10.3389/978-2-83251-139-8

# Table of contents

frontiers | Frontiers in Surgery

TYPE Editorial
PUBLISHED 12 December 2022
DOI 10.3389/fsurg.2022.1064768



OPEN ACCESS

EDITED AND REVIEWED BY
Greg Randolph,
Harvard University, United States

*CORRESPONDENCE
Gianlorenzo Dionigi
gianlorenzo.dionigi@unimi.it

SPECIALTY SECTION
This article was submitted to Otorhinolaryngology - Head and Neck Surgery, a section of the journal Frontiers in Surgery

RECEIVED 08 October 2022
ACCEPTED 15 November 2022
PUBLISHED 12 December 2022

CITATION
Wu C-W, Dionigi G and Tae K (2022) Editorial: Improving voice outcomes after thyroid surgery and ultrasound-guided ablation procedures.
Front. Surg. 9:1064768.
doi: 10.3389/fsurg.2022.1064768



# Editorial: Improving voice outcomes after thyroid surgery and ultrasound-guided ablation procedures

Che-Wei Wu[1], Gianlorenzo Dionigi[2,3]* and Kyung Tae[4]

[1]Department of Otorhinolaryngology-Head and Neck Surgery, Kaohsiung Medical University Hospital, College of Medicine, Faculty of Medicine and Post-Baccalaureate Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan, [2]Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy, [3]Division of Surgery, Istituto Auxologico Italiano, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Milan, Italy, [4]Department of Otorhinolaryngology-Head and Neck Surgery, College of Medicine, Hanyang University, Seoul, South Korea

KEYWORDS

thyroid surgery, ultrasound-guided ablation, dysphonia, recurrent laryngeal nerve, vocal fold paralysis, voice, intraoperative neuromonitoring, external branch of superior laryngeal nerve

Editorial on the Research Topic
Improving voice outcomes after thyroid surgery and ultrasound-guided ablation procedures

Thyroid nodules are a common clinical problem, and thyroid surgery remains one of the more common head and neck procedures (1). In recent years, the field of thyroid procedures for benign and malignant thyroid nodules has expanded from the traditional open-neck approach to include remote robotic or endoscopic access techniques (2) as well as minimally invasive ultrasound (US)-guided ablation procedures, including ethanol ablation (EA), radiofrequency ablation (RFA), microwave ablation (MWA), laser ablation (LA), and high-intensity focused ultrasound (HIFU) (3).

Post-thyroid procedures dysphonia (PTD) is a common complaint of patients that not only affects the performance of professional voice users but also causes a decline in the quality of life of nonprofessional voice users (4). Possible causes of PTD include intra- procedure injury to the recurrent laryngeal nerve (RLN) or the external branch of the superior laryngeal nerve (EBSLN); vascular congestion; laryngeal edema; surgical trauma to the cricothyroid muscle or to the cricoarytenoid joint; endotracheal intubation-related trauma; surgical adhesions; strap muscle injury; and pain or psychological distress (5–8). Given the worldwide diffusion of thyroid procedures and the worldwide growing interest concerning the medico-legal implications of PTD and vocal fold paralysis (VFP), this special issue of Frontiers in surgery concerning the research topic "Improving Voice Outcomes after Thyroid Surgery and Ultrasound-guided Ablation Procedures" included several studies focusing on the patient's voice issues when undergoing thyroid surgery or US-guided ablation procedures during the preoperative, intraoperative, and postoperative period (Figure 1).

Papillary thyroid carcinoma (PTC) is the most common histological subtype of thyroid cancer, and surgery remains the mainstay of treatment. In PTC with thyroid capsule invasion (TCI), extrathyroid invasion (ETE), and central lymph node metastasis (CLNM), the risk of RLN injury is increased during surgery. Therefore, accurate preoperative evaluation TCI, ETE, or CLNM for PTC is important to determine surgical strategies and improve voice outcomes. Wu et al. reported combined models based on machine learning incorporated with CT radiomics features and the clinicoradiological risk factor and proved the model could be an effective, non-invasive, and safe tool for the preoperative prediction of TCI in PTC. In the study by Liu et al., the authors investigated the impact of Hashimoto's Thyroiditis (HT) on the predictive risk factors of CLNM in PTC and suggested that different predictive systems should be used for HT and non-HT patients to have a more accurate evaluation of central lymph node and determine the appropriate scope of lymph node dissection. In addition, Wang et al. proposed a risk assessment system for CLNM in papillary thyroid microcarcinoma (PTMC) of stage cN0 and explored its application value in clinical practice.

Compared to surgery for thyroid cancer, there has been a growing interest in developing the minimally invasive US-guided ablation treatment for benign thyroid nodules. Yan et al. constructed a nomogram to predict regrowth in patients with benign thyroid nodules after RFA with good discrimination and calibration capabilities. Patients with a high score had an increased probability of nodule regrowth and were potential candidates for additional ablation or surgical treatment. This reliable prognostic nomogram can guide the physician in stratifying patients and provide precise guidance for individualized treatment protocols and improve voice outcomes.

In the review article by Pace-Asciak et al., surgical and nonsurgical techniques for minimizing and treating PTD caused by an open approach or remote access thyroidectomy and RFA were introduced. Among the techniques for improving voice outcomes, intraoperative neural monitoring (IONM) has now gained widespread acceptance in the international community as an adjunct to visual nerve identification of the RLN and a useful tool for the external branch of superior laryngeal nerve (EBSLN) mapping during thyroid surgery (9). Wu et al. proposed the International

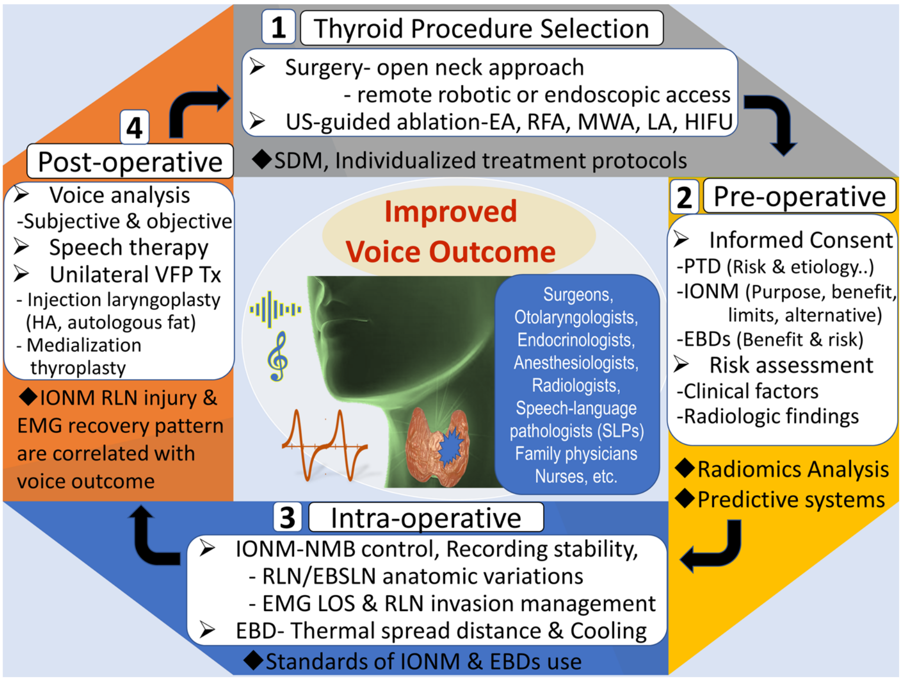



FIGURE 1
The use of a multifaceted approach to improve voice outcomes after thyroid surgery and ultrasound-guided ablation procedures. US, ultrasound; EA, ethanol ablation; RFA, radiofrequency ablation; MWA, microwave ablation, LA, laser ablation; HIFU, high-intensity focused ultrasound; SDM, shared-decision making, PTD, post-thyroid procedures dysphonia; IONM, intraoperative neural monitoring; EBDs, energy-based devices; NMB, neuromuscular block; RLN, recurrent laryngeal nerve; EBSLN, external branch of superior laryngeal nerve; EMG, electromyography; LOS, loss of signal; VFP, vocal fold paralysis; HA, hyaluronic acid.

Neural Monitoring Study Group (INMSG) consensus statement, which outlines general and specific considerations as well as recommended criteria for informed consent for the use of IONM. This consensus statement can assist surgeons and patients in the processes of informed consent and shared decision-making before thyroid surgery.

Teamwork between surgeons and anesthesiologists plays an important role in successful IONM. The utilization of neuromuscular blocking (NMB) agents facilitates tracheal intubation for general anesthesia. Once tracheal intubation is complete, the degree of NMB turns into a key factor for EMG signaling during IONM. Proper NMB management through the timing and dosage of reversal agents such as sugammadex and neostigmine are undergoing increasing amounts of investigations (10). Lu et al. proposed a useful clinical surgeon-centered sugammadex protocol according to NMB degree (0.5 mg/kg for deep block and 0.25 mg/kg for others) that provided high IONM quality and adequate surgical relaxation. Recently, Lu et al. also explored the feasibility of neostigmine (0.04 mg/kg) timely reversing NMB by both cisatracurium (0.2 mg/kg) and rocuronium (0.6 mg/kg) in a porcine model. These clinical and experimental studies can expand the options for precision NMB management during monitored thyroidectomy to improve vocal outcomes.

During IONM, the major limitation of the EMG tube recording system is the difficulty in maintaining stable contact between tube electrodes and vocal folds during surgical manipulation. Liu et al. reviewed the major recent developments of newly emerging transcartilage, percutaneous, and transcutaneous anterior laryngeal recording techniques used in IONM and highlighted their contribution to improved voice outcomes in modern thyroid surgery.

With the application of IONM, Aygun et al. analyzed the clinical and anatomical factors that affect RLN injury and reported that the RLN–inferior thyroid artery (ITA) relationship, extralaryngeal branches, and entrapment of the RLN at the Berry ligament are important factors affecting the development of postoperative VFP. This study concluded that revealing anatomical features with IONM and careful dissection can contribute to the risk reduction of PTD. Chiu et al. analyzed the intraoperative EMG recovery patterns and outcomes after RLN traction injury during IONM. The result shows different recovery patterns have different vocal cord function outcomes, and elucidating the recovery patterns can assist surgeons in intraoperative decision-making and postoperative management.

In addition to the IONM, another important technological advance in thyroid surgery in recent years is the introduction and development of energy-based devices (EBDs). The use of EBDs has many advantages such as reduced blood loss, lower rate of post-operative hypocalcemia, and shorter operation time. However, EBDs generate high temperatures that can cause iatrogenic thermal injury to the RLN by direct or indirect thermal spread. Wang et al. reviewed relevant medical literature and compares the safety parameters, such as safe activation distance and cooling time, between different types of EBDs used for thyroid surgery When using EBDs near the RLN in thyroid surgery, surgeons can adopt these safety parameters and follow the standard procedures to avoid laryngeal nerves or soft tissue injuries to improve the postoperative voice outcomes.

Unrecovered VFP and subjective voice impairment after thyroid surgery causes extreme distress in patients. Huang et al. investigated the correlations between IONM findings and voice outcomes in patients with impaired VFM after thyroid surgery. The result showed that severe type RLN injury (e.g., thermal injury or injury causing EMG decrease >90%) raises the risk of unrecovered VFM and moderate/severe long-term postoperative subjective voice impairment. This study suggested that objective voice parameters (e.g., pitch range) can be used as prognostic indicators not only to enable surgeons to earlier identify patients with low voice satisfaction after surgery, but also to enable the implementation of interventions sufficiently early to maintain quality of life.

High-pitched voice impairment (HPVI) is not uncommon in patients without RLN or EBSLN injury after thyroidectomy, which is commonly caused by fibrosis and limited movement of the strap, lateral extralaryngeal, or cricothyroid muscles. Huang et al. evaluated the correlation between subjective and objective HPVI in patients after thyroid surgery. The result showed factors that affect a patient's subjective HPVI are complex, and voice stability (Jitter and Shimmer) is no less important than the Fmax level. Therefore, the authors suggested that maximum frequency (Fmax) and Index of voice and swallowing handicap of thyroidectomy (IVST) scores should be interpreted comprehensively, and surgeons and speech-language pathologists (SLPs) should work together to identify patients with HPVI early and arrange speech therapy for them.

Concerning the treatment in patients with unilateral VFP after thyroidectomy, Wen et al. reported a retrospective case series in a tertiary teaching hospital to compare the clinical outcomes between different treatment options, including voice therapy (VT), hyaluronic acid (HA) injection, autologous fat injection (FI), and medialization thyroplasty (MT). The results revealed that VT, HA, FI, and MT can all improve the voice outcomes of patients and suggested that the optimal treatment approach should be individualized according to the patient's preference, vocal demand, and the interval between thyroidectomy and intervention. Finally, Liao et al., performed a literature review using the PubMed, Medline, and EMBASE databases to determine the timing, materials, methods, and outcomes of injection laryngoplasty (IL) for unilateral VFP after thyroid surgery. This state of art review supported that IL could improve the voice outcome for unilateral VFP after thyroid surgery, and the autologous fat remains a good augmentation material with a potential longer lasting effect.

In conclusion, this special issue comprises highly qualified papers, which provide novel and comprehensive information for clinicians involved in managing thyroid tumor patients, which includes surgeons, otolaryngologists, endocrinologists, radiologists, internists, speech-language pathologists, family physicians, and other primary care providers, anesthesiologists, nurses, and others. The increasing interest in prevention rather than treatment of PTD may lead to a greater increase in the cost-effectiveness of thyroid tumor treatment, a reduction in procedure-related morbidity, and better health-related quality-of-life (**Figure 1**).

## Author contributions

C-WW, GD, and KT contributed to the conception, design, and writing of the editorial. All authors contributed to editorial revision, and read, and approved the submitted editorial.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



## References

1. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid*. (2016) 26:1–133. doi: 10.1089/thy.2015.0020

2. Tae K, Ji YB, Song CM, Ryu J. Robotic and endoscopic thyroid surgery: evolution and advances. *Clin Exp Otorhinolaryngol*. (2019) 12:1–11. doi: 10.21053/ceo.2018.00766

3. Orloff LA, Noel JE, Stack Jr BC, Russell MD, Angelos P, Baek JH, et al. Radiofrequency ablation and related ultrasound-guided ablation technologies for treatment of benign and malignant thyroid disease: an international multidisciplinary consensus statement of the American Head and Neck Society Endocrine Surgery Section with the Asia Pacific Society of Thyroid Surgery, Associazione Medici Endocrinologi, British Association of Endocrine and Thyroid Surgeons, European Thyroid Association, Italian Society of Endocrine Surgery Units, Korean Society of Thyroid Radiology, Latin American Thyroid Society, and Thyroid Nodules Therapies Association. *Head Neck*. (2022) 44:633–60. doi: 10.1002/hed.26960

4. Yu WV, Wu CW. Speech therapy after thyroidectomy. *Gland Surg*. (2017) 6:501–9. doi: 10.21037/gs.2017.06.06

5. Dionigi G, Wu CW, Kim HY, Rausei S, Boni L, Chiang FY. Severity of recurrent laryngeal nerve injuries in thyroid surgery. *World J Surg*. (2016) 40:1373–81. doi: 10.1007/s00268-016-3415-3

6. Iwata AJ, Liddy W, Barczyński M, Wu CW, Huang TY, Van Slycke S, et al. Superior laryngeal nerve signal attenuation influences voice outcomes in thyroid surgery. *Laryngoscope*. (2021) 131(6):1436–42. doi: 10.1002/lary.29413

7. Huang TY, Yu WV, Chiang FY, Wu CW. Regarding: cricothyroid muscle twitch could be a preventive tool for EBSLN injury in thyroid surgery. *Laryngoscope*. (2019) 129(8):E263. doi: 10.1002/lary.28033

8. Sung ES, Kim KY, Yun BR, Song CM, Ji YB, Lee JC, et al. Long-term functional voice outcomes after thyroidectomy, and effect of endotracheal intubation on voice. *Eur Arch Oto-Rhino-Laryngol*. (2018) 275:3049–58. doi: 10.1007/s00405-018-5145-7

9. Wu CW, Randolph GW, Barczyński M, Schneider R, Chiang FY, Huang TY, et al. Training courses in laryngeal nerve monitoring in thyroid and parathyroid surgery- the INMSG consensus statement. *Front Endocrinol*. (2021) 12:705346. doi: 10.3389/fendo.2021.705346

10. Lu IC, Wu SH, Wu CW. Neuromuscular blockade management for intraoperative neural monitoring. *Kaohsiung J Med Sci*. (2020) 36:230–5. doi: 10.1002/kjm2.12153

frontiers in Endocrinology

REVIEW
published: 29 October 2021
doi: 10.3389/fendo.2021.763170

Check for updates

# New Developments in Anterior Laryngeal Recording Technique During Neuromonitored Thyroid and Parathyroid Surgery

*Cheng-Hsin Liu[1,2], Tzu-Yen Huang[1,3], Che-Wei Wu[1,4], Jia Joanna Wang[1,2], Ling-Feng Wang[1,4], Leong-Perng Chan[1,4,5], Gianlorenzo Dionigi[6,7], Feng-Yu Chiang[8,9], Hsin-Yi Tseng[1]* and Yi-Chu Lin[1]**

*[1] International Thyroid Surgery Center, Department of Otolaryngology-Head and Neck Surgery, Kaohsiung Medical University Hospital, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan, [2] Department of Otolaryngology-Head and Neck Surgery, Kaohsiung Municipal Siaogang Hospital, Kaohsiung Medical University Hospital, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan, [3] Department of Biological Science and Technology, National Yang Ming Chiao Tung University, Hsinchu, Taiwan, [4] Center for Liquid Biopsy and Cohort Research, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan, [5] Department of Otolaryngology-Head and Neck Surgery, Kaohsiung Municipal Tatung Hospital, Kaohsiung Medical University Hospital, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan, [6] Division of Surgery, Istituto Auxologico Italiano IRCCS, Piazzale Brescia, Milan, Italy, [7] Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy, [8] Department of Otolaryngology-Head and Neck Surgery, E-Da Hospital, Kaohsiung, Taiwan, [9] School of Medicine, College of Medicine, I-Shou University, Kaohsiung, Taiwan*



**Edited by:**
*Loredana Pagano, University of Turin, Italy*

**Reviewed by:**
*Yushi Sun, First Affiliated Hospital of Xi'an Jiaotong University, China*
*Mehmet Uludag, Şişli Hamidiye Etfal Education and Research Hospital, Turkey*
*Nurcihan Aygun, Şişli Etfal Eğitim ve Araştırma Hastanesi, Turkey*

***Correspondence:**
*Hsin-Yi Tseng*
*sycatlovestar@gmail.com*
*Yi-Chu Lin*
*yichulin.ent@gmail.com*

**Specialty section:**
*This article was submitted to Thyroid Endocrinology, a section of the journal Frontiers in Endocrinology*

**Received:** 23 August 2021
**Accepted:** 14 October 2021
**Published:** 29 October 2021

**Citation:**
*Liu C-H, Huang T-Y, Wu C-W, Wang JJ, Wang L-F, Chan L-P, Dionigi G, Chiang F-Y, Tseng H-Y and Lin Y-C (2021) New Developments in Anterior Laryngeal Recording Technique During Neuromonitored Thyroid and Parathyroid Surgery. Front. Endocrinol. 12:763170. doi: 10.3389/fendo.2021.763170*

A recurrent laryngeal nerve (RLN) injury resulting in vocal fold paralysis and dysphonia remains a major source of morbidity after thyroid and parathyroid surgeries. Intraoperative neural monitoring (IONM) is increasingly accepted as an adjunct to the standard practice of visual RLN identification. Endotracheal tube (ET) surface recording electrode systems are now widely used for IONM; however, the major limitation of the clinical use of ET-based surface electrodes is the need to maintain constant contact between the electrodes and vocal folds during surgery to obtain a high-quality recording. An ET that is malpositioned during intubation or displaced during surgical manipulation can cause a false decrease or loss of electromyography (EMG) signal. Since it may be difficult to distinguish from an EMG change caused by a true RLN injury, a false loss or decrease in EMG signal may contribute to inappropriate surgical decision making. Therefore, researchers have investigated alternative electrode systems that circumvent common causes of poor accuracy in ET-based neuromonitoring. Recent experimental and clinical studies have confirmed the hypothesis that needle or adhesive surface recording electrodes attached to the thyroid cartilage (transcartilage and percutaneous recording) or attached to the overlying neck skin (transcutaneous recording) can provide functionality similar to that of ET-based electrodes, and these recording methods enable access to the EMG response of the vocalis muscle that originates from the inner surface of the thyroid cartilage. Studies also indicate that, during surgical manipulation of the trachea, transcartilage, percutaneous, and transcutaneous anterior laryngeal (AL) recording electrodes could be more stable than ET-based surface electrodes and could be equally accurate in depicting RLN stress during IONM. These findings show that these AL electrodes have potential applications in future designs of recording electrodes and support the use of IONM as a high-quality quantitative tool in thyroid and parathyroid surgery. This article reviews the major recent developments of newly emerging transcartilage, percutaneous, and transcutaneous AL recording techniques used in IONM and evaluates their contribution to improved voice outcomes in modern thyroid surgery.

**Keywords: voice, vocal fold paralysis, thyroid surgery, intraoperative neural monitoring (IONM), recurrent laryngeal nerve (RLN), laryngeal electromyography (EMG), anterior laryngeal recording, thyroid cartilage recording**

# INTRODUCTION

## Neural Monitoring for Improving Voice Outcomes After Thyroid Surgery

Although thyroid surgery is among the most common and safe interventions in endocrine surgery, the risk of complications is still evitable due to the unique anatomical structure and physiological function of the thyroid gland (1). Recurrent laryngeal nerve (RLN) paralysis remains a common thyroid surgery complication that can cause dysphonia, aspiration, and, in some cases, interference with breathing. Therefore, RLN paralysis is a common cause of litigation after thyroid surgery in the current era in which quality of life change is included in assessment of surgical outcome (2, 3). One major change in the past two decades is the growing acceptance of intraoperative neural monitoring (IONM) as a tool for minimizing surgical risk by assisting surgeons in the early localization and identification of the RLN and as a tool for assisting clinical decision-making by enabling real-time monitoring of evoked electrophysiologic laryngeal electromyography (EMG) responses during thyroid surgery.

## Advantages and Disadvantages of EMG Endotracheal Tube Recording for IONM

Currently, EMG recording during neuromonitored thyroid surgery is almost always performed using endotracheal tube (ET) surface electrodes placed in contact with vocal folds during intubation for general anesthesia because of the advantages including their noninvasiveness, wide commercial availability, and capacity to monitor larger areas of the target muscle (4, 5). However, maintaining consistent and stable contact between the ET-based surface electrodes and vocal folds during surgery has become the major clinical challenge to obtain a high-quality recording. Improper positioning of the ET during intubation is not uncommon and may result from an ET that is undersized, rotated, or inserted to the incorrect depth (6, 7). During surgical manipulation, an ET may be displaced by tracheal and neck extension, which inevitably raises the possibility of rotation or depth change (8–10). Both malpositioning and displacement can cause a false decrease or loss of EMG signal. Since false signals may be difficult to distinguish from EMG signal changes caused by true RLN injuries, they may lead to inappropriate surgical decision making. During IONM with ET recording, a malpositioned or displaced ET requires adjustment by the anesthesiologist, which can be troublesome and time-consuming. Intraoperative adjustment of the ET is particularly disruptive in remote thyroid surgery and is virtually impossible in procedures such as transoral robotic approach (11). Additionally, EMG changes have a larger impact in continuous IONM (C-IONM) compared to conventional intermittent IONM (I-IONM) because unstable or shifting baseline EMG cause a C-IONM system malfunction and limit its use for early identification of RLN lesions (12, 13). In addition to the above issues of malpositioning or displacement that may occur during surgical manipulation, other disadvantages of ET include its high expense, the potential for accumulation of saliva to interfere with signal acquisition, and its limited use in pediatric patients and patients with airway abnormality.

## Alternative Electrode Systems That Circumvent the Factors Affecting ET Recording

To avoid the time-consuming processes of verifying and readjusting the ET position during neuromonitored thyroid surgery and to minimize the safety hazard of signal inconsistency and instability. Regarding the basis of anatomy, there are many innovative hypotheses and possible solutions including novel electrodes designs have been proposed. For example, many experimental (14–18) and clinical studies (19–28) have confirmed the hypothesis that needle or adhesive surface recording electrodes attached to the thyroid cartilage (transcartilage or percutaneous recordings) or attached to the overlying neck skin (transcutaneous recording) can function like ET electrodes by enabling access to the EMG response of the vocal fold muscles (vocalis muscle and thyroarytenoid muscle) originating from the inner TC surface **(Table 1**, **Figure 1)**. These studies have also demonstrated that transcutaneous or transcartilage anterior laryngeal (AL) recording electrodes are as accurate as ET-based surface electrodes in depicting RLN stress during IONM. However, transcutaneous or transcartilage AL recording electrodes could be more stable than ET-based surface electrodes during surgical manipulation on the trachea. These findings indicate that AL electrodes have potential applications in future designs of recording electrodes and support the use of IONM as a high-quality quantitative tool in thyroid and parathyroid surgery. This article reviews recent studies of new and emerging transcutaneous or transcartilage AL recording techniques used during IONM and compares these

**TABLE 1 |** Current published papers on AL EMG recording technique during neuromonitored thyroid and parathyroid surgery.

| Technique | Study design | Author, year | Electrode form | Number of subject | Highlights |
|---|---|---|---|---|---|
| **Transcartilage** | Experimental | Wu et al. 2018 (14) | Two disposable adhesive pre-gelled ECG surface electrode on bilateral TC | Porcine model(12 pigs and 24 RLNs at risk) | A proof of concept for transcartilage technique. Confirm the stability and accuracy by trachea displacement and traction injury experiments. |
| | | Zhao et al. 2019 (16) | Two disposable paired subdermal needle electrode (12-mm long, uninsulated) on bilateral TC | Porcine model(4 pigs and 8 RLNs at risk) | Test and identify an optimal site for placement of needle electrodes. |
| | | Zhao et al. 2021 (18) | Two disposable adhesive pre-gelled ECG surface electrode on bilateral TC | Porcine model(4 pigs and 8 RLNs at risk) | Determine the optimal placement locations and sizes of adhesive electrodes. |
| | Clinical | Chiang et al. 2017 (19) | Two disposable single subdermal needle electrode (12-mm long, uninsulated) on bilateral TC | Comparative Study. Open thyroidectomy(110 patients, 205 RLNs at risk) | First clinical study on needle transcartilage approach and report it obtain higher and more stable EMG signals as well as fewer false EMG results as compared to ET recording. |
| | | Liddy et al. 2018 (20) | One disposable paired adhesive laryngeal EMG surface electrode on bilateral TC | Comparative Study. Open thyroidectomy and parathyroidectomy (15 patients, 20 RLNs at risk) | Demonstrate the transcartilage technique is useful and offer significantly more robust monitoring of the EBSLN. |
| | | Van Slycke et al., 2019 (21) | One disposable paired laryngeal EMG surface electrode suture fixed on bilateral TC | Comparative Study. Open thyroidectomy (25 patients, 25 RLNs at risk) | Confirm the transcartilage technique can obtain higher amplitudes after stimulating RLN and also EBSLN. |
| | | Chiang et al., 2020 (22) | Two disposable paired subdermal needle electrode (12-mm long, uninsulated) on bilateral TC | Case series. Open thyroidectomy (100 patients, 200 RLNs at risk) | Report an optimal technique of needle placement by inserting into the TC subperichondrium from the anterior margin of the thyrohyoid muscle with a slope of 10 to 15 degree. |
| | | Jung et al., 2020 (23) | One disposable paired twisted subdermal needle electrode (22-mm, uninsulated) on bilateral TC | Comparative Study. Open thyroidectomy (38 patients, 54 RLNs at risk) | Report the positive predictive values of loss of signal in ET and TC electrodes were 40% and 100%, respectively. |
| | | Lee et al., 2021 (24) | One disposable paired subdermal needle electrode (12-mm long, uninsulated) on ipsilateral TC | Case series. Unilateral hemithyroidectomy (34 patients, 34 RLNs at risk) | Introduce an alternative method with the advantage of minimal exposure of the TC lamina during unilateral hemithyroidectomy. |
| | | Türk et al., 2021 (27) | One disposable paired twisted subdermal needle electrode (22-mm, uninsulated) on bilateral TC | Case-control study. Open thyroidectomy (885 patients, 1717 RLNs at risk) | The first case-control study to compare ET and TC electrodes, and concluded that TC electrodes are an inexpensive and efficient alternative to ET electrodes. |
| | | Huang et al. (28) | Two disposable paired subdermal needle electrode (12-mm long, uninsulated) on bilateral TC | Comparative Study. Open thyroidectomy (33 pediatric patients, 58 RLNs at risk) | First pediatric study. TC electrodes show excellent stability and quality of EMG signals, and can be a preferable monitoring method for pediatric thyroid surgery |
| **Percutaneous** | Experimental Clinical | Huang et al., 2020 (17) | Two disposable paired subdermal needle electrodes (25 and 38-mm long, insulated to within 5 mm of tip) percutaneously inserted to TC | Porcine model. (4 pigs, 8 RLNs at risk), 1 case of Transoral robotic thyroidectomy | A proof of concept for percutaneous technique in remote endoscopic or robotic thyroidectomy without neck incision wound. |
| | Clinical | Li et al., 2020 (25) | Two disposable paired subdermal needle electrode (12-mm long, uninsulated) percutaneously inserted to TC | Case series. Minimally invasive unilateral parathyroidectomy (20 patients, 20 RLNs at risk) | Verify this technique is a feasible, convenient, reliable, and inexpensive method for thyroid or parathyroid surgery with small incision wound. |
| **Transcutaneous** | Experimental | Wu et al., 2018 (15) | Two disposable adhesive pre-gelled ECG surface electrode | Porcine model (12 pigs, 24 RLNs at risk) | A proof of concept for transcutaneous technique. Confirm the stability and accuracy by trachea displacement and traction injury experiments. |
| | Clinical | Lee et al., 2020 (26) | Two disposable adhesive pre-gelled EMG surface electrode | Comparative Study. Open thyroidectomy (30 patients, 39 RLNs at risk) | The first published clinical study verifies the usefulness of transcutaneous technique using adhesive skin electrodes. |

*(Continued)*

**TABLE 1** | Continued

| Technique | Study design | Author, year | Electrode form | Number of subject | Highlights |
|---|---|---|---|---|---|
| | Experimental Clinical | Shin et al., 2021 (29) | Two disposable adhesive pre-gelled EMG surface electrode | Porcine model (4pigs, 8 RLNs at risk) Comparative study. Open thyroidectomy (78 patients, 115 RLNs at risk) | Adhesive skin electrode was feasible in both animal models and human patients. Adhesive skin electrode was suggested to the lateral side of the thyroid cartilage lamina closer to the cricoarytenoid joint. |

*AL, anterior laryngeal; EMG, electromyography; ECG, Electrocardiography; TC, thyroid cartilage; ET, endotracheal tube; RLN, recurrent laryngeal nerve.*

techniques in terms of their contribution to improved voice outcomes after modern thyroid surgery.

## TRANSCARTILAGE ANTERIOR LARYNGEAL RECORDING

The trans-cartilage recording system has yielded many novel surgical applications of IONM technology in recent years. Since vocal fold muscles are innervated only by the RLN and are attached to the anterior inner surface of the thyroid cartilage (TC), surface recording electrodes placed on the outer surface of TC should enable access to EMG signals evoked in vocal fold muscles during IONM (**Figure 1** and **Figure 2A**) (14). To test this hypothesis, Wu et al. (14) performed an animal study using 12 male piglets under standard IONM settings. Adhesive pre-gelled EMG electrodes were attached to the outer surface of the TC for transcartilage AL recording. Evoked EMG signals detected by TC electrodes were compared with those detected by ET electrodes. Typical evoked laryngeal EMG waveforms for the vagus nerve (VN) and RLN were obtained under 1 mA stimulation. Experimental displacements and surgical manipulations of the trachea confirmed the stability and consistency of transcartilage method. Additionally, RLN traction experiments confirmed that transcartilage method accurately reflected neurophysiologic events (14). Zhao et al. (18) investigated the feasibility, EMG stability, and optimal location and size of adhesive surface arrays attached to the TC for use in IONM. Their experiments confirmed that, during surgical manipulations, EMG profiles obtained by transcartilage

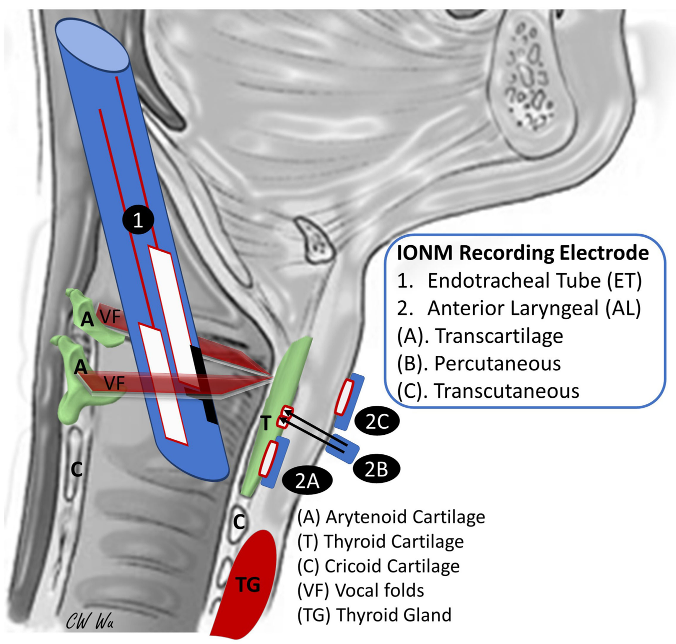



**FIGURE 1** | Anatomic relationship between the thyroid cartilage (TC) - vocal folds and intraoperative neural monitoring (IONM) recording electrode placement in different electromyography (EMG) recording techniques used in thyroid and parathyroid surgery. The vocal fold (VF, vocalis and thyroarytenoid muscle) originates from the inner surface of the TC and inserts to the arytenoid cartilage (A). Conventional endotracheal tube (ET) surface electrodes are designed to be placed in contact with vocal folds during intubation for general anesthesia. However, potential displacement of the ET electrode during surgery may affect signal quality and stability. Recent studies have confirmed that anterior laryngeal (AL) transcartilage, percutaneous, and transcutaneous surface recording electrodes placed on the TC outer surface also enable access to the EMG response of the vocal folds and can circumvent factors that negatively affect ET electrode performance.

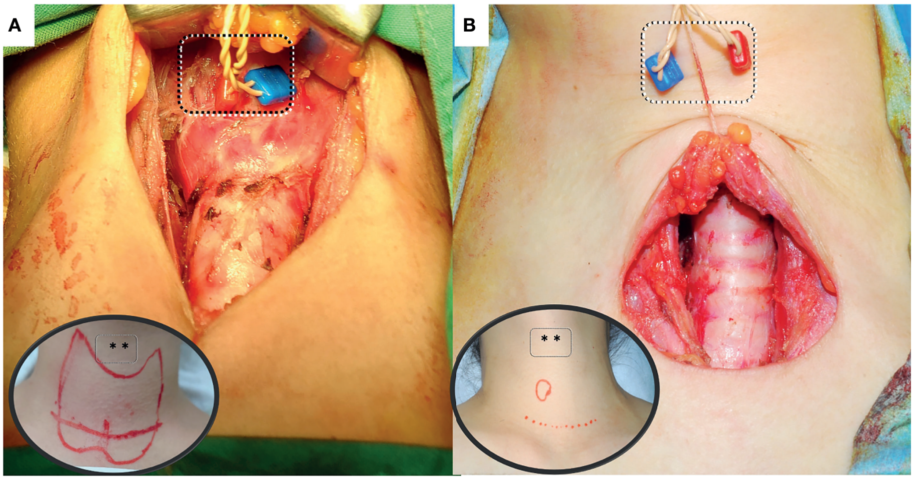



**FIGURE 2** | Anterior laryngeal (AL) recording electrode placement for intraoperative neural monitoring. **(A)** Transcartilage Anterior Laryngeal Recording: Skin flaps are elevated superiorly to expose the thyroid cartilage. Needle electrodes are placed onto the subperichondrium layer of thyroid lamina. Inserting the needle at the anterior margin of the thyrohyoid muscle with a 10- to 15-degree angle from the surface of lamina. **(B)** Percutaneous Anterior Laryngeal Recording: The needle electrodes are percutaneously inserted and fixed onto the perichondrium layer of thyroid cartilage. It may be applied in surgeries with lower/smaller incision wound or in remote surgery. However, excessive traction may cause percutaneous needle displacement during the surgery.

recording method were more stable than those obtained by ET recording method.

Similarly, Zhao et al. (16) performed an experimental porcine model to test the transcartilage recording by placing needle electrodes on the TC in a porcine model. They confirmed that a perichondral needle electrode can be safely inserted into the avascular area of the TC. Comparing to ET electrodes, TC electrodes registered earlier changes in EMG amplitudes when the nerve is in traction injury. Additionally, TC electrodes obtained higher and more stable EMG amplitudes. Their findings indicate that transcartilage recording electrodes have superior function, easier placement, and lower cost compared to ET electrodes (16). Researchers are increasingly discussing clinical applications of transcartilage AL recording in IONM, and several methods of affixing electrodes to the TC have been reported. For example, one proposed method is to perform transcartilage AL recording using a commercially available 12mm subdermal single needle electrode. Chiang et al. (19) analyzed 205 at-risk RLNs in 110 patients in a clinical comparison of EMG signals recorded by ET and TC surface electrodes in the standardized monitored thyroidectomy. A pair of one-channel electrodes were inserted into the perichondrium of the TC lamina on bilateral side. According to their comparisons, transcartilage AL recording and ET recording had comparable efficacy and reliability during monitored thyroidectomy. In contrast with the complicated and time-consuming procedures for adjusting ET electrodes and verifying their proper position, the setup procedure for transcartilage AL electrodes can be performed quicker (approximately 2 minutes) and easier. Additionally, compared to ET recording, transcartilage AL recording obtains higher and more stable EMG signals during IONM as well as fewer false EMG results. Chiang et al. (22) developed a technique for using two-channel paired subdermal needle electrodes for transcartilage AL recording. Based on their experience in performing the technique in 100 consecutive monitored total thyroidectomies, the authors concluded that, in clinical practice, the technique can be performed without ET electrodes and that it provides high sensitivity and stability of EMG signals. Therefore, it improves the safety and reliability of thyroid surgery and is particularly suitable for use in C-IONM. Another recent study by Jung et al. (23) reported the efficacy of transcartilage recording during standardized monitored thyroidectomy. A pair of 22-mm twisted needle electrodes was attached to the TC in 38 patients with 54 at-risk RLNs. The positive predictive values of loss of signal were 40% and 100% for ET and TC electrodes, respectively. In 2021, Lee et al. (24) reported the advantage of minimizing exposure of one side of the TC by applying a single ipsilateral transcartilage needle electrode during unilateral monitored hemithyroidectomy. Additionally, Türk et al. (27) reported the first case-control study to compare ET and TC electrodes and concluded that TC electrodes are an inexpensive and effective alternative to ET electrodes.

In a prospective clinical cohort study of 25 patients, Van Slycke et al. (21) affixed electrodes directly to the TC perichondrium with two stitches. Compared to ET electrodes, the TC electrodes obtained higher EMG amplitudes induced by stimulation of the VN, RLN and external branch of the superior laryngeal nerve (EBSLN). Liddy et al. (20) proposed and evaluated the use of adhesive dragonfly bipolar surface electrodes (Neurovision Medical, Inomed, Medtronic & Stryker) in 15 consecutive patients undergoing monitored thyroid and parathyroid surgery. Their approach entailed cutting the adhesive electrode in half to create two recording surfaces and then positioning the electrodes over the TC on either side of the midline. The electrodes were then secured by suturing them to the perichondrium. Their experiments again demonstrated that, compared to ET electrodes, adhesive transcartilage AL electrodes provide EMG signals with comparable stability and amplitude and have comparable sensitivity in recording evoked responses during IONM. Additionally, since adhesive transcartilage AL electrodes are accessible in the operative field, they are easily monitored and controlled by the surgeon, and they are unaffected by potential ET displacement during surgery (20). Finally, since transcartilage AL electrodes enable robust EBSLN monitoring, they reduce the risk of high-pitched voice function loss in thyroid and parathyroid surgery (30).

In pediatric patients, anatomical characteristics, e.g., smaller RLN diameter compared to adults, can make IONM challenging. One consensus statement suggested that IONM is beneficial in pediatric patients with a bulky thyroid and lymph node disease (31). Since the larynx and trachea are relatively small in pediatric patients, the limited selection of commercially available ET electrode sizes combined with the increased difficulty of confirming ET electrode position in pediatric patients may result in unstable and inconsistent contact between the ET electrode and the vocal fold (28, 32). Huang et al. (28) compared electrode types in 33 pediatric patients who had received neuromonitored thyroid surgery and concluded that, compared to EMG signals obtained by ET electrodes, signals obtained by TC electrodes had superior amplitude, stability, and quality, which greatly facilitates the meticulous RLN dissection required in pediatric thyroidectomies, especially in pediatric patients with thyroid cancer.

## PERCUTANEOUS ANTERIOR LARYNGEAL RECORDING

The feasibility of using TC perichondral needle electrodes as recording electrodes and their good signal stability have been well established in many animal and clinical studies. However, these electrodes require a standard neck incision for open exposure of the TC. That is, TC perichondral needle electrodes are inapplicable when invasiveness must be minimized and in remotely-performed endoscopic or robotic thyroidectomy. To overcome this limitation, Huang et al. (17) designed a novel IONM percutaneous recording method for remotely performed thyroid surgery **(Figure 1** and **Figure 2B)** in which pairs of insulated needle electrodes (lengths, 25 mm and 38 mm) were inserted percutaneously into the TC perichondrium to within 5 mm of the tip. The four most widely used remote thyroidectomy techniques (bilateral axillary-breast, transoral, transaxillary, and retroauricular approaches) were evaluated in animal experiments and in their initial case series. They concluded that percutaneous TC recording technique is feasible and can be modified according to the approach used for remote access. This technique reduces interruption of the surgical procedure while still providing reliable EMG signals (17).

Percutaneous AL recording during IONM in minimally invasive parathyroidectomy was recently reported by Li, et al. (25). The authors used paired 12mm long needle electrodes for percutaneous recording in 20 patients and successfully detected typical EMG signals. Based on their findings, the authors concluded that their technique is feasible, convenient, reliable, and cost-effective when IONM is used to assist minimally invasive thyroid or parathyroid surgery (25).

## TRANSCUTANEOUS ANTERIOR LARYNGEAL RECORDING

In addition to transcartilage AL recording, transcutaneous AL recording is another innovative procedure that is proposed for modern IONM technology (15). **Figure 1** shows that transcartilage recording is effective for evaluating vocal fold muscle function and RLN function in TC, and transcutaneous recording may be effective for the same purpose.

Technical advances in epidermal electronics now enable fabrication of sensors in the ideal form can be affixed as an electronic second skin. In 2018, Wu et al. used a porcine model with well-established applicability in IONM research to verify the hypothesis of transcutaneous AL recording. Electrically evoked EMGs were recorded from surface electrodes attached to the ET and from adhesive pre-gelled surface electrodes (Neotrode II®-ConMed) attached to the anterior neck skin. In their experiments, ET electrodes and neck adhesive skin electrodes successfully recorded typical evoked laryngeal EMG waveforms from RLNs and VNs under 1 mA stimulation. Additionally, both electrode types accurately detected adverse EMG events under experimentally induced RLN traction stress. Under experimentally induced tracheal displacement, however, EMG signals obtained by ET electrodes widely varied whereas EMG signals obtained by transcutaneous electrodes were stable (15). Although this proof-of-concept study confirmed the stability and accuracy of EMG signals obtained by transcutaneous approach, it also revealed the need for new electrode designs that provide more consistent and accurate EMG amplitudes before practical clinical application of this approach.

In 2020, Lee et al. (26) performed the first clinical study to evaluate the efficacy of transcutaneous AL recording during monitored thyroidectomy. A disposable pre-gelled adhesive surface electrode (1.5 cm x 2.0 cm x 2.5 cm; DSE3125; Medtronic Xomed; Jacksonville, FL, USA) was attached to each of the two upper margins of the TC surface. The setup time for the skin electrodes was less than 1 minute in all cases. Their experimental results confirmed the effectiveness of IONM for recording evoked biphasic EMG signals of acceptable quality in all at-risk nerves.

Recently, Shin et al. (29) investigated the optimal attachment location of transcutaneous adhesive skin electrodes for IONM. In porcine animal model, the mean amplitude obtained using laterally attached transcutaneous electrodes was significantly higher than that obtained using medially attached skin surface electrodes. However, there was no significant difference in amplitude according to vertical levels (upper/middle/lower). In human patients, they reported that the ET electrode (716.25 ± 543.35 μV) showed a significantly higher mean amplitude than laterally attached transcutaneous electrodes (258.48 ± 77.31 μV), and the laterally attached transcutaneous electrodes showed a significantly higher mean amplitude than the medially attached skin electrodes (185.22 ± 66.56 μV) on RLN stimulation. Therefore, they concluded that transcutaneous recording is feasible and the lateral side of the thyroid cartilage lamina may be better than the medial side for electrode attachment to obtain better EMG signals from the intrinsic laryngeal muscles.

## DISCUSSION

Although thyroid surgery is now a commonly performed procedure worldwide, RLN injuries are still common complications and a major cause of low satisfaction with thyroid surgery outcomes and medical malpractice litigation. Use of IONM in thyroid surgery has become well established in the past two decades, and surgical applications of IONM are increasingly accepted throughout the world. Recent registry-based studies performed in Sweden (SQRTPA) (33), Europe (EUROCRINE®) (34), United Kingdom (UKRETS) (35), and other regions (36) provide insight into current IONM practices. Most studies agree that a large and growing majority of thyroid surgeons currently use IONM for anatomical identification of the RLN and for evaluating RLN injury. Another common motivation for using IONM is to reduce the risk of temporary and permanent RLN paralysis.

The most important issue when IONM is performed using an ETT as the recording side is that IONM has a high negative predictive value (92%-100%) but a relatively low and variable positive predictive value (10%-90%) (37). The IONM recording quality (i.e., stability and consistency) depends on the stability of contact between the ET electrodes and the vocal folds, and contact quality may vary widely during surgical manipulations. Therefore, alternative electrode types such as transcartilage, percutaneous, and transcutaneous AL recording electrodes have been extensively studied in recent years to minimize factors that negatively affect ET-IONM accuracy and efficacy. This article presents a complete overview of state-of-the-art transcartilage, percutaneous, and transcutaneous AL recording techniques used in IONM and compares their contribution to improved voice outcomes in modern thyroid surgery.

This is the first comprehensive review in the literature of IONM with transcartilage (14, 16, 18–24, 27, 28), percutaneous (17, 25), and transcutaneous (15, 26) AL recording electrodes. The techniques are illustrated (**Figure 1**), major findings of each study are summarized and highlighted (**Table 1**), and the pros and cons of each method are discussed and compared (**Figure 2**, **Figure 3** and **Table 2**). In comparison with conventional ET recording IONM, advantages of AL recording IONM reported in both animal and clinical studies include lower invasiveness, better quality and stability of EMG signals, and avoidance of time-consuming disturbances such as the need to verify the ET position. In addition, the high reliability and quality of EMG response making these recording methods not only useful during routine ordinary thyroid and parathyroid surgery, but also practical during thyroid surgery with small incision, remote access, and in specific (e.g., pediatric) populations. In addition to ensuring stable EMG signals, AL recording IONM has several advantages. First, the equipment setup is user-friendly; reported setup times approximate 2 minutes for transcartilage needle electrodes (19) and less than 1 minute for transcutaneous electrodes (26). Second, only a short setup time is required for rapid implementation when an unexpected need for IONM occurs during surgery. Third, dislodged electrodes can be identified and managed intraoperatively. Finally, AL electrodes are apparently more cost effective than ET electrodes (28). A pair of adhesive pre-gelled electrodes or needle electrodes can be purchased for the equivalent of less than 100 USD, which is at least five-fold lower than the cost of EMG ET electrodes.

Whereas these novel techniques are apparently practicable and have no major disadvantages in most clinical applications, disadvantages of transcartilage electrodes include the higher skin flap elevation required to expose the TC (**Figure 2A**), and the difficulty of manipulating the electrodes in procedures performed within a limited operative space, e.g., in endoscopic thyroidectomy or in procedures in which the size of the incision is minimized to improve cosmetic outcome. Additionally, a needle electrode insertion may be complicated by scar tissue caused by revision surgery or, in older adults, by calcified TC, both of which can substantially impair recording of compound muscle action potential responses (14). Finally, patients undergoing such procedures have a low but still risk of laryngeal hematoma, laceration, infection, or rupture of an endotracheal cuff, especially in procedures performed with needle electrodes. Therefore, the recommendation is to insert the needle gently into the subperichondrium of the middle thyroid lamina from the anterior margin of the thyrohyoid muscle with a 10- to 15-degree slope on each side (22).

Although percutaneous AL electrodes are applicable in small incision thyroid and parathyroid surgery and in remote thyroidectomy, insertion of needle electrodes into the TC should be performed with extreme caution to avoid inadvertent injury to the cricothyroid muscle or EBSLN, which can cause muscular hematoma or scar tissue formation and subsequent alterations in vocal pitch. Additionally, percutaneous needle recording electrodes can inadvertently record far field potentials. Therefore, the recommended practices are confirming the stimulation site and comparing corresponding VN, RLN, or EBSLN waveforms, and adjusting the current intensity to minimize recording of far field potentials. Finally, excessive skin retraction or the use of skin retraction for counter-traction during remote thyroidectomy (17) could cause percutaneous needle displacement (**Figure 2B**).

Although transcutaneous AL recording in IONM has proven feasible and reliable, further technical refinement is needed to address some technical flaws. The skin electrode could be affected by patient characteristics such as obese or short neck,

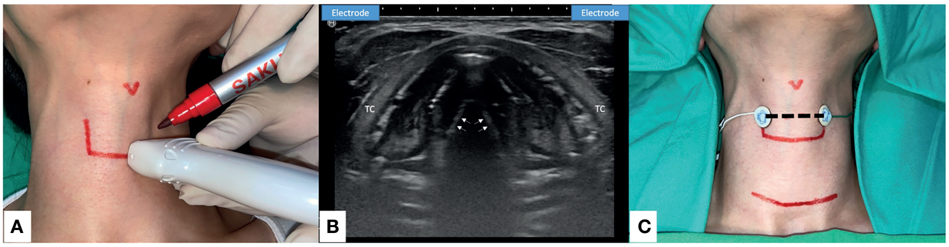



**FIGURE 3** | Transcutaneous Anterior Laryngeal Recording electrode placement for Intraoperative neural monitoring. **(A)** Preoperative skin marking: lateral border of thyroid cartilage and the level of true vocal fold. Precise localization may be done with the application of ultrasound (US). **(B)** The axial view of true vocal folds (white arrow). Lateral side of the thyroid cartilage (TC) lamina is the optimal location to place the skin surface electrodes (US illustration). **(C)** Transcutaneous recording electrodes are placed at the level of true vocal fold (dotted line). Transcutaneous recording method is applicable in small incision wound or remote thyroid surgery. Skin flap beneath the surface electrodes should be avoided.

degree of subplatysmal flap elevation, and large tumor size. During surgery, subplatysmal flap and retraction of the strap muscle during dissection of the thyroid upper pole may hinder neural signal transmission. The EMG signals actually recorded after upper pole dissection might also be diminished (38). Therefore, this technique may not be useful in procedures that require a large incision or involve a large tumor size (15). Additionally, since both animal and clinical studies agree that low amplitude remains the major limitation of this technique, further research is needed to improve electrode designs and recording quality. Shin et al. (29) suggest that the lower amplitude could be overcome by attaching the skin electrodes more laterally and close to the cricoarytenoid joint. Therefore, the authors of this review suggest the surgeons may consider using ultrasonography to decide the optimal location of the AL electrodes preoperatively (**Figure 3**).

In summary, this review of the recent literature regarding the feasibility, stability, safety, and efficiency of new and emerging techniques for obtaining transcartilage, percutaneous, or transcutaneous AL recordings during IONM found that recently developed techniques increase the potential applications of IONM as a high-quality quantitative tool in thyroid and parathyroid surgery. However, this review also revealed that most clinical studies have enrolled a relatively small number of patients. Therefore, future prospective studies in larger populations are needed to explore and verify the applicability and benefits of these techniques. Several novel techniques that can further improve AL recordings have been recently reported in the literature. One study uses a nanosheet-based microneedle for EMG recording, which minimizes the risk of laryngeal injury caused by needle insertion (39). Instead of using electrophysiologic laryngeal EMG to evaluate muscle movement, several recent animal studies have also evaluated the use of novel devices that use a piezo-electric surface pressure sensor (40, 41) or an accelerometer sensor (42) to measure muscle twitch. Another interesting development is an "electronic skin" (e-skin) fabricated by embedding various serpentine sensors in a highly stretchable net sandwiched between two protective layers of equal thickness (43). Like a bandage, the device can be attached to the skin surface to acquire

**TABLE 2** | The pros and cons of different AL EMG recording techniques during neuromonitored thyroid and parathyroid surgery.

| Technique | Advantages | Disadvantages |
|---|---|---|
| **Transcartilage** | (1). EMG signal shows less affected by surgical manipulation and is comparable sensitive in reflecting a neurophysiologic event*<br>(2). Cost-effectiveness and surgeon-friendly electrode setup*<br>(3). Higher (needle electrode) or comparable (adhesive electrode) EMG amplitudes*<br>(4). Enable of more robust EBSLN monitoring*<br>(5). Suitable for pediatric and tracheostomy cases | (1). Requires an adequate skin flap elevation to expose the thyroid cartilage, limit of use in procedures with small or no neck incision wound.<br>(2). Electrode (needle) insertion may be complicated by scar tissue caused by revision surgery or, in older adults, by calcified TC<br>(3). Intralaryngeal penetration of (needle) electrode may cause laryngeal hematoma, laceration, infection, or rupture of an endotracheal cuff |
| **Percutaneous** | (1). and (2). same as Transcartilage method<br>(3). High (needle electrode) EMG amplitudes recorded*<br>(4). Feasible and useful for small incision and remote access procedures | (1). Longer electrode (needle) may be required according to different approach of remote access.<br>(2). Electrode (needle) insertion may cause inadvertent injury to the cricothyroid or strap muscle, and can inadvertently record far field potentials.<br>(3). Excessive skin retraction could cause percutaneous electrode displacement. |
| **Transcutaneous** | (1). and (2) same as Transcartilage/Percutaneous method<br>(3). Biphasic EMG signals of acceptable quality recorded (adhesive skin electrode) | (1) The recorded EMG amplitude of skin electrode is relatively lower*<br>(2) The electrode sensitivity could be affected by patient characteristics (short or obese neck), tumor size, and degree of subplatysmal flap elevation. |

**as compared to EMG endotracheal tube recording.*
*AL, anterior laryngeal; EMG, electromyography; TC, thyroid cartilage; EBSLN, external branch of superior laryngeal nerve.*

physiological information that may be applicable in transcutaneous AL recording. In the future, these sensors may be integrated in various transcutaneous, transcartilage or ET-base surface electrode designs for IONM recording during thyroid surgery.

## CONCLUSION

In the current era in which quality of life is increasingly included as a surgical outcome measure, voice outcome after thyroidectomy is an important consideration for both patients and any clinician involved in managing such patients. Several methods and technologies are being developed to overcome the limitations and disadvantages of the current IONM system that relies on EMG ET recording. This article reviews major recent developments and progress in new and emerging transcartilage, percutaneous, and transcutaneous AL recording techniques used during IONM. In comparison with the conventional ET recording method, many experimental and clinical studies have shown that these up-to-date AL recording methods have advantages of lower invasiveness, better EMG quality and stability, and avoidance of time-consuming disturbances for ET position verification. In addition, these methods are not only feasible for routine ordinary thyroid and parathyroid surgery, but also practical during thyroid or parathyroid surgery with a small incision, remote access, and in pediatric operations. Additional advantages of AL recordings include a cost-effective and surgeon-friendly set-up, allow for rapid implementation when an unexpected need, and the dislodged electrodes can be easily identified and managed intraoperatively. Although there are still some limitations of each recording method, we believe the continuous practical application and implementation of these developments will further optimize IONM to the ultimate benefit of thyroid surgery patients.

## AUTHOR CONTRIBUTIONS

CL, TY-H, CW-W, and GD conceived and designed the study. Administrative support was obtained by LF-W, HY-T, and YC-L. Provision of study materials by JW, L-PC, H-YT, Y-CL had collected and assembled the data. Data analysis and interpretation was done by F-YC, T-YH, and CL. All authors contributed to the article and approved the submitted version.

## FUNDING

This study was supported by grants from Kaohsiung Medical University Hospital (KMUH109-9M44), Kaohsiung Municipal Siaogang Hospital/Kaohsiung Medical University Research Center grants (KMHK-DK (C)110009, I-109-04, H-109-05, I-108-02) and Ministry of Science and Technology (MOST 108-2628-B-037-006, MOST 109-2628-B-037-014, MOST 110-2314-B-037-104-MY2, MOST 110-2314-B-037-120), Taiwan.

## ACKNOWLEDGMENTS

The authors would like to thank all authors of the papers included in this study, as well as participants in the contributing studies.

## REFERENCES

1. Jin S, Sugitani I. Narrative Review of Management of Thyroid Surgery Complications. *Gland Surg* (2021) 10(3):1135–46. doi: 10.21037/gs-20-859
2. Dralle H, Lorenz K, Machens A. Verdicts on Malpractice Claims After Thyroid Surgery: Emerging Trends and Future Directions. *Head Neck* (2012) 34(11):1591–6. doi: 10.1002/hed.21970
3. Gualniera P, Scurria S, Mondello C, Asmundo A, Sapienza D, Gianlorenzo D. Narrative Review of Proving the Causal Link of Recurrent Laryngeal Nerve Injury and Thyroidectomy: A Medico Legal Appraisal. *Gland Surg* (2020) 9 (5):1564–72. doi: 10.21037/gs-20-203
4. Randolph GW, Kamani D, Wu C-W, Schneider R. 36 - Surgical Anatomy and Monitoring of the Recurrent Laryngeal Nerve. In: Randolph GW, editor. *Surgery of the Thyroid and Parathyroid Glands*, *3rd ed.* Boston: Elsevier (2021). p. 326–59.e10.
5. Randolph GW, Dralle H, Abdullah H, Barczynski M, Bellantone R, Brauckhoff M, et al. Electrophysiologic Recurrent Laryngeal Nerve Monitoring During Thyroid and Parathyroid Surgery: International Standards Guideline Statement. *Laryngoscope* (2011) 121(Suppl 1):S1–16. doi: 10.1002/lary.21119
6. Tsai CJ, Tseng KY, Wang FY, Lu IC, Wang HM, Wu CW, et al. Electromyographic Endotracheal Tube Placement During Thyroid Surgery in Neuromonitoring of Recurrent Laryngeal Nerve. *Kaohsiung J Med Sci* (2011) 27(3):96–101. doi: 10.1016/j.kjms.2010.08.002
7. Lu IC, Chu KS, Tsai CJ, Wu CW, Kuo WR, Chen HY, et al. Optimal Depth of NIM EMG Endotracheal Tube for Intraoperative Neuromonitoring of the Recurrent Laryngeal Nerve During Thyroidectomy. *World J Surg* (2008) 32 (9):1935–9. doi: 10.1007/s00268-008-9549-1
8. Wu CW, Wang MH, Chen CC, Chen HC, Chen HY, Yu JY, et al. Loss of Signal in Recurrent Nerve Neuromonitoring: Causes and Management. *Gland Surg* (2015) 4(1):19–26. doi: 10.3978/j.issn.2227-684X.2014.12.03
9. Kim HY, Tufano RP, Randolph G, Barczynski M, Wu CW, Chiang FY, et al. Impact of Positional Changes in Neural Monitoring Endotracheal Tube on Amplitude and Latency of Electromyographic Response in Monitored Thyroid Surgery: Results From the Porcine Experiment. *Head Neck* (2016) 38(Suppl 1):E1004–8. doi: 10.1002/hed.24145
10. Barber SR, Liddy W, Kyriazidis N, Cinquepalmi M, Lin BM, Modi R, et al. Changes in Electromyographic Amplitudes But Not Latencies Occur With Endotracheal Tube Malpositioning During Intraoperative Monitoring for Thyroid Surgery: Implications for Guidelines. *Laryngoscope* (2017) 127 (9):2182–8. doi: 10.1002/lary.26392
11. Zhang D, Wu CW, Wang T, Zhao Y, Kim HY, Pino A, et al. Drawbacks of Neural Monitoring Troubleshooting Algorithms in Transoral Endoscopic Thyroidectomy. *Langenbeck's Arch Surg* (2021). doi: 10.1007/s00423-021-02217-6
12. Brauckhoff K, Vik R, Sandvik L, Heimdal JH, Aas T, Biermann M, et al. Impact of EMG Changes in Continuous Vagal Nerve Monitoring in High-Risk Endocrine Neck Surgery. *World J Surg* (2016) 40(3):672–80. doi: 10.1007/s00268-015-3368-y
13. Mazzone S, Esposito A, Giacomarra V. Continuous Intraoperative Nerve Monitoring in Thyroid Surgery: Can Amplitude Be a Standardized Parameter? *Front Endocrinol* (2021) 12:873. doi: 10.3389/fendo.2021.714699

14. Wu CW, Chiang FY, Randolph GW, Dionigi G, Kim HY, Lin YC, et al. Feasibility of Intraoperative Neuromonitoring During Thyroid Surgery Using Transcartilage Surface Recording Electrodes. *Thyroid Off J Am Thyroid Assoc* (2018) 28(11):1508–16. doi: 10.1089/thy.2017.0680
15. Wu CW, Chiang FY, Randolph GW, Dionigi G, Kim HY, Lin YC, et al. Transcutaneous Recording During Intraoperative Neuromonitoring in Thyroid Surgery. *Thyroid Off J Am Thyroid Assoc* (2018) 28(11):1500–7. doi: 10.1089/thy.2017.0679
16. Zhao Y, Li C, Zhang D, Zhou L, Liu X, Li S, et al. Experimental Study of Needle Recording Electrodes Placed on the Thyroid Cartilage for Neuromonitoring During Thyroid Surgery. *Br J Surg* (2019) 106(3):245–54. doi: 10.1002/bjs.10994
17. Huang TY, Lin YC, Tseng HY, Kim HY, Dionigi G, Lu IC, et al. Full Percutaneous Intraoperative Neuromonitoring Technique in Remote Thyroid Surgery: Porcine Model Feasibility Study. *Head Neck* (2021) 43 (2):505–13. doi: 10.1002/hed.26500
18. Zhao Y, Zhang D, Zhou L, Li S, Wang T, Li F, et al. Proprieties of Adhesive Surface Arrays to Thyroid Cartilage for Recurrent Laryngeal Nerve Monitoring. *Ann Trans Med* (2021) 9(8):690. doi: 10.21037/atm-21-1229
19. Chiang F-Y, Lu IC, Chang P-Y, Dionigi G, Randolph GW, Sun H, et al. Comparison of EMG Signals Recorded by Surface Electrodes on Endotracheal Tube and Thyroid Cartilage During Monitored Thyroidectomy. *Kaohsiung J Med Sci* (2017) 33(10):503–9. doi: 10.1016/j.kjms.2017.06.014
20. Liddy W, Lawson BR, Barber SR, Kamani D, Shama M, Soylu S, et al. Anterior Laryngeal Electrodes for Recurrent Laryngeal Nerve Monitoring During Thyroid and Parathyroid Surgery: New Expanded Options for Neural Monitoring. *Laryngoscope* (2018) 128(12):2910–5. doi: 10.1002/lary.27362
21. Van Slycke S, Van Den Heede K, Magamadov K, Brusselaers N, Vermeersch H. New Placement of Recording Electrodes on the Thyroid Cartilage in Intra-Operative Neuromonitoring During Thyroid Surgery. *Langenbeck's Arch Surg* (2019) 404(6):703–9. doi: 10.1007/s00423-019-01825-7
22. Chiang FY, Wu CW, Chang PY, Wu SH, Chen HY, Lin YC, et al. Trans-Thyroid Cartilage Recording for Neural Monitoring of the Recurrent Laryngeal Nerve in Thyroid Surgery. *Laryngoscope* (2020) 130(4):E280–e3. doi: 10.1002/lary.28049
23. Jung SM, Tae K, Song CM, Lee SH, Jeong JH, Ji YB. Efficacy of Transcartilaginous Electrodes for Intraoperative Neural Monitoring During Thyroid Surgery. *Clin Exp otorhinolaryngol* (2020) 13(4):422–8. doi: 10.21053/ceo.2019.01529
24. Lee HS, Seo SG, Kim DY, Kim SW, Choi Y, Lee KD. Intraoperative Neuromonitoring Using a Single Transcartilage Needle Electrode During Thyroidectomy. *Laryngoscope* (2021) 131(2):448–52. doi: 10.1002/lary.28835
25. Li P, Liang QZ, Wang DL, Han B, Yi X, Wei W, et al. The Transcutaneous Electromyography Recording Method for Intraoperative Neuromonitoring of Recurrent Laryngeal Nerve During Minimally Invasive Parathyroidectomy. *Sci Rep* (2020) 10(1):7609. doi: 10.1038/s41598-020-64675-0
26. Lee HS, Oh J, Kim SW, Jeong YW, Wu CW, Chiang FY, et al. Intraoperative Neuromonitoring of Recurrent Laryngeal Nerve During Thyroidectomy With Adhesive Skin Electrodes. *World J Surg* (2020) 44(1):148–54. doi: 10.1007/s00268-019-05208-3
27. Türk Y, Kıvratma G, Özdemir M, İçöz G, Makay Ö. The Use of Thyroid Cartilage Needle Electrodes in Intraoperative Neuromonitoring During Thyroidectomy: A Case-Control Study. *Head Neck* (2021) 43(11):3287–93. doi: 10.1002/hed.26810
28. Huang TY, Kim HY, Dionigi G, Lu IC, Chang PY, Chiang FY, et al. Laryngeal Neural Monitoring During Pediatric Thyroid Cancer Surgery-Is Transcartilage Recording a Preferable Method? *Cancers (Basel)* (2021) 13 (16):4051. doi: 10.3390/cancers13164051
29. Shin SC, Sung ES, Kwon HK, Cheon YI, Lee M, Lee JC, et al. Investigation of Attachment Location of Adhesive Skin Electrodes for Intraoperative Neuromonitoring in Thyroid Surgery: Preclinical and Clinical Studies. *Surgery* (2021). doi: 10.1016/j.surg.2021.07.037
30. Iwata AJ, Liddy W, Barczyński M, Wu CW, Huang TY, Van Slycke S, et al. Superior Laryngeal Nerve Signal Attenuation Influences Voice Outcomes in Thyroid Surgery. *Laryngoscope* (2021) 131(6):1436–42. doi: 10.1002/lary.29413
31. Stack BC Jr, Twining C, Rastatter J, Angelos P, Baloch Z, Diercks G, et al. Consensus Statement by the American Association of Clinical Endocrinologists (Aace) and the American Head and Neck Society Endocrine Surgery Section (Ahns-Es) on Pediatric Benign and Malignant Thyroid Surgery. *Endocr Pract* (2020) 43(4):1027–42. doi: 10.1002/hed.26586
32. Schneider R, Machens A, Sekulla C, Lorenz K, Weber F, Dralle H. Twenty-Year Experience of Paediatric Thyroid Surgery Using Intraoperative Nerve Monitoring. *Br J Surg* (2018) 105(8):996–1005. doi: 10.1002/bjs.10792
33. Bergenfelz A, Salem AF, Jacobsson H, Nordenström E, Almquist M. Risk of Recurrent Laryngeal Nerve Palsy in Patients Undergoing Thyroidectomy With and Without Intraoperative Nerve Monitoring. *Br J Surg* (2016) 103 (13):1828–38. doi: 10.1002/bjs.10276
34. Staubitz JI, Watzka F, Poplawski A, Riss P, Clerici T, Bergenfelz A, et al. Effect of Intraoperative Nerve Monitoring on Postoperative Vocal Cord Palsy Rates After Thyroidectomy: European Multicentre Registry-Based Study. *BJS Open* (2020) 4(5):821–9. doi: 10.1002/bjs5.50310
35. Abdelhamid A, Aspinall S. Intraoperative Nerve Monitoring in Thyroid Surgery: Analysis of United Kingdom Registry of Endocrine and Thyroid Surgery Database. *Br J Surg* (2021) 108(2):182–7. doi: 10.1093/bjs/znaa081
36. Feng AL, Puram SV, Singer MC, Modi R, Kamani D, Randolph GW. Increased Prevalence of Neural Monitoring During Thyroidectomy: Global Surgical Survey. *Laryngoscope* (2020) 130(4):1097–104. doi: 10.1002/lary.28210
37. Dralle H, Sekulla C, Lorenz K, Brauckhoff M, Machens A. Intraoperative Monitoring of the Recurrent Laryngeal Nerve in Thyroid Surgery. *World J Surg* (2008) 32(7):1358–66. doi: 10.1007/s00268-008-9483-2
38. Wong KP. Non-Invasive Recording During Intra-Operative Neuro-Monitoring in Thyroid Surgery: Omitting Surface Electrode and Oversize Endotracheal Tube. *Gland Surg* (2019) 8(4):312–4. doi: 10.21037/gs.2018.10.07
39. Yang Y-C, Lin Y-T, Yu J, Chang H-T, Lu T-Y, Huang T-Y, et al. MXene Nanosheet-Based Microneedles for Monitoring Muscle Contraction and Electrostimulation Treatment. *ACS Appl Nano Mater* (2021) 4(8):7917–24. doi: 10.1021/acsanm.1c01237
40. Sung ES, Lee JC, Shin SC, Kwon HG, Kim MS, Kim DJ, et al. Development of a Novel Intraoperative Neuromonitoring System Using a Surface Pressure Sensor to Detect Muscle Movement: A Rabbit Model Study. *Clin Exp Otorhinolaryngol* (2019) 12(2):217–23. doi: 10.21053/ceo.2018.01207
41. Sung ES, Shin SC, Kwon HK, Kim J, Park DH, Choi SW, et al. Application of Novel Intraoperative Neuromonitoring System Using an Endotracheal Tube With Pressure Sensor During Thyroid Surgery: A Porcine Model Study. *Clin Exp Otorhinolaryngol* (2020) 13(3):291–8. doi: 10.21053/ceo.2019.01249
42. Sung ES, Lee JC, Shin SC, Kwon HK, Na HS, Park DH, et al. Development of a Novel Intraoperative Neuromonitoring System Using an Accelerometer Sensor in Thyroid Surgery: A Porcine Model Study. *Clin Exp Otorhinolaryngol* (2019) 12(4):420–6. doi: 10.21053/ceo.2019.00423
43. Kim DH, Lu N, Ma R, Kim YS, Kim RH, Wang S, et al. Epidermal Electronics. *Sci (New York NY)* (2011) 333(6044):838–43. doi: 10.1126/science.1206157


**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Endocrinology

ORIGINAL RESEARCH
published: 11 November 2021
doi: 10.3389/fendo.2021.788878

Check for updates

# Correlation Between Objective and Subjective High-Pitched Voice Impairment in Patients After Thyroid Surgery

*Tzu-Yen Huang*[1,2,3], *Wing-Hei Viola Yu*[1], *Feng-Yu Chiang*[4,5], *Che-Wei Wu*[1,6], *Shih-Chen Fu*[7,8], *An-Shun Tai*[7,8], *Yi-Chu Lin*[1], *Hsin-Yi Tseng*[1], *Ka-Wo Lee*[1,9] *and Sheng-Hsuan Lin*[7,8,10,11]*

[1] International Thyroid Surgery Center, Department of Otolaryngology-Head and Neck Surgery, Kaohsiung Medical University Hospital, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan, [2] Department of Biological Science and Technology, National Yang Ming Chiao Tung University, Hsinchu, Taiwan, [3] Department of Biological Science and Technology, National Chiao Tung University, Hsinchu, Taiwan, [4] Department of Otolaryngology-Head and Neck Surgery, E-Da Hospital, Kaohsiung, Taiwan, [5] School of Medicine, College of Medicine, I-Shou University, Kaohsiung, Taiwan, [6] Department of Otolaryngology-Head and Neck Surgery, Kaohsiung Municipal Siaogang Hospital, Kaohsiung Medical University Hospital, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan, [7] Institute of Statistics, National Yang Ming Chiao Tung University, Hsinchu, Taiwan, [8] Institute of Statistics, National Chiao Tung University, Hsinchu, Taiwan, [9] Department of Otolaryngology-Head and Neck Surgery, Kaohsiung Municipal Tatung Hospital, Kaohsiung Medical University Hospital, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan, [10] Institute of Data Science and Engineering, National Yang Ming Chiao Tung University, Hsinchu, Taiwan, [11] Institute of Data Science and Engineering, National Chiao Tung University, Hsinchu, Taiwan



**Edited by:**
*Akira Sugawara,*
*Tohoku University, Japan*

**Reviewed by:**
*Pietro Giorgio Calo',*
*University of Cagliari, Italy*
*Zhao Yishen,*
*Jilin University, China*

***Correspondence:**
*Sheng-Hsuan Lin*
*shenglin@nctu.edu.tw*

**Specialty section:**
*This article was submitted to Thyroid Endocrinology, a section of the journal Frontiers in Endocrinology*

**Received:** *03 October 2021*
**Accepted:** *25 October 2021*
**Published:** *11 November 2021*

**Citation:**
*Huang T-Y, Yu W-HV, Chiang F-Y, Wu C-W, Fu S-C, Tai A-S, Lin Y-C, Tseng H-Y, Lee K-W and Lin S-H (2021) Correlation Between Objective and Subjective High-Pitched Voice Impairment in Patients After Thyroid Surgery. Front. Endocrinol. 12:788878. doi: 10.3389/fendo.2021.788878*

**Objectives:** High-pitched voice impairment (HPVI) is not uncommon in patients without recurrent laryngeal nerve (RLN) or external branch of superior laryngeal nerve (EBSLN) injury after thyroidectomy. This study evaluated the correlation between subjective and objective HPVI in patients after thyroid surgery.

**Methods:** This study analyzed 775 patients without preoperative subjective HPVI and underwent neuromonitored thyroidectomy with normal RLN/EBSLN function. Multi-dimensional voice program, voice range profile and Index of voice and swallowing handicap of thyroidectomy (IVST) were performed during the preoperative(I) period and the immediate(II), short-term(III) and long-term(IV) postoperative periods. The severity of objective HPVI was categorized into four groups according to the decrease in maximum frequency (Fmax): <20%, 20-40%, 40-60%, and >60%. Subjective HPVI was evaluated according to the patient's answers on the IVST.

**Results:** As the severity of objective HPVI increased, patients were significantly more to receive bilateral surgery (p=0.002) and have subjective HPVI (p<0.001), and there was no correlation with IVST scores. Among 211(27.2%) patients with subjective HPVI, patients were significantly more to receive bilateral surgery (p=0.003) and central neck dissection (p<0.001). These patients had very similar trends for Fmax, pitch range, and mean fundamental frequency as patients with 20-40% Fmax decrease (p>0.05) and had higher Jitter, Shimmer, and IVST scores than patients in any of the objective HPVI groups; subjective HPVI lasted until period-IV.

**Conclusion:** The factors that affect a patient's subjective HPVI are complex, and voice stability (Jitter and Shimmer) is no less important than the Fmax level. When patients have subjective HPVI without a significant Fmax decrease after thyroid surgery, abnormal voice stability should be considered and managed. Fmax and IVST scores should be interpreted comprehensively, and surgeons and speech-language pathologists should work together to identify patients with HPVI early and arrange speech therapy for them. Regarding the process of fibrosis formation, anti-adhesive material application and postoperative intervention for HPVI require more future research.

**Keywords: thyroid surgery, high-pitched voice impairment (HPVI), Index of Voice and Swallowing Handicap of Thyroidectomy (IVST), intraoperative neuromonitoring (IONM), voice stability**

## INTRODUCTION

Thyroid surgery is a precise operation that requires, to the greatest extent possible, the preservation of the function of adjacent nerves when removing thyroid lesions. Intraoperative neural monitoring (IONM), as an adjunct technique for localizing and identifying the recurrent laryngeal nerve (RLN) and the external branch of the superior laryngeal nerve (EBSLN), has been widely studied and used in routine thyroid surgery (1, 2). The qualitative and quantitative information provided by IONM is far superior to visual identification of nerves alone, and standardized procedures and guidelines have been proposed in several studies, enabling more reliable recording of RLN status (3–7).

High-pitched voice impairment (HPVI) is not uncommon after thyroid surgery, and HPVI not only affects the performance of professional voice users but may cause a decline in the quality of life of nonprofessional voice users (8). The cricothyroid muscle (CTM) innervated by the EBSLN can lengthen the vocal fold and increase the fundamental frequency of vocal fold vibration to produce a higher-pitched voice; thus, many studies have focused on the relationship between the EBSLN and HPVI (9, 10). However, there are more studies that support the finding that HPVI can frequently appear in patients without RLN or EBSLN injury (11–13). After thyroidectomy, fibrosis may form between the strap muscles and laryngotracheal unit and impair the vertical movement (14), and may form in lateral extralaryngeal muscles when overtraction during the surgery. If fibrosis is formed between strap muscle and CTM, HPVI may be caused by limited movement of CTM.

To the best of our knowledge, there is currently no research investigating patients with objective and subjective HPVI after thyroid surgery by serial objective and subjective voice analysis. Furthermore, a standardized IONM procedure was applied in this study to exclude intraoperative RLN or EBSLN injury. This study aims to evaluate the correlation between objective and subjective HPVI in patients after thyroid surgery.

## MATERIALS AND METHODS

This study retrospectively enrolled 1,027 patients who underwent neuromonitored primary thyroid surgery at Kaohsiung Medical University Hospital from June 2013 to December 2019. The exclusion criteria included patients younger than 18 years at the time of surgery (n=25), patients who received previous neck surgery or previous neck irradiation, patients who had head and neck malignancy other than thyroid cancer (n=51), patients who underwent lateral neck dissection (n=30), patients who had impaired vocal fold motion before surgery (n=17), patients who had intraoperative RLN or EBSLN injury (n=88), and patients who had preoperative subjective HPVI (n=41). A flow diagram illustrating the inclusion and exclusion of patients is shown in **Figure 1**. 775 patients were analyzed in this study. All surgeries were performed by experienced thyroid surgeons (F-Y. C, C-W. W, and T-Y. H) in the IONM team at Kaohsiung Medical University Hospital (3, 15). Ethical approval for this study was obtained from the Kaohsiung Medical University Hospital Institutional Review Board (KMUHIRB-E(I)-20200358). In all patients, vagus nerve and RLN function were routinely evaluated using the standard (V1-R1-S1-S2-R2-V2) procedure under IONM (2, 3). The EMG amplitudes of R2 and R1 signals were compared, and an R2 signal showing a >50% decrease from the R1 signal was defined as RLN injury. EBSLN integrity is measured by EBSLN monitoring according to international guidance (5). The five steps included the following: E (Expose the space harboring the EBSLN), B (Bluntly dissect tissues), S (Stimulate tissues during dissection), L (Look for CTM twitch), and N (Navigate the dissection using the nerve mapping technique). S2 stimulation at the most proximal EBSLN was performed at the end of the operation. Once CTM twitching could not observed after S2 stimulation, it was defined as EBSLN injury.

Patient information, including gender, age, surgical extent (unilateral or bilateral surgery), pathology report (benign or malignant), and central neck dissection (CND), was recorded

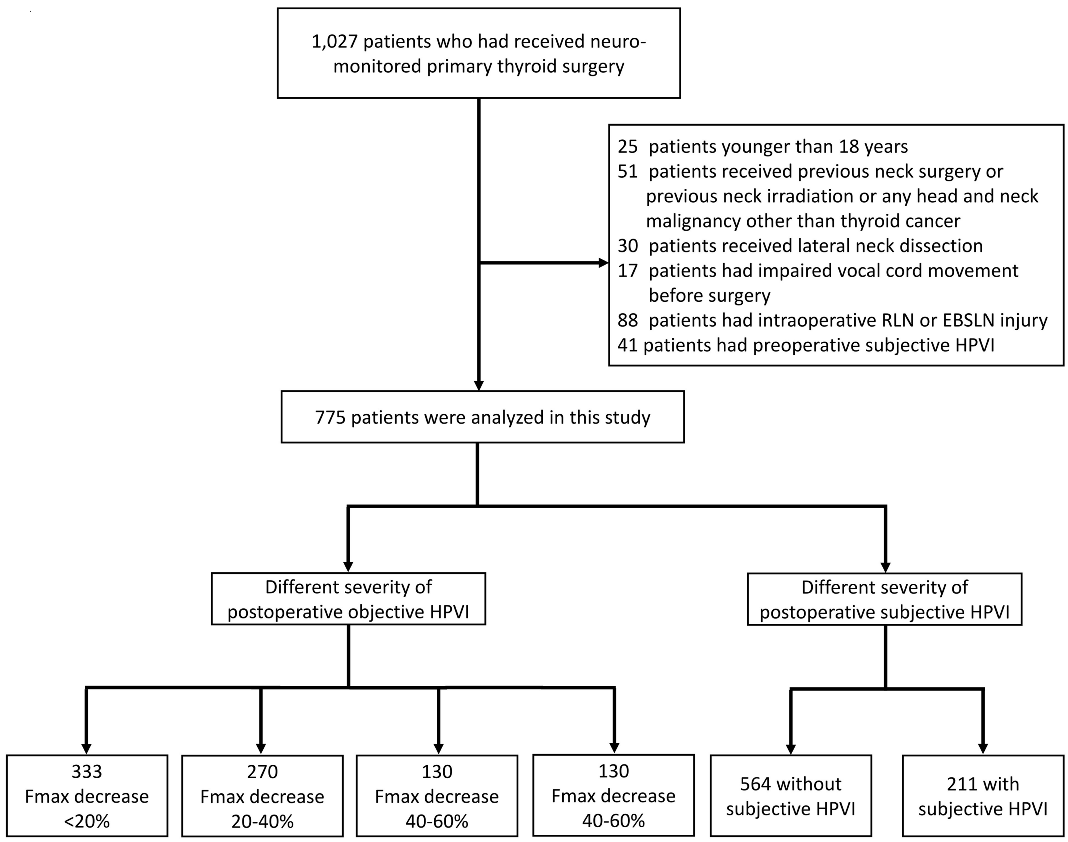



**FIGURE 1** | Flow diagram for inclusion and exclusion of patients. RLN, recurrent laryngeal nerve; EBSLN, external branch of superior laryngeal nerve; HPVI, high-pitched voice impairment; Fmax, maximum pitch frequency.

and compared between groups. Laryngofiberscopy was documented by video in all patients before surgery and 2 weeks after surgery, and no patient in this study had preoperative asymmetric vocal fold motion.

## Objective and Subjective Voice Analysis

Subjective and objective voice analyses were performed for all patients in four periods: preoperative period (period-I, within 2 months before surgery); immediate postoperative period (period-II, median duration of 3 days, range of 1-7 days); short-term postoperative period (period-III, median duration of 12 days, range of 7-30 days); and long-term postoperative period (period IV, median duration of 40 days, range of 30-90 days).

All objective voice analyses were performed by a single experienced speech-language pathologist (WHV. Y). The Multidimensional Voice Program (MDVP, model 5105, version 3.1.7; KayPENTAX, USA) results included mean fundamental frequency (Mean F0), Jitter, Shimmer and noise-to-harmonic ratio (NHR). The Voice Range Profile (VRP, model 4326, version 3.3.0; KayPENTAX, USA) results included maximum pitch frequency (Fmax), minimum pitch frequency (Fmin), and pitch range (PR). PR was defined as the number of semitones between Fmax and Fmin. The comparison of preoperative Fmax and the worst Fmax more than 7 days after surgery was used as the Fmax grouping. The groups were divided into four categories according to Fmax decrease: <20%, 20-40%, 40-60%, and >60%.

The subjective voice analysis was evaluated by the Index of Voice and Swallowing Handicap of Thyroidectomy (IVST) (**Table 1**). The IVST was designed based on the main symptoms observed before and after thyroid surgery. Each of the 10 questionnaire items in this subjective assessment is assigned a score of 0 (never), 1 (sometimes), or 2 (always). The voice domain (IVST-V) includes items 1-7 and has a score range of 0-14. The swallowing domain (IVST-S) includes items 8-10 and has a score range of 0 to 6. Thus, the total IVST score (IVST-T) has a score range of 0 to 20. The sixth question on the IVST is "I find it difficult to make a high-pitched voice." All patients in this study answered "never" (0 points) to this question preoperatively. The patients who answered "sometimes" (1 point) or "always" (2 points) at least 7 days postoperatively were defined as having postoperative subjective HPVI.

The equation for calculating postoperative change in objective voice analysis data was $\Delta = (B - A)/A$; the equation for calculating postoperative change in subjective voice analysis data was $\Delta = B - A$, where A and B are the preoperative and postoperative values, respectively.

**TABLE 1 |** Index of voice and swallowing handicap of thyroidectomy (IVST).

| Questions | Never (0 point) | Sometimes (1 point) | Always (2 points) |
|---|---|---|---|
| Voice domain | | | |
| 1. My overall voice quality is abnormal. | 0 | 1 | 2 |
| 2. My voice difficulties restrict personal and social life. | 0 | 1 | 2 |
| 3. I feel my voice is hoarse. | 0 | 1 | 2 |
| 4. I feel as though I have to strain to produce voice. | 0 | 1 | 2 |
| 5. The sound of my voice varies throughout the day. | 0 | 1 | 2 |
| 6. I find it difficult to make a high-pitched voice. | 0 | 1 | 2 |
| 7. I find it difficult to make a low-pitched voice. | 0 | 1 | 2 |
| | | **IVST-V = ______ (Range from 0-14)** | |
| Swallowing domain | | | |
| 8. I feel strained when I speak or swallow. | 0 | 1 | 2 |
| 9. I choke when I drink (water or tea). | 0 | 1 | 2 |
| 10. I choke when I eat. | 0 | 1 | 2 |
| | | **IVST-S = ______ (Range from 0-6)** | |
| Total score | | **IVST-T = ______ (Range from 0-20)** | |

## Statistical Analysis

To analyze the variables, independent t tests, Pearson chi-square tests, and ANOVA tests were performed using R software (version-3.4). A two-tailed p value less than 0.05 was considered statistically significant.

# RESULTS

## Demographic Characteristics of Patients With Different Severity of Postoperative Objective HPVI

775 patients were analyzed in this study. The comparison between different severity of Fmax decrease (<20%, 20-40%, 40-60%, and >60%) is shown in **Table 2**. Age, gender and pathology report showed no significant difference between groups. Significantly more bilateral surgeries were performed in the group with higher severity of Fmax decrease (p=0.002). There were significant differences (p<0.001) in the proportion of patients receiving CNDs among the different Fmax decrease groups but not in the order of Fmax decrease severity. Significantly more patients with higher severity of Fmax decrease had subjective HPVI (p<0.001).

## Demographic Characteristics of Patients With and Without Postoperative Subjective HPVI

The comparison is shown in **Table 3**. Age and pathology report showed no significant differences between groups. The proportion of female patients was significantly higher in patients with subjective HPVI than in those without subjective HPVI (88.2% vs. 81.2%, p=0.022). The proportion of patients who received bilateral surgery was significantly higher in patients with subjective HPVI than in those without subjective HPVI (81.0% vs. 70.6%, p=0.003). The proportion of patients who received CND was significantly higher in patients with subjective

**TABLE 2 |** Demographic characteristics of patients with different severity of objective high-pitched voice impairment (HPVI).

| Total 775 patients | Fmax decrease | | | | p value |
|---|---|---|---|---|---|
| | <20% | 20-40% | 40-60% | >60% | |
| Case number | 333 (42.3%) | 270 (34.8%) | 130 (16.8%) | 42 (5.4%) | |
| Age ± SD | 50.9 ± 12.8 | 51.8 ± 13.1 | 53.4 ± 12.8 | 55.6 ± 13.3 | 0.073 |
| Gender (%) | | | | | 0.139 |
| male | 48 (14.4%) | 50 (18.5%) | 27 (20.8%) | 6 (14.3%) | |
| female | 285 (85.6%) | 220 (81.5%) | 103 (79.2%) | 36 (85.7%) | |
| Surgical extent (%) | | | | | 0.002 |
| unilateral | 105 (31.5%) | 70 (25.9%) | 26 (20.0%) | 5 (11.9%) | |
| bilateral | 228 (68.5%) | 200 (74.1%) | 104 (80.0%) | 37 (88.1%) | |
| CND | | | | | <0.001 |
| without | 294 (88.3%) | 231 (85.6%) | 101 (77.7%) | 36 (85.7%) | |
| with | 39 (11.7%) | 39 (14.4%) | 29 (22.3%) | 6 (14.3%) | |
| Pathology | | | | | 0.547 |
| benign | 228 (68.5%) | 183 (67.8%) | 80 (61.5%) | 30 (71.4%) | |
| malignant | 105 (31.5%) | 87 (32.2%) | 50 (38.5%) | 12 (28.6%) | |
| Patients with subjective HPVI | 29 (8.7%) | 74 (27.4%) | 73 (56.2%) | 35 (83.3%) | <0.001 |

*SD, standard deviation; CND, Central neck dissection.*

**TABLE 3 |** Demographic characteristics of patients with and without subjective high-pitched voice impairment (HPVI).

| Total 775 patients | Without subjective HPVI | With subjective HPVI | p value |
|---|---|---|---|
| Case number | 564 (72.8%) | 211 (27.2%) | |
| Age ± SD | 51.5 ± 12.7 | 52.9 ± 11.6 | 0.163 |
| Gender (%) | | | 0.022 |
| male | 106 (18.8%) | 25 (11.8%) | |
| female | 458 (81.2%) | 186 (88.2%) | |
| Surgical extent (%) | | | 0.003 |
| unilateral | 166 (29.4%) | 40 (19.0%) | |
| bilateral | 398 (70.6%) | 171 (81.0%) | |
| CND | | | <0.001 |
| without | 504 (89.4%) | 158 (74.9%) | |
| with | 60 (10.6%) | 53 (25.1%) | |
| Pathology | | | 0.315 |
| benign | 385 (68.3%) | 136 (64.5%) | |
| malignant | 179 (31.7%) | 75 (35.5%) | |

*SD, standard deviation; CND, central neck dissection.*

HPVI than in patients without subjective HPVI (25.1% vs. 10.6%, p<0.001).

## Voice Parameter Changes in Patients With Different Severity of Objective HPVI And Patients With Subjective HPVI

The voice parameter changes are shown in **Figure 2**. There were no significant differences between groups for Fmin or NHR. The Fmax and PR of patients with subjective HPVI were not significantly different than those of patients with an Fmax 20-40% decrease, and their results in the chart show a high degree of overlap. There was a significant difference in Mean F0 for patients with subjective HPVI and patients with Fmax decreases of 40-60% and >60%. The greater the Fmax decrease was, the lower the Mean F0.

The greater the Fmax decrease was, the higher the Jitter and Shimmer values. The Jitter and Shimmer values for patients with subjective HPVI were higher than those for patients in any of the objective HPVI groups.

The IVST-T, IVST-V and IVST-S scores showed no correlation with the different degrees of Fmax decrease. The postoperative IVST-T and IVST-V values for patients with subjective HPVI were higher than those for patients in any of the objective HPVI groups, especially during period IV.

## DISCUSSION

In this study, we investigated the correlation between subjective and objective HPVI in patients after monitored thyroid surgery and confirmed normal RLN/EBSLN function. We found that as the Fmax severity increased, significantly more patients received bilateral surgery (p=0.002) and had subjective HPVI (p<0.001) (**Table 2**). The objective HPVI patients tended to have decreased PR and Mean F0 and increased Jitter and Shimmer. However, the severity of objective HPVI was not correlated with subjective IVST scores (**Figure 2**). When patients had subjective HPVI, significantly more of them received bilateral surgery (p=0.003) and CND (p<0.001) (**Table 3**). Patients with subjective HPVI had very similar trends for Fmax, PR and Mean F0 as patients with an Fmax decrease of 20-40%. In addition, patients with subjective HPVI had higher Jitter, Shimmer, IVST-T and IVST-V levels than patients in any of the objective HPVI groups, and subjective HPVI lasted until period-IV (**Figure 2**). These data show the factors that affect a patient's subjective HPVI are very complex and voice stability (Jitter and Shimmer) is no less important than Fmax level. Therefore, when patients have subjective HPVI without a significant Fmax decrease after thyroid surgery, abnormal voice stability should be considered and managed.

In this study, bilateral surgery and CND were factors that were related to subjective HPVI in patients, while only bilateral surgery was a factor for Fmax decrease. The voice parameters, including PR and Mean F0, were correlated with Fmax decrease. CTM contraction elongates the vocal ligaments; when the tension of the vocal ligament is insufficient, Fmax, PR and Mean F0 will decrease (9, 16, 17). In this study, all patients received IONM-assisted thyroidectomy, all EBSLNs were stimulated, and CTM twitches were observed during surgery. There are fewer neurological factors for decreased CTM function, and patients with decreased CTM function are more likely to have decreased muscle contraction. During the operation, the fascia of CTM is usually left intact, but when there is local adhesion or the tumor is adjacent, it may still be partially exposed. After thyroid tumor resection, the strap muscles divided after the midline approach are routinely sutured; however, fibrosis formation between the CTM and strap muscles is still inevitable. Therefore, future studies are needed to verify whether anti-adhesive interventions can improve fibrosis on CTM, and voice parameters, including Fmax, PR and Mean F0, may be applicable in outcome evaluation.

The factors that affect subjective HPVI are much more complicated, and the subjective and objective voice parameters showed less correlation. Patients with a greater Fmax decrease had a higher proportion of subjective HPVI, however, the trends for Fmax, PR and Mean F0 in subjective HPVI patients were very similar as patients with an Fmax decrease of 20-40%, rather than closer to the more severe objective HPVI groups. This indicated that Fmax was not the only factor that causes subjective HPVI. For example, a higher proportion of CND in patients with

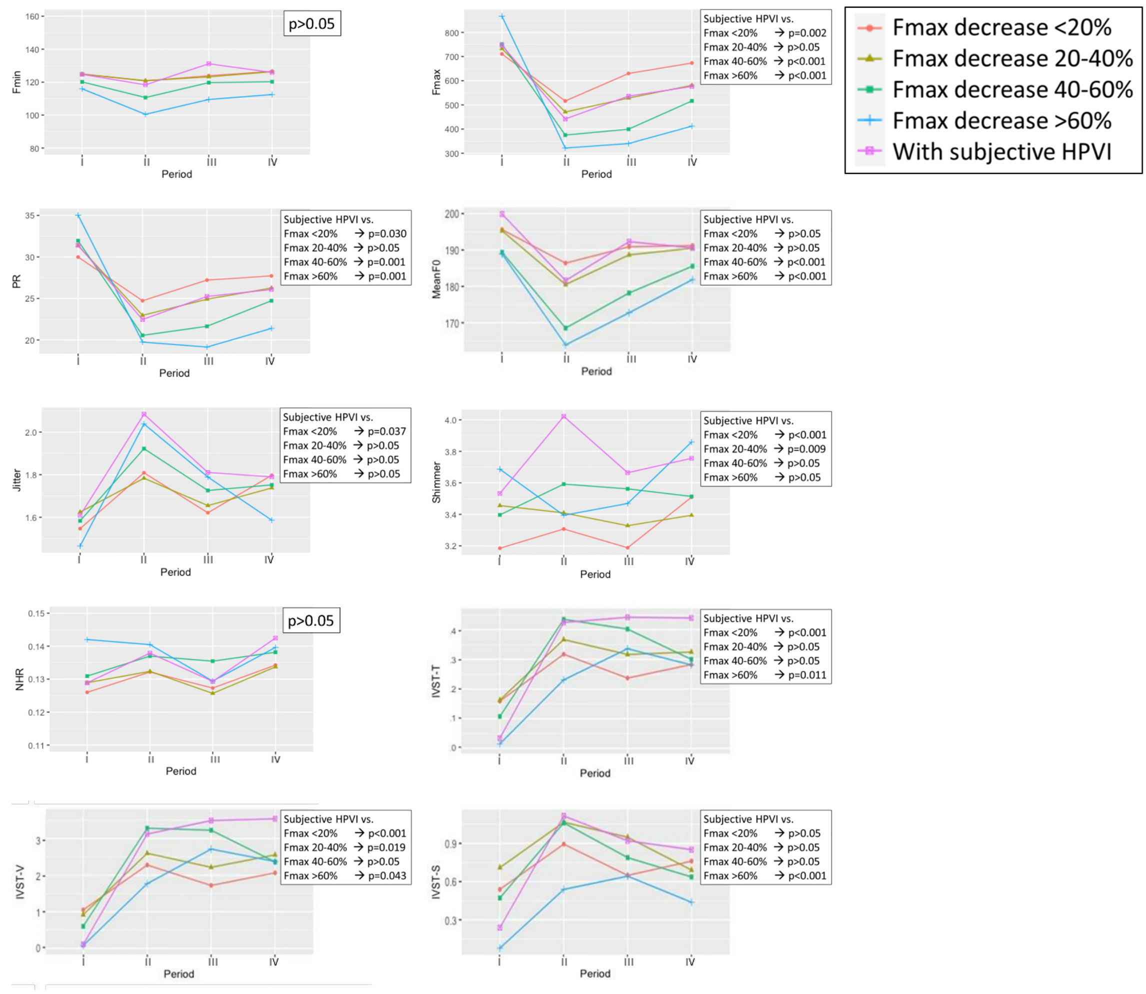



**FIGURE 2** | Voice parameter changes in patients with different severity of objective high-pitched voice impairment (HPVI) and patients with subjective HPVI in each follow-up period. Red line = Fmax decrease <20%; Olive line = Fmax decrease 20-40%; Green line = Fmax decrease 40-60%; Blue line = Fmax decrease > 60%; Purple line = Patients with subjective HPVI. period-I = Preoperative period (within 2 months before surgery); period-II = Immediate postoperative period (median duration of 3 days; range of 1-7 days); period-III = Short-term postoperative period (median duration of 12 days; range of 7-30 days); period-IV = Long-term postoperative period (median duration of 40 days, range of 30-90 days). A p value less than 0.05 was considered statistically significant.

subjective HPVI may imply that even if the dissection is performed away from CTM, there are still other factors that cause subjective HPVI. Although a higher degree of Fmax decrease was associated with higher values for Jitter and Shimmer, postoperative Jitter and Shimmer values were higher for patients with subjective HPVI than for patients in any of the objective HPVI groups. The factors related to subjective HPVI may be highly correlated with voice stability rather than simple CTM contractility. All patients enrolled in this study had comprehensive EMG signal recording, and none of the patients had EMG amplitude decreases >50%. The possible factors associated with decreased voice stability during thyroid surgery include fibrosis of the strap muscle or other extrinsic muscles or local soft tissue fibrosis (18). Therefore, varied anti-adhesive materials applied in thyroidectomy with different surgical routes may have a role in preventing fibrosis-related symptoms (19).

IVST-T and IVST-V showed no correlation with Fmax decrease, and patients with subjective HPVI had greater IVST-T and IVST-V, especially during period-IV. The factors most affecting subjective voice in the immediate postoperative and short-term postoperative period include intubation, laryngeal edema, and wound factors that restrict patients' phonation (20). However, during period-IV, the influence of these factors gradually subsided, suggesting that postoperative fibrosis may play an important role and may mainly affect voice stability. To prevent fibrosis after thyroidectomy, instructing patients to perform stretching exercises to reduce the symptoms of postoperative neck discomfort is suggested (21). To determine whether postoperative fibrosis is related to CTM, the Fmax and IVST scores should be interpreted comprehensively. Surgeons and speech-language pathologists should work together to identify patients with postoperative HPVI early and arrange speech therapy for them. For example, when patients have persistent subjective HPVI 3 months after thyroid surgery and the objective voice parameters have gradually improved, the treatment target should include strap muscles and other extrinsic muscles not limited to the CTM. The precise duration of fibrosis-related HPVI remains unclear, and the treatment strategy also needs to be further studied.

Unlike objective voice analysis, subjective voice analysis based on data collected *via* a questionnaire will inevitably exhibit response bias (22). Among the patients with subjective HPVI, there were significantly more female patients. Females may be more likely to notice a change to a higher voice pitch, and males may be more likely to ignore it; a similar finding was also described by Park et al. (12) Acquiescence bias is a category of response bias in which respondents have a tendency to choose a positive response option (23), and approximately 10% to 20% of respondents exhibit this behavior (24). In our study, the IVST-S of the subjective HPVI patients had a higher value than that for any of the objective HPVI groups. Although the difference is not significant, it is still hard to identify an anatomical explanation. Given that the subjective HPVI patients had higher IVST-V values, there may have been an acquiescence bias that increased the average IVST-S value. It is notable that the IVST-S of subjective HPVI patients decreased during period IV, similar to the trend observed for the IVST-S of objective HPVI patients; this was not observed for IVST-T and IVST-V. Fibrosis as a main factor influencing HPVI has only a limited effect on swallowing. Short-term swallowing impairment and long-term improvements were also described in the study by Lombardi et al. (14)

This study has several limitations. First, patients with preoperative subjective HPVI were excluded from this study, as the purpose was to exclude other long-term nonsurgical factors causing HPVI. Patients with preoperative HPVI may need preoperative preventive treatment and postoperative evaluation and management, and this requires further research and analysis. Second, patients with thyroid cancer may require lateral neck dissection, and how surgical dissection and postoperative fibrosis impact HPVI remains unclear and requires future research. Last, Jitter and Shimmer of MDVP is measured by the fundamental frequency of patients' voices. Evaluating Jitter and Shimmer with a high-pitched frequency (high-pitched MDVP) or other novel objective voice analysis parameters could provide more information about high-pitched voice stability.

## CONCLUSION

In this study, the demographic characteristics and voice parameter changes of patients with subjective and objective HPVI after thyroidectomy were evaluated. A decrease in Fmax accompanied by PR and a decrease in Mean F0 showed an association with CTM contraction reduction. The factors that cause subjective HPVI in thyroidectomy patients are very complex, and voice stability (Jitter and Shimmer) is no less important than Fmax level. When patients have subjective HPVI without a significant Fmax decrease after thyroid surgery, abnormal voice stability should be considered and managed. Fmax and IVST scores should be interpreted comprehensively, and surgeons and speech-language pathologists should work together to identify patients with HPVI early and arrange speech therapy for them. Regarding the process of fibrosis formation, anti-adhesive material application and postoperative intervention for HPVI require more research in the future.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Kaohsiung Medical University Hospital Institutional Review Board (KMUHIRB-E(I)-20200358). The ethics committee waived the requirement of written informed consent for participation.

## AUTHOR CONTRIBUTIONS

Supervision – F-YC, C-WW, K-WL, and S-HL. Materials – T-YH, W-HV, F-YC, and C-WW. Data collection and processing – T-YH, W-HV, and S-HL. Analysis and interpretation- T-YH, S-CF, A-ST, and S-HL. Literature search - T-YH, W-HV, Y-CL, H-YT, and S-HL. Writing manuscript – All authors. All authors have read and agreed to the published version of the manuscript.


## FUNDING

This study was supported by grants from Kaohsiung Medical University Hospital, Kaohsiung Medical University (KMUH109-9M44), Kaohsiung Municipal Siaogang Hospital/Kaohsiung Medical University Research Center grants (KMHK-DK(C) 110009, I-109-04, H-109-05, I-108-02), and Ministry of Science and Technology (MOST 108-2628-B-037-006, MOST 109-2628-B-037-014, MOST 110-2636-B-009-008, MOST 110-2314-B-037-104-MY2, MOST 110-2314-B-037-120), Taiwan.

## ACKNOWLEDGMENTS

The authors would like to thank all authors of the papers included in this study, as well as participants in the contributing studies.

## REFERENCES


1. Chiang F-Y, Lu I-C, Tsai C-J, Hsiao P-J, Lee K-W, Wu C-W. Detecting and Identifying Nonrecurrent Laryngeal Nerve With the Application of Intraoperative Neuromonitoring During Thyroid and Parathyroid Operation. *Am J Otolaryngol* (2012) 33(1):1–5. doi: 10.1016/j.amjoto.2010.11.011
2. Chiang FY, Lu IC, Kuo WR, Lee KW, Chang NC, Wu CW. The Mechanism of Recurrent Laryngeal Nerve Injury During Thyroid Surgery–the Application of Intraoperative Neuromonitoring. *Surgery* (2008) 143(6):743–9. doi: 10.1016/j.surg.2008.02.006
3. Chiang FY, Lee KW, Chen HC, Chen HY, Lu IC, Kuo WR, et al. Standardization of Intraoperative Neuromonitoring of Recurrent Laryngeal Nerve in Thyroid Operation. *World J Surg* (2010) 34(2):223–9. doi: 10.1007/s00268-009-0316-8
4. Randolph GW, Dralle HGroup wtIIMS, , Abdullah H, Barczynski M, Bellantone R, et al. Electrophysiologic Recurrent Laryngeal Nerve Monitoring During Thyroid and Parathyroid Surgery: International Standards Guideline Statement. *Laryngoscope* (2011) 121(S1):S1–S16. doi: 10.1002/lary.21119
5. Barczyński M, Randolph GW, Cernea CR, Dralle H, Dionigi G, Alesina PF, et al. External Branch of the Superior Laryngeal Nerve Monitoring During Thyroid and Parathyroid Surgery: International Neural Monitoring Study Group Standards Guideline Statement. *Laryngoscope* (2013) 123:S1–14. doi: 10.1002/lary.24301
6. Schneider R, Randolph GW, Dionigi G, Wu CW, Barczynski M, Chiang FY, et al. International Neural Monitoring Study Group Guideline 2018 Part I: Staging Bilateral Thyroid Surgery With Monitoring Loss of Signal. *Laryngoscope* (2018) 128:S1–S17. doi: 10.1002/lary.27359
7. Wu CW, Dionigi G, Barczynski M, Chiang FY, Dralle H, Schneider R, et al. International Neuromonitoring Study Group Guidelines 2018: Part II: Optimal Recurrent Laryngeal Nerve Management for Invasive Thyroid Cancer—Incorporation of Surgical, Laryngeal, and Neural Electrophysiologic Data. *Laryngoscope* (2018) 128:S18–27. doi: 10.1002/lary.27360
8. Watt T, Groenvold M, Rasmussen AK, Bonnema SJ, Hegedüs L, Bjorner JB, et al. Quality of Life in Patients With Benign Thyroid Disorders. *A Rev Eur J Endocrinol* (2006) 154(4):501–10. doi: 10.1530/eje.1.02124
9. Kim SW, Kim ST, Park HS, Lee HS, Hong JC, Kwon SB, et al. Voice Examination in Patients With Decreased High Pitch After Thyroidectomy. *Indian J Otolaryngol Head Neck Surg* (2012) 64(2):120–30. doi: 10.1007/s12070-012-0516-7
10. Barczyński M, Konturek A, Stopa M, Honowska A, Nowak W. Randomized Controlled Trial of Visualization Versus Neuromonitoring of the External Branch of the Superior Laryngeal Nerve During Thyroidectomy. *World J Surg* (2012) 36(6):1340–7. doi: 10.1007/s00268-012-1547-7
11. Soylu L, Ozbas S, Uslu HY, Kocak S. The Evaluation of the Causes of Subjective Voice Disturbances After Thyroid Surgery. *Am J Surg* (2007) 194(3):317–22. doi: 10.1016/j.amjsurg.2006.10.009
12. Park J-O, Bae J-S, Lee S-H, Shim M-R, Hwang Y-S, Joo Y-H, et al. The Long-Term Prognosis of Voice Pitch Change in Female Patients After Thyroid Surgery. *World J Surg* (2016) 40(10):2382–90. doi: 10.1007/s00268-016-3511-4
13. Myers EN, Hong KH, Kim YK. Phonatory Characteristics of Patients Undergoing Thyroidectomy Without Laryngeal Nerve Injury. *Otolaryngology–Head Neck Surg* (1997) 117(4):399–404. doi: 10.1016/S0194-5998(97)70133-5
14. Lombardi CP, Raffaelli M, D'Alatri L, Marchese MR, Rigante M, Paludetti G, et al. Voice and Swallowing Changes After Thyroidectomy in Patients Without Inferior Laryngeal Nerve Injuries. *Surgery* (2006) 140(6):1026–34. doi: 10.1016/j.surg.2006.08.008
15. Chiang FY, Lu IC, Chang PY, Dionigi G, Randolph GW, Sun H, et al. Comparison of EMG Signals Recorded by Surface Electrodes on Endotracheal Tube and Thyroid Cartilage During Monitored Thyroidectomy. *Kaohsiung J Med Sci* (2017) 33(10):503–9. doi: 10.1016/j.kjms.2017.06.014
16. Titze IR, Hunter EJ. Normal Vibration Frequencies of the Vocal Ligament. *J Acoustical Soc America* (2004) 115(5):2264–9. doi: 10.1121/1.1698832
17. Lowell SY, Story BH. Simulated Effects of Cricothyroid and Thyroarytenoid Muscle Activation on Adult-Male Vocal Fold Vibration. *J Acoustical Soc America* (2006) 120(1):386–97. doi: 10.1121/1.2204442
18. Park KS, Lee KE, Ku DH, Kim S-J, Park WS, Kim HY, et al. Antiadhesive Effect and Safety of Oxidized Regenerated Cellulose After Thyroidectomy: A Prospective, Randomized Controlled Study. *J Korean Surg Soc* (2013) 84(6):321–9. doi: 10.4174/jkss.2013.84.6.321
19. Alkan Z, Yigit O, Adatepe T, Uzun N, Kocak I, Sunter V, et al. Effect of Anti-Adhesive Barrier Use on Laryngotracheal Movement After Total Thyroidectomy: An Electrophysiological Study. *Indian J Otolaryngol Head Neck Surg* (2014) 66(1):71–7. doi: 10.1007/s12070-011-0319-2
20. Debruyne F, Ostyn F, Delaere P, Wellens W. Acoustic Analysis of the Speaking Voice After Thyroidectomy. *J Voice* (1997) 11(4):479–82. doi: 10.1016/S0892-1997(97)80046-X
21. Takamura Y, Miyauchi A, Tomoda C, Uruno T, Ito Y, Miya A, et al. Stretching Exercises to Reduce Symptoms of Postoperative Neck Discomfort After Thyroid Surgery: Prospective Randomized Study. *World J Surg* (2005) 29(6):775–9. doi: 10.1007/s00268-005-7722-3
22. Gove WR, Geerken MR. Response Bias in Surveys of Mental Health: An Empirical Investigation. *Am J Sociolo* (1977) 82(6):1289–317. doi: 10.1086/226466
23. Baron-Epel O, Kaplan G, Weinstein R, Green MS. Extreme and Acquiescence Bias in a Bi-Ethnic Population. *Eur J Public Health* (2010) 20(5):543–8. doi: 10.1093/eurpub/ckq052
24. Kuru O, Pasek J. Improving Social Media Measurement in Surveys: Avoiding Acquiescence Bias in Facebook Research. *Comput Hum Behav* (2016) 57:82–92. doi: 10.1016/j.chb.2015.12.008


**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Publisher's Note:** All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Endocrinology

ORIGINAL RESEARCH
published: 16 November 2021
doi: 10.3389/fendo.2021.772071

Check for updates

# The Impact of Coexistent Hashimoto's Thyroiditis on Central Compartment Lymph Node Metastasis in Papillary Thyroid Carcinoma

*Yang Liu*[1], *Hongjun Lv*[2], *Shaoqiang Zhang*[3], *Bingyin Shi*[2] *and Yushi Sun*[2*]

[1] *Department of Breast Surgery, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China,* [2] *Department of Endocrinology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China,* [3] *Department of Otolaryngology-Head and Neck Surgery, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China*

**Background:** Hashimoto's thyroiditis (HT) is the most prevalent inflammatory disorder of the thyroid gland. Current studies have reported the coexistence rate between HT and papillary thyroid carcinoma (PTC) is quite high. The objective of this study was to evaluate the impact of HT on the predictive factors of central compartment lymph node metastasis (CLNM) in PTC.

**Methods:** A retrospective investigation was performed on PTC patients. They were subclassified into HT and non-HT groups. The results of preoperative neck ultrasound (US) examinations were reviewed. The clinical characteristics and the predictive value for CLNM were explored and compared between the two groups.

**Results:** A total of 756 patients were included in this study. There were more female patients (86.1%) in the PTC coexistent with the HT group than non-HT group. The patients with HT group had higher preoperative serum level of TSH. There was statistically significant difference between the HT patients and non-HT patients in nodular vascularization. Univariate and multivariate analyses showed that male, age ≤45 years old, tumor diameter >1 cm, and presence of suspicious central compartment lymph node on US, irregular nodular shape, multifocal carcinoma were independent predictive factors of CLNM in PTC patients. It was showed that male, age ≤45 years old, tumor diameter >1 cm, multifocality, and presence of suspicious central lymph node on US were risk factors for CLNM in non-HT patients. Only tumor diameter >1 cm and presence of suspicious central lymph node on US were independently correlated with CLNM in HT patients. The sensitivity of the multivariate model was 63.5%, and specificity was 88.9% for prediction CLNM in HT patients. For non-HT patients, the AUC was 80.6%, the sensitivity of the multivariate model was 64.5%, and specificity was 85.2%

**Conclusion:** PTC combined with HT is more common in women, and TSH level in HT group is higher than that in patients with PTC alone. Regardless of that HT is not a related risk factor of CLNM in PTC, our result suggested that different predictive systems should be used for HT and non-HT patients respectively to have a more accurate evaluation of CLNM in clinic.

**Keywords: papillary thyroid carcinoma, Hashimoto's thyroiditis, central compartment lymph node metastasis, multivariate analysis, receiver operating characteristic analysis**

OPEN ACCESS

***Edited by:***
*Che-Wei Wu,*
*Kaohsiung Medical University, Taiwan*

***Reviewed by:***
*Tzu-Yen Huang,*
*Kaohsiung Medical University Hospital, Taiwan*
*Yong Bae Ji,*
*Hanyang University, South Korea*

***Correspondence:***
*Yushi Sun*
*296165610@qq.com*

***Specialty section:***
*This article was submitted to Thyroid Endocrinology, a section of the journal Frontiers in Endocrinology*

***Received:*** *07 September 2021*
***Accepted:*** *21 October 2021*
***Published:*** *16 November 2021*

***Citation:***
*Liu Y, Lv H, Zhang S, Shi B and Sun Y (2021) The Impact of Coexistent Hashimoto's Thyroiditis on Central Compartment Lymph Node Metastasis in Papillary Thyroid Carcinoma. Front. Endocrinol. 12:772071. doi: 10.3389/fendo.2021.772071*

## INTRODUCTION

Hashimoto's thyroiditis (HT), also known as chronic lymphocytic thyroiditis, is the most prevalent inflammatory disorder of the thyroid gland, with an incidence of 0.3%–5.1% (1, 2). Thyroid cancer is the most common malignant tumor of the endocrine system, and its incidence rate is rapidly increasing with an annual growth rate of 4.5%–6.6% (3). The papillary thyroid carcinoma (PTC) accounts for 80%–90% of all thyroid malignant tumors (3, 4).

Since Dailey et al. (5) proposed the association between HT and PTC in 1952, many etiological and epidemiological studies have focused on the relationship between the two diseases. Notably, current studies have reported that the average coexistence rate between HT and PTC is quite high, approximately 23% (range from 10% to 58%) (6). Several previous reports have shown that PTC coexistent with HT is associated with a better prognosis (7–10). However, this conclusion has not been confirmed in some other studies, and the pathogenesis of the coexistence of PTC and HT remains controversial (11, 12).

PTC is usually considered as an indolent tumor and mostly has a good prognosis. However, it is prone to lymph node metastasis, especially central compartment lymph node metastasis (CLNM). In addition, there is still a significant controversy regarding routine prophylactic central compartment lymph node dissection in cN0 PTC patients because of the potential high incidence of postoperative complications and uncertainty of improved prognosis (13, 14). At present, neck ultrasound (US) is the most valuable method for preoperative evaluation of lymph node status (15–17). However, the sensitivity of US for predicting CLNM in PTC is only 23%–30.0% (15, 18).

Recurrent laryngeal nerve (RLN) injury is one of the most common causes of litigation after thyroidectomy (19). RLN paralysis after lymph node dissection can be unilateral or bilateral. It can result in a group of voice symptoms such as breathiness due to air leakage, hoarseness, and vocal fatigue leading to using short sentences in unilateral paralysis of RLN (20). Pereira found that voice changes after thyroidectomy with intact voice nerves were present in 28% of the involved patients (21). Several studies have shown that voice changes after lymph node dissection have a negative impact on life (20). Accurate preoperative evaluation of CLNM is particularly crucial for determining the appropriate scope of lymph node dissection. However, there are few studies on the effects of coexisting HT with PTC on the characteristics of lymph node metastasis in the central region. In this study, PTC patients were subclassified into HT and non-HT groups. The clinical characteristics and the predictive value for CLNM were explored and compared between the two groups.

## MATERIALS AND METHODS

A retrospective investigation was performed on PTC patients at The First Affiliated Hospital of Xi'an Jiaotong University from January 2014 to May 2017. The study was approved by the institutional review board. All of the PTC patients had received initial thyroidectomy with at least one side central neck dissection (CND). Those who did not receive CND were excluded from this study. Patients who had received preoperative $I^{131}$ ablation or prior head and neck oncological surgery were excluded from our study. Those who had undergone TSH suppression therapy or antithyroid therapy before surgery were also excluded (22). A total of 756 patients were included in this study. The mean age was 42 years (range, 9–84 years). Patients were staged according to the American Joint Committee on Cancer (AJCC) 8th edition of the tumor–node–metastasis (TNM) staging standard for thyroid cancer (23). HT was defined as the presence of diffuse lymphoplasmacytic infiltration, germinal centers, and enlarged epithelial cells with large nuclei and eosinophilic cytoplasm (24). Coexistence of HT with PTC was confirmed by the postoperative pathological examination in 130 (17.20%) patients. CLNM was histologically proven in 60.19% (455/756) patients. Patients were divided into HT group (n = 130) and non-HT group (n = 626). The clinical features of PTC were compared between the two groups.

The measurements of preoperative serum thyroid function and thyroid relative autoantibodies were done by radioimmunoassay. The results of preoperative neck US examinations were reviewed. The ultrasonographic characteristics of the suspicious thyroid nodules, including size, number (multifocal/unifocal), location (bilateral/unilateral), shape (regular/irregular), border (clear/obscure), echogenicity (hypoechoic/hyperechoic or isoechoic), calcification (non-calcification/microcalcification/coarse calcification), and degree of vascularization (none/low/middle/high), were recorded. Thyroid nodules that were diagnosed TI-RADS fourth or fifth grade by radiologists were defined as suspicious thyroid nodules in this study. The diameter of the largest suspicious thyroid nodule was used as tumor size for analysis. Lymph node showing one or more suspicious features (focal or diffuse hyperechogenicity, presence of internal calcification, cystic change, round shape, or chaotic vascularity) on US was regarded as clinical pathologic lymph nodes (22).

SPSS statistical software version 22.0 (SPSS Inc, Chicago, IL) was used to analyze the data. $p < 0.05$ was considered statistically significant. Differences in single variables were tested with the chi-square test or unpaired non-parametric test (Mann–Whitney U-test). Multivariate analysis using logistic regression analysis was performed on the variables that showed $p < 0.1$ in univariate analysis. Predictive value of those factors was measured using the area under the receiver operating characteristic (ROC) curve.

## RESULTS

### Basic Clinical Features of HT Group and Non-HT Group

There were more female patients (86.1%) in the PTC coexistent with the HT group than non-HT group ($p < 0.001$). Compared with non-HT group, the patients with HT group had higher preoperative serum level of TSH ($p < 0.05$). There was statistically significant difference between the HT patients and non-HT patients in nodular vascularization ($p = 0.022$). There were no statistically significant differences between the two groups in age, preoperative T4 level, T3 level, nodular size, number, location, nodular shape, border, internal echo, and calcification, and the presence of suspicious central compartment lymph node (CLN) on US ($p > 0.05$). There was no difference in the CLNM rate between the HT and non-HT groups. During lymphadenectomy, 0–41 lymph nodes were removed in the central compartment region. The number of lymph node dissections in the central compartment region of PTC coexistent with the HT group was more than those in the PTC group ($p < 0.001$; **Table 1**). However, the number of metastatic lymph nodes in the central compartment region was fewer in the HT group ($p = 0.02$; **Table 1**). There were more patients with stage I (94.6%) in HT group than in non-HT group ($p < 0.001$; **Table 1**).

## Sonographic Characteristics of Suspicious Lymph Node

A total of 175 patients were regarded as clinical pathological lymph nodes (cN1) in this study. There were 152 patients with round shape (86.8%), 76 with internal calcification (43.4%), 64 with focal or diffuse hyperechogenicity (36.6%), 21 with cystic change (12%), and 14 with chaotic vascularity (8%). There were 23 patients with HT in the cN1 group. Seventeen of the 23 (73.9%) patients were round shape on US. There were no statistically significant differences between the two groups in focal or diffuse hyperechogenicity, presence of internal calcification, cystic change, round shape, and chaotic vascularity on US ($p > 0.05$; **Table 2**).

## Predictive Risk Factors of CLNM in PTC Patients

Univariate analysis showed that age, gender, preoperative T4 level, T3 level, nodular size, number, location, nodular shape, border, calcification, presence of suspicious CLN on US, and the number of lymph node dissections in the central compartment region were all correlated with CLNM ($p < 0.05$; **Table 3**). Then, multivariate analysis was used to detect the risk factors of CLNM in PTC patients. It was showed that male, age ≤45 years old, tumor diameter >1 cm, and presence of suspicious CLN on US, irregular nodular shape, and multifocal carcinoma were all risk factors for CLNM in PTC patients (**Table 4**).

**TABLE 1** | Clinicopathological characteristic of HT and non-HT PTC patients.

| | HT (n = 130) | Non-HT (n = 626) | *p* |
|---|---|---|---|
| Age at diagnosis, M ($P_{25}$; $P_{75}$) | 40 (31; 48) | 43 (33; 51) | 0.107 |
| Age (≤45 y/>45 y) | 85/45 | 369/257 | 0.137 |
| | 65.4%/34.6% | 58.9%/41.1% | |
| Gender (male/female) | 18/112 | 181/445 | <0.001 |
| | 13.8%/86.2% | 28.9%/71.1% | |
| TSH, µIU/ml, M ($P_{25}$; $P_{75}$) | 2.42 (1.44; 3.97) | 1.96 (1.24; 3.02) | 0.013 |
| T4, µg/dl, M ($P_{25}$; $P_{75}$) | 15.4 (12.7; 17.1) | 15.6 (13.7; 17.5) | 0.309 |
| T3, ng/ml, M ($P_{25}$; $P_{75}$) | 5.27 (4.49; 6.01) | 5.38 (4.67; 6.07) | 0.328 |
| **Ultrasonographic characteristics of suspicious nodules** | | | |
| Tumor size (≤1 cm/>1 cm) | 39/91 | 151/475 | 0.151 |
| | 30%/70% | 24.1%/75.9% | |
| Unilateral/bilateral | 86/44 | 451/175 | 0.178 |
| | 66.1%/33.9% | 72%/28% | |
| Unifocal/multifocal | 72/58 | 358/268 | 0.705 |
| | 55.3%/44.7% | 57.2%/42.8% | |
| Border (clear/obscure) | 66/64 | 312/314 | 0.847 |
| | 50.7%/49.3% | 49.8%/50.2% | |
| Margin (regular/irregular) | 60/70 | 253/373 | 0.227 |
| | 46.1%/53.9% | 40.4%/59.6% | |
| Non-/micro-/coarse calcification | 26/92/12 | 116/442/88 | 0.333 |
| | 20%/70.7%/9.3% | 18.5%/70.6%/10.9% | |
| Hypoechoic/hyper- or isoechoic | 121/9 | 605/21 | 0.058 |
| | 93.1%/6.9% | 96.6%/3.4% | |
| Vascularization, none/low/middle/high | 49/36/31/14 | 173/188/166/99 | 0.022 |
| | 37.7%/27.7%/23.8%/10.8% | 27.6%/30%/26.5%15.9% | |
| Absence/presence of suspicious CLN on ultrasonography | 107/23 | 474/152 | 0.105 |
| | 82.3%/17.7% | 75.7%/24.3% | |
| **CLNM** | | | |
| CLNM, presence/absence | 70/60 | 385/241 | 0.105 |
| | 53.8%/46.2% | 61.5%/38.5% | |
| Number of removed CLNs, M($P_{25}$; $P_{75}$) | 9 (6; 13) | 5 (3; 9) | <0.001 |
| Number of metastatic CLNS, M ($P_{25}$; $P_{75}$) | 1 (0; 3) | 1 (0; 4) | 0.02 |
| TNM staging | | | <0.001 |
| Stage I | 123 (94.6%) | 578 (92.3%) | |
| Stage II | 5 (3.9%) | 40 (6.4%) | |
| Stage III | 2 (1.5%) | 8 (1.3%) | |
| Stage IV | 0 (0) | 0 (0) | |

*CLNM, central lymph node metastases; CLN, central lymph node; PTC, papillary thyroid cancer; M, median value.*

**TABLE 2 |** Sonographic characteristics of suspicious lymph node.

| | HT (23) | Non-HT (152) | *p* |
|---|---|---|---|
| Round shape (yes/no) | 17/6<br>73.9%/26.1% | 135/17<br>88.8%/11.2% | 0.101 |
| Internal calcification (yes/no) | 13/10<br>56.5%/43.5% | 63/89<br>41.4%/58.6% | 0.174 |
| Cystic change (yes/no) | 3/20<br>13%/87% | 18/134<br>11.8%/88.2% | 1.000 |
| Hyperechogenicity (yes/no) | 7/16<br>30.4%/69.6% | 57/95<br>37.5%/62.5% | 0.512 |
| Chaotic vascularity (yes/no) | 2/21<br>8.7%/91.3% | 12/140<br>7.9%/92.1% | 1.000 |

ROC analysis was performed to predict CLNM in PTC patients. The area under the curve (AUC) was 80.6% (**Figure 1**). A cutoff point for the prediction of CLNM was defined as a value 65% for PTC patients. The sensitivity of the multivariate model was 61%, and specificity was 86% for prediction CLNM in PTC patients (**Figure 1**).

## Predictive Risk Factors of CLNM in HT Patients and Non-HT Patients

Patients were divided into HT group and non-HT group. In univariate analysis, age ($p = 0.021$), gender ($p = 0.028$), T3 ($p = 0.022$), nodular size ($p = 0.002$), nodular number ($p = 0.041$), and presence of suspicious central cervical lymph node on US ($P<0.001$) were all correlated with CLNM in HT patients. In non-HT patients, age ($p < 0.001$), gender ($p < 0.001$), T4 ($p = 0.035$), nodular size ($p < 0.001$), nodular number ($p = 0.004$), nodular shape ($p = 0.003$), calcification ($p < 0.001$) and presence of suspicious central cervical lymph node on US ($p < 0.001$) were significantly associated with CLNM (**Table 5**).

Next, we investigated the risk factors associated with CLNM in HT patients and non-HT patients. It was showed that male, age ≤45 years old, tumor diameter >1 cm, multifocality, and presence of suspicious CLN on US were all risk factors for CLNM in non-HT patients (**Table 6**). However, only tumor diameter >1

**TABLE 3 |** Univariate analysis of the correlation between clinical factors of the primary tumor and rate of CLNM in PTC patients.

| | CLNM (n = 455) | NCLNM (n = 301) | *p* |
|---|---|---|---|
| Age at diagnosis, M($P_{25}$; $P_{75}$) | 38 (30; 48) | 47 (29; 53) | <0.001 |
| Age (≤45 years/>45 years) | 323/132<br>71.0%/29.0% | 131/170<br>43.5%/56.5% | <0.001 |
| Gender (male/female) | 149/306<br>32.7%/67.3% | 50/251<br>16.6%/83.4% | <0.001 |
| Hashimoto's thyroiditis, absent/present | 385/70<br>84.6%/15.4% | 241/60<br>80.1%/19.9% | 0.105 |
| TSH, μIU/ml, M ($P_{25}$; $P_{75}$) | 2.03 (1.28; 3.02) | 1.85 (1.27; 3.21) | 0.614 |
| T4, μg/dl, M ($P_{25}$; $P_{75}$) | 15.7 (13.9; 17.6) | 15.3 (13.1; 16.9) | 0.018 |
| T3, ng/ml, M($P_{25}$; $P_{75}$) | 5.48 (4.71; 6.15) | 5.21 (4.55; 5.98) | 0.017 |
| **Ultrasonographic characteristics of suspicious nodules** | | | |
| Tumor size (≤1 cm/>1 cm) | 79/376<br>17.4%/82.6% | 111/190<br>36.9%/63.1% | <0.001 |
| Unilateral/bilateral | 311/144<br>68.4%/31.6% | 226/75<br>75.1%/24.9% | 0.046 |
| Unifocal/multifocal | 236/219<br>51.9%/48.1% | 194/107<br>64.5%/35.5% | 0.001 |
| Border (clear/obscure) | 214/241<br>47.0%/53.0% | 164/137<br>54.5%/45.5% | 0.045 |
| Margin (regular/irregular) | 165/290<br>36.3%/63.7% | 148/153<br>49.2%/50.8% | <0.001 |
| Non-/micro-/coarse calcifification | 62/336/57<br>13.6%/73.9%/12.5% | 80/178/43<br>26.6%/59.1%/14.3% | <0.001 |
| Hypoechoic/hyper- or isoechoic | 437/18<br>96.0%/4% | 289/12<br>96.0%/4.0% | 0.983 |
| Vascularization None/low/middle/high | 134/127/118/76<br>29.5%/27.9%/25.9%/16.7% | 88/97/79/37<br>29.2%/32.2%/26.3%/12.3% | 0.338 |
| absence/presence of suspicious CLN on ultrasonography | 295/160<br>64.8%/35.2% | 286/15<br>95%/5% | <0.001 |
| Number of removed CLNs, M($P_{25}$; $P_{75}$) | 7 (4; 10) | 5 (2; 8) | <0.001 |

*CLNM, central lymph node metastases; CLN, central lymph node; PTC, papillary thyroid cancer; M, Median value.*

**TABLE 4** | Multivariate analysis of the correlation between clinical factors of the primary tumor and rate of CLNM in all PTC patients.

| Variables | OR | CI | *p* |
|---|---|---|---|
| Gender (male) | 2.278 | 1.458-3.56 | <0.001 |
| Age (≤45 years) | 3.211 | 2.222-4.641 | <0.001 |
| Margin (regular) | 0.629 | 0.425-0.930 | 0.020 |
| Multifocal | 2.444 | 1.437-4.159 | 0.001 |
| Tumor size (≤1 cm) | 0.314 | 0.207-0.476 | <0.001 |
| Presence of suspicious CLN on ultrasonography | 8.470 | 4.597-15.606 | <0.001 |

*CLNM, central lymph node metastases; CLN, central lymph node; PTC, papillary thyroid cancer.*

cm and presence of suspicious CLN on US were independently correlated with CLNM in HT patients (**Table 6**).

ROC analysis was performed to predict CLNM in HT and non-HT patients, respectively. The AUC was 83.4% (**Figure 2**) in HT patients. A cutoff point for prediction of CLNM in HT group was defined as a value 64%. The sensitivity of the multivariate model was 63.5%, and specificity was 88.9% for prediction CLNM in HT patients (**Figure 2**). For non-HT patients, the AUC was 80.6%. A cutoff point for prediction of CLNM was defined as a value 66%; the sensitivity of the multivariate model was 64.5%, and specificity was 85.2% (**Figure 3**).

## DISCUSSION

HT, which was first identified by Hashimoto in 1912, is regarded as a destructive autoimmune disease of thyroid (24). An obvious increase in the incidence of the coexistence of PTC and HT has been reported during the past 20 years, and the impact of HT in PTC has been a research hotspot (25–27). Most of the studies show that PTC in the presence of HT is associated with an earlier stage of disease at the time of initial treatment and a better prognosis (8–11, 28, 29). However, only a handful of studies investigate the influence of HT on lymph node metastasis in PTC. Our study confirmed the influence of HT on the clinical characteristics of PTC and also showed that the predictive factors of CLNM varied in HT and non-HT group.

Our results showed that there were more female patients in HT group than in non-HT group. Our study also indicated that the TSH in HT patients was higher than that in patients with PTC alone. These results were consistent with many other previous observations (24, 30). HT, which is characterized by the infiltration of abundant lymphocytes, fibrosis, and parenchymal atrophy of thyroid tissue, is an autoimmune inflammation of the thyroid. The autoimmune response of HT

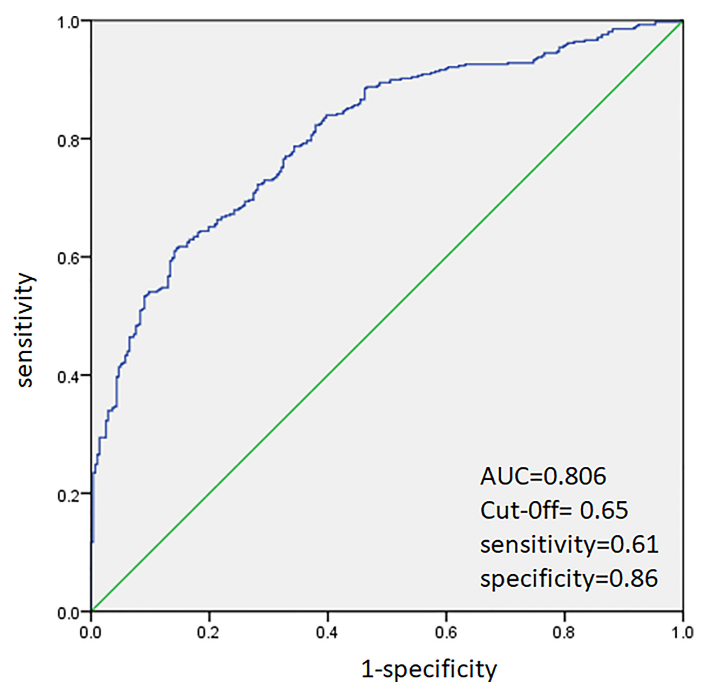



**FIGURE 1** | Receiver operating characteristic curve analysis for prediction of central lymph node metastases using the multivariate model in PTC patients.

**TABLE 5 |** Univariate analysis of the correlation between clinical factors of the primary tumor and rate of CLNM in HT and non-HT PTC patients.

| | HT (n = 130) | | | Non-HT (n =626) | | |
|---|---|---|---|---|---|---|
| | CLNM (n = 70) | NCLNM (n = 60) | *p* | CLNM (n = 385) | NCLNM (n = 241) | *p* |
| Age at diagnosis, M($P_{25}$; $P_{75}$) | 37 (31; 47) | 42.5 (31; 51) | 0.034 | 38 (30; 48) | 48 (40; 53) | <0.001 |
| Age (≤45 years/>45 years) | 52/18<br>74.3%/25.7% | 33/27<br>55.0%/45.0% | 0.021 | 271/114<br>70.4%/29.6% | 98/143<br>40.7%/59.3% | <0.001 |
| Gender (male/female) | 14/56<br>20%/80% | 4/56<br>6.7%/93.3% | 0.028 | 135/250<br>35.0%/65.0% | 46/195<br>19.1%/80.9% | <0.001 |
| TSH, μIU/ml, M ($P_{25}$; $P_{75}$) | 2.33 (1.28;3.72) | 2.53 (1.58;4.13) | 0.721 | 2.01 (1.27; 2.90) | 1.76 (1.23; 3.14) | 0.353 |
| T4, μg/dl, M ($P_{25}$; $P_{75}$) | 15.8 (12.6;17.6) | 15 (12.7;16.9) | 0.419 | 15.7 (13.9; 17.6) | 15.3 (13.5; 16.8) | 0.035 |
| T3, ng/ml, M ($P_{25}$; $P_{75}$) | 5.61 (4.61;6.41) | 4.99 (4.45;5.63) | 0.022 | 5.46 (4.73; 6.07) | 5.26 (4.59; 6.1) | 0.141 |
| **Ultrasonographic characteristics of suspicious nodules** | | | | | | |
| Tumor size (≤1 cm/>1 cm) | 13/57<br>18.6%/81.4% | 26/34<br>43.3%/56.7% | 0.002 | 66/319<br>17.1%/82.9% | 85/156<br>35.3%/64.7% | <0.001 |
| Unilateral/bilateral | 41/29<br>58.6%/41.4% | 45/15<br>75.0%/25.0% | 0.048 | 270/115<br>70.1%/29.9% | 181/60<br>75.1%/24.9% | 0.177 |
| Unifocal/multifocal | 33/37<br>47.1%/52.9% | 39/21<br>65%/35.0% | 0.041 | 203/182<br>52.7%/47.3% | 155/86<br>64.3%/35.7% | 0.004 |
| Border (clear/obscure) | 34/36<br>48.6%/51.4% | 32/28<br>53.3%/46.7% | 0.588 | 180/205<br>46.8%/53.2% | 132/109<br>54.8%/45.2% | 0.051 |
| Margin (regular/irregular) | 27/43<br>38.6%/61.4% | 33/27<br>55.0%/45.0% | 0.061 | 138/247<br>35.8%/64.2% | 115/126<br>47.7%/52.3% | 0.003 |
| Non-/micro-/coarse calcification | 12/51/7<br>17.1%/72.9%/10% | 14/41/5<br>23.3%/68.3%/8.4% | 0.667 | 50/285/50<br>13.0%/74.0%/13.0% | 66/137/38<br>27.4%/56.8%/15.8% | <0.001 |
| Hypoechoic/hyper- or isoechoic | 64/6<br>91.4%/8.6% | 57/3<br>95.0%/5.0% | 0.504 | 373/12<br>96.9%/3.1% | 232/9<br>96.3%/3.7% | 0.676 |
| Vascularization<br>None/low/middle/high | 30/15/17/8<br>42.8%/21.4%/24.3%/<br>11.5% | 19/21/14/6<br>31.7%/35.0%/23.3%/<br>10.0% | 0.565 | 104/112/101/68<br>27.0%/29.1%/26.2%/<br>17.7% | 69/76/65/31<br>28.6%/31.5%/27.0%/<br>12.9% | 0.250 |
| Absence/presence of suspicious CLN on ultrasonography | 49/21<br>70.0%/30.0% | 58/2<br>96.7%/3.3% | <0.001 | 246/139<br>63.9%/36.1% | 228/13<br>94.6%/5.4% | <0.001 |

*CLNM, central lymph node metastases; CLN, central lymph node; PTC, papillary thyroid cancer; M, Median value.*

can result in an increase in TSH (31, 32). What's more, the incidence of PTC increases gradually with the increase in TSH levels. Thus, HT patients with thyroid nodules need to be carefully monitored in our clinical practice.

Some studies have shown that the rate of CLNM is lower in patients with PTC coexistent with HT (33, 34). However, there was no statistical significance in the rate of CLNM between the HT group and non-HT group in this study. We had a very interesting finding that although the number of lymph node dissections in the central compartment region of PTC coexistent with the HT group were more than those in the PTC group, the number of metastatic lymph nodes were fewer in the HT group. Similar findings have also been found in previous studies (27, 35, 36). In fact, it is unclear whether HT influences the CLNM in PTC patients due to lack of relevant studies. Increasing results suggest that the inflammatory process of thyroiditis confers a protective effect on PTC.

In fact, many patients with PTC coexistent with HT always have more enlarged lymph nodes in the neck (37), and it brings more difficulties in determining the metastasis of lymph node using preoperative color Doppler ultrasound. PTC patients with HT appear to undergo a more excessive lymph node dissection because of the presence of more enlarged lymphadenopathy identified at the time of thyroidectomy, which is likely to result

**TABLE 6 |** Multivariate analysis of the correlation between clinical factors of the primary tumor and rate of CLNM in HT and non-HT patients.

| Variables | OR | CI | *p* |
|---|---|---|---|
| **Non-HT group** | | | |
| Age (≤45 years) | 3.323 | 2.223–4.968 | <0.001 |
| Gender (male) | 2.156 | 1.346–3.454 | 0.001 |
| Tumor size (≤1 cm) | .378 | 0.240–0.597 | <0.001 |
| Multifocal | 1.669 | 1.109–2.510 | 0.014 |
| Presence of suspicious CLN on ultrasonography | 8.0 | 4.132–15.488 | <0.001 |
| **HT group** | | | |
| Tumor size (≤1 cm) | 0.181 | .057–0.572 | 0.004 |
| Presence of suspicious CLN on ultrasonography | 14.743 | 2.593–83.821 | 0.002 |

*CLNM, central lymph node metastases; CLN, central lymph node; PTC, papillary thyroid cancer.*

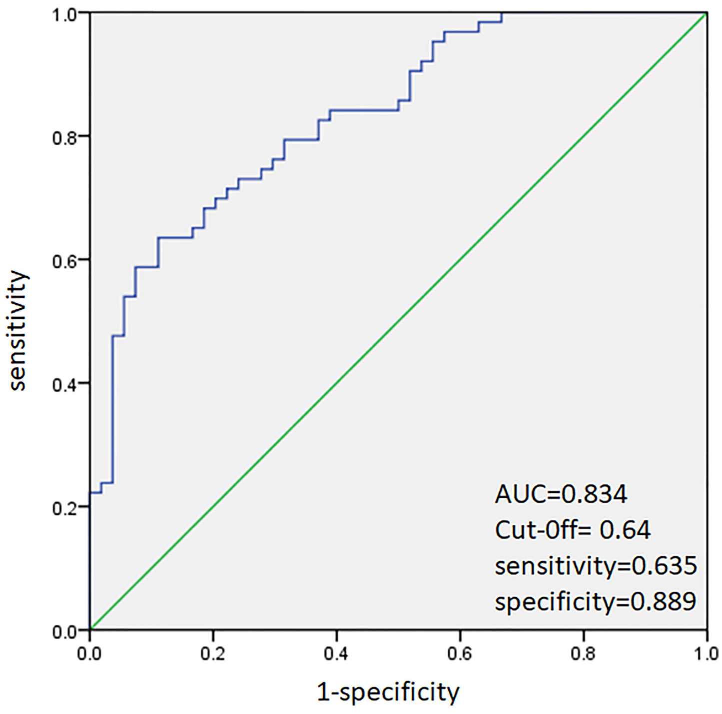



**FIGURE 2** | Receiver operating characteristic curve analysis for prediction of central lymph node metastases using the multivariate model in HT patients.

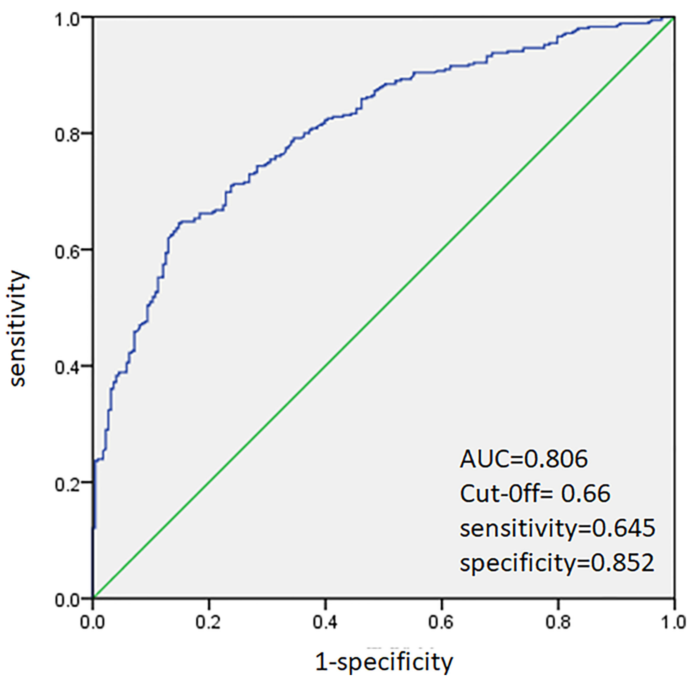



**FIGURE 3** | Receiver operating characteristic curve analysis for prediction of central lymph node metastases using the multivariate model in non-HT patients.

in more postoperative complications. The rates of RLN injury have been reported to increase significantly during therapeutic central compartment lymph node dissection (38). Previous systematic meta-analyses have reported RLN injury rates of 2.8%–9.8% (39). Voice, swallowing, and coughing can be affected in RLN injury. The voice is weak and breathy with a loss of vocal projection and phonation time, which may have greater impact on patients working in teaching, training, management, and administrative support and make them more vulnerable to experiencing voice disorders in their daily lives. PTC patients with HT are more likely to have enlarged lymph nodes, thus prompting the surgeon to perform a more extensive CND. However, an overly aggressive dissection that may damage the normal function of the RLN is not necessary (37). Therefore, the accurate identification of risk factors of CLNM is helpful to evaluate the status of CLN and determine the necessity of lymph node dissection, especially for PTC patients with HT (30).

Previous studies have revealed that age of onset and multifocality are independently associated with CLNM in PTC (34, 40). It has been established that the risk of CLNM positively correlates with the number of tumor foci (34, 41), and tumor size >1 cm was also reported to be a risk factor of CLNM in PTC (42, 43). Our study confirmed that age, multifocality, and tumor size were independent risk factors of CLNM in PTC patients. In addition, male gender, irregular nodules, and presence of suspicious CLN on US were independent risk factors of CLNM.

We further explored differences in CLNM between patients with and without HT. Our study confirmed the predictive value of tumor size and presence of suspicious CLN on US in both groups with and without HT and showed that age, gender, and the number of suspicious CLN on US lost their predictive value for CLNM in PTC patients with HT. It suggested that HT might have an impact against aggressive behaviors and play a protective role in the natural history to some extent.

Then, we performed different multivariate models to calculate the probability of CLNM for HT and non-HT patients, respectively. ROC analysis was performed to predict CLNM in both groups (AUCs, 83.4% and 80.6%, respectively). Compared with the whole PTC group, the sensitivity of those models in predicting CLNM was both higher for HT and non-HT groups (63.5% *versus* 61% and 64.5% *versus* 61%, respectively), and the specificity of those models was a little higher for HT group (88.9% versus 86%), while the specificity of those models was a little lower for non-HT group than the whole PTC group (85.2% versus 86%).

However, the present study also had some potential limitations. A limitation of the present study is its retrospective nature. Further prospective studies are needed to clarify the potential causal relationship between HT and PTC. Second, our study is a single-center study, and the sample size is a little small. Further multicenter studies with a larger number of patients are needed. What is worse, there are not enough statistical data and tracking data for postoperative complications. Therefore, multicenter collaboration and long-term follow-up are needed to obtain more reliable results in the future.

## CONCLUSIONS

In summary, our study explored and confirmed the impact of HT on the predictive risk factors of CLNM in PTC. PTC combined with HT is more common in women, and TSH level in HT group is higher than that in patients with PTC alone. Regardless of the fact that HT is not a related risk factor of CLNM in PTC, our result suggested that different predictive systems should be used for HT and non-HT patients, respectively, to have a more accurate evaluation of CLNM in clinics. Considering the possible influence of HT on CLNM in PTC, the scope of lymph node dissection should be performed more accurately in HT patients.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the institutional review board of the First Affiliated Hospital of Xi'an Jiaotong University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

## AUTHOR CONTRIBUTIONS

YS designed the research. YL, HL, SZ, BS, and YS conducted research. HL and SZ the analyzed data. YL wrote the initial draft of the manuscript. BS and YS revised the manuscript. All authors contributed to the article and approved the submitted version.

## FUNDING

This study was supported by the Shaanxi Provincial Natural Science Foundation (Grant No. 2021SF-010) and the Basic Research Foundation of the First Affiliated Hospital of Xi'an Jiaotong University (Grant No. 2020QN-24).

## ACKNOWLEDGMENTS

The authors would like to acknowledge the support of other team members and the participating students and teachers.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2021.772071/full#supplementary-material

# REFERENCES


1. Ahmed R, Al-Shaikh S, Akhtar M. Hashimoto Thyroiditis: A Century Later. *Adv Anat Pathol* (2012) 19:181–6. doi: 10.1097/PAP.0b013e3182534868
2. Latina A, Gullo D, Trimarchi F, Benvenga S. Hashimoto's Thyroiditis: Similar and Dissimilar Characteristics in Neighboring Areas. Possible Implications for the Epidemiology of Thyroid Cancer. *PloS One* (2013) 8:e55450. doi: 10.1371/journal.pone.0055450
3. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2015. *CA Cancer J Clin* (2015) 65:5–29. doi: 10.3322/caac.21254
4. Mao Y, Xing M. Recent Incidences and Differential Trends of Thyroid Cancer in the USA. *Endocr Relat Cancer* (2016) 23:313–22. doi: 10.1530/ERC-15-0445
5. Lindsay S, Dailey ME, Friedlander J, Yee G, Soley MH. Chronic Thyroiditis: A Clinical and Pathologic Study of 354 Patients. *J Clin Endocrinol Metab* (1952) 12:1578–600. doi: 10.1210/jcem-12-12-1578
6. Lee JH, Kim Y, Choi JW, Kim YS. The Association Between Papillary Thyroid Carcinoma and Histologically Proven Hashimoto's Thyroiditis: A Meta-Analysis. *Eur J Endocrinol* (2013) 168:343–9. doi: 10.1530/EJE-12-0903
7. Schaffler A, Palitzsch KD, Seiffarth C, Hohne HM, Riedhammer FJ, Hofstadter F, et al. Coexistent Thyroiditis Is Associated With Lower Tumour Stage in Thyroid Carcinoma. *Eur J Clin Invest* (1998) 28:838–44. doi: 10.1046/j.1365-2362.1998.00363.x
8. Matsubayashi S, Kawai K, Matsumoto Y, Mukuta T, Morita T, Hirai K, et al. The Correlation Between Papillary Thyroid Carcinoma and Lymphocytic Infiltration in the Thyroid Gland. *J Clin Endocrinol Metab* (1995) 80:3421–4. doi: 10.1210/jcem.80.12.8530576
9. Kashima K, Yokoyama S, Noguchi S, Murakami N, Yamashita H, Watanabe S, et al. Chronic Thyroiditis as a Favorable Prognostic Factor in Papillary Thyroid Carcinoma. *Thyroid* (1998) 8:197–202. doi: 10.1089/thy.1998.8.197
10. Loh KC, Greenspan FS, Dong F, Miller TR, Yeo PP. Influence of Lymphocytic Thyroiditis on the Prognostic Outcome of Patients With Papillary Thyroid Carcinoma. *J Clin Endocrinol Metab* (1999) 84:458–63. doi: 10.1210/jcem.84.2.5443
11. Singh B, Shaha AR, Trivedi H, Carew JF, Poluri A, Shah JP. Coexistent Hashimoto's Thyroiditis With Papillary Thyroid Carcinoma: Impact on Presentation, Management, and Outcome. *Surgery* (1999) 126:1070–6; discussion 6-7. doi: 10.1067/msy.2099.101431
12. Del Rio P, Cataldo S, Sommaruga L, Concione L, Arcuri MF, Sianesi M. The Association Between Papillary Carcinoma and Chronic Lymphocytic Thyroiditis: Does It Modify the Prognosis of Cancer? *Minerva Endocrinol* (2008) 33:1–5. doi: 10.1159/000127404
13. Hughes CJ, Shaha AR, Shah JP, Loree TR. Impact of Lymph Node Metastasis in Differentiated Carcinoma of the Thyroid: A Matched-Pair Analysis. *Head Neck* (1996) 18:127–32. doi: 10.1002/(SICI)1097-0347(199603/04)18:2<127::AID-HED3>3.0.CO;2-3
14. Ito Y, Tomoda C, Uruno T, Takamura Y, Miya A, Kobayashi K, et al. Clinical Significance of Metastasis to the Central Compartment From Papillary Microcarcinoma of the Thyroid. *World J Surg* (2006) 30:91–9. doi: 10.1007/s00268-005-0113-y
15. Lee DW, Ji YB, Sung ES, Park JS, Lee YJ, Park DW, et al. Roles of Ultrasonography and Computed Tomography in the Surgical Management of Cervical Lymph Node Metastases in Papillary Thyroid Carcinoma. *Eur J Surg Oncol* (2013) 39:191–6. doi: 10.1016/j.ejso.2012.07.119
16. Ahn JE, Lee JH, Yi JS, Shong YK, Hong SJ, Lee DH, et al. Diagnostic Accuracy of CT and Ultrasonography for Evaluating Metastatic Cervical Lymph Nodes in Patients With Thyroid Cancer. *World J Surg* (2008) 32:1552–8. doi: 10.1007/s00268-008-9588-7
17. Morita S, Mizoguchi K, Suzuki M, Iizuka K. The Accuracy of (18)[F]-Fluoro-2-Deoxy-D-Glucose-Positron Emission Tomography/Computed Tomography, Ultrasonography, and Enhanced Computed Tomography Alone in the Preoperative Diagnosis of Cervical Lymph Node Metastasis in Patients With Papillary Thyroid Carcinoma. *World J Surg* (2010) 34:2564–9. doi: 10.1007/s00268-010-0733-8
18. Hwang HS, Orloff LA. Efficacy of Preoperative Neck Ultrasound in the Detection of Cervical Lymph Node Metastasis From Thyroid Cancer. *Laryngoscope* (2011) 121:487–91. doi: 10.1002/lary.21227
19. Lynch J, Parameswaran R. Management of Unilateral Recurrent Laryngeal Nerve Injury After Thyroid Surgery: A Review. *Head Neck* (2017) 39:1470–8. doi: 10.1002/hed.24772
20. Beka E, Gimm O. Voice Changes Without Laryngeal Nerve Alterations After Thyroidectomy: The Need For Prospective Trials - A Review Study. *J Voice* (2021). doi: 10.1016/j.jvoice.2021.07.012
21. Pereira JA, Girvent M, Sancho JJ, Parada C, Sitges-Serra A. Prevalence of Long-Term Upper Aerodigestive Symptoms After Uncomplicated Bilateral Thyroidectomy. *Surgery* (2003) 133:318–22. doi: 10.1067/msy.2003.58
22. Sun Y, Lv H, Zhang S, Bai Y, Shi B. Gender-Specific Risk of Central Compartment Lymph Node Metastasis in Papillary Thyroid Carcinoma. *Int J Endocrinol* (2018) 2018:6710326. doi: 10.1155/2018/6710326
23. Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, et al. *AJCC Cancer Staging Manual Eighth Edition*. Switzerland: Springer International Publishing (2017) p. 873–90.
24. Liang J, Zeng W, Fang F, Yu T, Zhao Y, Fan X, et al. Clinical Analysis of Hashimoto Thyroiditis Coexistent With Papillary Thyroid Cancer in 1392 Patients. *Acta Otorhinolaryngol Ital* (2017) 37:393–400. doi: 10.14639/0392-100X-1709
25. Tamimi DM. The Association Between Chronic Lymphocytic Thyroiditis and Thyroid Tumors. *Int J Surg Pathol* (2002) 10:141–6. doi: 10.1177/106689690201000207
26. Kebebew E, Treseler PA, Ituarte PH, Clark OH. Coexisting Chronic Lymphocytic Thyroiditis and Papillary Thyroid Cancer Revisited. *World J Surg* (2001) 25:632–7. doi: 10.1007/s002680020165
27. Zhang L, Li H, Ji QH, Zhu YX, Wang ZY, Wang Y, et al. The Clinical Features of Papillary Thyroid Cancer in Hashimoto's Thyroiditis Patients From an Area With a High Prevalence of Hashimoto's Disease. *BMC Cancer* (2012) 12:610. doi: 10.1186/1471-2407-12-610
28. Kim EY, Kim WG, Kim WB, Kim TY, Kim JM, Ryu JS, et al. Coexistence of Chronic Lymphocytic Thyroiditis Is Associated With Lower Recurrence Rates in Patients With Papillary Thyroid Carcinoma. *Clin Endocrinol (Oxf)* (2009) 71:581–6. doi: 10.1111/j.1365-2265.2009.03537.x
29. Yoon YH, Kim HJ, Lee JW, Kim JM, Koo BS. The Clinicopathologic Differences in Papillary Thyroid Carcinoma With or Without Co-Existing Chronic Lymphocytic Thyroiditis. *Eur Arch Otorhinolaryngol* (2012) 269:1013–7. doi: 10.1007/s00405-011-1732-6
30. Jin K, Li L, Liu Y, Wang X. The Characteristics and Risk Factors of Central Compartment Lymph Node Metastasis in Cn0 Papillary Thyroid Carcinoma Coexistent With Hashimoto's Thyroiditis. *Gland Surg* (2020) 9:2026–34. doi: 10.21037/gs-20-699
31. Liu X, Zhu L, Cui D, Wang Z, Chen H, Duan Y, et al. Coexistence of Histologically Confirmed Hashimoto's Thyroiditis With Different Stages of Papillary Thyroid Carcinoma in a Consecutive Chinese Cohort. *Int J Endocrinol* (2014) 2014:769294. doi: 10.1155/2014/769294
32. Resende de Paiva C, Gronhoj C, Feldt-Rasmussen U, von Buchwald C. Association Between Hashimoto's Thyroiditis and Thyroid Cancer in 64,628 Patients. *Front Oncol* (2017) 7:53. doi: 10.3389/fonc.2017.00053
33. Wen X, Wang B, Jin Q, Zhang W, Qiu M. Thyroid Antibody Status is Associated With Central Lymph Node Metastases in Papillary Thyroid Carcinoma Patients With Hashimoto's Thyroiditis. *Ann Surg Oncol* (2019) 26:1751–8. doi: 10.1245/s10434-019-07256-4
34. Zhu F, Shen YB, Li FQ, Fang Y, Hu L, Wu YJ. The Effects of Hashimoto Thyroiditis on Lymph Node Metastases in Unifocal and Multifocal Papillary Thyroid Carcinoma: A Retrospective Chinese Cohort Study. *Med (Baltimore)* (2016) 95:e2674. doi: 10.1097/MD.0000000000002674
35. Jara SM, Carson KA, Pai SI, Agrawal N, Richmon JD, Prescott JD, et al. The Relationship Between Chronic Lymphocytic Thyroiditis and Central Neck Lymph Node Metastasis in North American Patients With Papillary Thyroid Carcinoma. *Surgery* (2013) 154:1272–80; discussion 80-2. doi: 10.1016/j.surg.2013.07.021
36. Schneider DF, Chen H, Sippel RS. Impact of Lymph Node Ratio on Survival in Papillary Thyroid Cancer. *Ann Surg Oncol* (2013) 20:1906–11. doi: 10.1245/s10434-012-2802-8
37. Lai V, Yen TW, Rose BT, Fareau GG, Misustin SM, Evans DB, et al. The Effect of Thyroiditis on the Yield of Central Compartment Lymph Nodes in Patients With Papillary Thyroid Cancer. *Ann Surg Oncol* (2015) 22:4181–6. doi: 10.1245/s10434-015-4551-y

38. Roh JL, Kim JM, Park CI. Central Compartment Reoperation for Recurrent/Persistent Differentiated Thyroid Cancer: Patterns of Recurrence, Morbidity, and Prediction of Postoperative Hypocalcemia. *Ann Surg Oncol* (2011) 18:1312–8. doi: 10.1245/s10434-010-1470-9
39. Cirocchi R, Arezzo A, D'Andrea V, Abraha I, Popivanov GI, Avenia N, et al. Intraoperative Neuromonitoring Versus Visual Nerve Identification for Prevention of Recurrent Laryngeal Nerve Injury in Adults Undergoing Thyroid Surgery. *Cochrane Database Syst Rev* (2019) 1:CD012483. doi: 10.1002/14651858.CD012483.pub2
40. Lee YS, Lim YS, Lee JC, Wang SG, Son SM, Kim SS, et al. Ultrasonographic Findings Relating to Lymph Node Metastasis in Single Micropapillary Thyroid Cancer. *World J Surg Oncol* (2014) 12:273. doi: 10.1186/1477-7819-12-273
41. Siddiqui S, White MG, Antic T, Grogan RH, Angelos P, Kaplan EL, et al. Clinical and Pathologic Predictors of Lymph Node Metastasis and Recurrence in Papillary Thyroid Microcarcinoma. *Thyroid* (2016) 26:807–15. doi: 10.1089/thy.2015.0429
42. Park JP, Roh JL, Lee JH, Baek JH, Gong G, Cho KJ, et al. Risk Factors for Central Neck Lymph Node Metastasis of Clinically Noninvasive, Node-Negative Papillary Thyroid Microcarcinoma. *Am J Surg* (2014) 208:412–8. doi: 10.1016/j.amjsurg.2013.10.032
43. Konturek A, Barczynski M, Nowak W, Wierzchowski W. Risk of Lymph Node Metastases in Multifocal Papillary Thyroid Cancer Associated With Hashimoto's Thyroiditis. *Langenbecks Arch Surg* (2014) 399:229–36. doi: 10.1007/s00423-013-1158-2

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Publisher's Note:** All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Endocrinology

REVIEW
published: 24 November 2021
doi: 10.3389/fendo.2021.793431

# Improving Voice Outcomes After Thyroid Surgery – Review of Safety Parameters for Using Energy-Based Devices Near the Recurrent Laryngeal Nerve

*Jia Joanna Wang*[1,2], *Tzu-Yen Huang*[1,3], *Che-Wei Wu*[1,4], *Yi-Chu Lin*[1], *Hsin-Yi Tseng*[1], *Cheng-Hsin Liu*[1,2], *I-Cheng Lu*[5], *Pi-Ying Chang*[6], *Hui-Chun Chen*[7], *Hsiu-Ya Chen*[8], *Gianlorenzo Dionigi*[9,10], *Feng-Yu Chiang*[11,12] and *Ling-Feng Wang*[1*]

[1] Department of Otorhinolaryngology-Head and Neck Surgery, International Thyroid Surgery Center, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan, [2] Department of Otolaryngology-Head and Neck Surgery, Kaohsiung Municipal Siaogang Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan, [3] Department of Biological Science and Technology, National Yang Ming Chiao Tung University, Hsinchu, Taiwan, [4] Center for Liquid Biopsy and Cohort Research, and Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan, [5] Department of Anesthesiology, Kaohsiung Municipal Siaogang Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan, [6] Department of Anesthesiology, Kaohsiung Municipal Tatung Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan, [7] Department of Nursing, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan, [8] Department of Anesthesiology, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan, [9] Division of General Surgery, Endocrine Surgery Section, Istituto Auxologico Italiano IRCCS, Milan, Italy, [10] Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy, [11] Department of Otolaryngology-Head and Neck Surgery, E-Da Hospital, Kaohsiung, Taiwan, [12] School of Medicine, College of Medicine, I-Shou University, Kaohsiung, Taiwan

OPEN ACCESS

**Edited by:**
*Paolo Miccoli,*
*University of Pisa, Italy*

**Reviewed by:**
*Aime Franco,*
*Children's Hospital of Philadelphia, United States*
*Yushi Sun,*
*First Affiliated Hospital of Xi'an Jiaotong University, China*

***Correspondence:**
*Ling-Feng Wang*
*lifewang@kmu.edu.tw*

**Specialty section:**
*This article was submitted to Thyroid Endocrinology, a section of the journal Frontiers in Endocrinology*

**Received:** 12 October 2021
**Accepted:** 08 November 2021
**Published:** 24 November 2021

**Citation:**
*Wang JJ, Huang T-Y, Wu C-W, Lin Y-C, Tseng H-Y, Liu C-H, Lu I-C, Chang P-Y, Chen H-C, Chen H-Y, Dionigi G, Chiang F-Y and Wang L-F (2021) Improving Voice Outcomes After Thyroid Surgery – Review of Safety Parameters for Using Energy-Based Devices Near the Recurrent Laryngeal Nerve. Front. Endocrinol. 12:793431. doi: 10.3389/fendo.2021.793431*

Technological advances in thyroid surgery have rapidly increased in recent decades. Specifically, recently developed energy-based devices (EBDs) enable simultaneous dissection and sealing tissue. EBDs have many advantages in thyroid surgery, such as reduced blood loss, lower rate of post-operative hypocalcemia, and shorter operation time. However, the rate of recurrent laryngeal nerve (RLN) injury during EBD use has shown statistically inconsistent. EBDs generate high temperature that can cause iatrogenic thermal injury to the RLN by direct or indirect thermal spread. This article reviews relevant medical literatures of conventional electrocauteries and different mechanisms of current EBDs, and compares two safety parameters: safe distance and cooling time. In general, conventional electrocautery generates higher temperature and wider thermal spread range, but when applying EBDs near the RLN adequate activation distance and cooling time are still required to avoid inadvertent thermal injury. To improve voice outcomes in the quality-of-life era, surgeons should observe safety parameters and follow the standard procedures when using EBDs near the RLN in thyroid surgery

**Keywords: energy-based devices, safety parameter, recurrent laryngeal nerve, thyroid surgery, voice**

## INTRODUCTION

Thyroidectomy is one of the most common head and neck surgeries. In the United States, more than 150,000 thyroidectomies were performed annually, and the case number of thyroid surgery is increasing each year (1). Specific challenges of thyroid surgery include the complex vascularization of anatomy, the proximity of the operating field to the recurrent laryngeal nerve (RLN), and the need to preserve the parathyroid gland. Therefore, thorough hemostasis is essential for avoiding further complications after thyroid surgery (2).

The "clamp-and-tie" technique was first introduced by Theodor Kocher in the 19th century. Since then, until the 1980s, clamp-and-tie, suture-ligation, electrocautery (monopolar or bipolar) and hemostatic clips have been widely adopted for hemostatic use in thyroid surgery (1, 3, 4). However, one of the most important technological advances in thyroid surgery occurred three decades ago: the introduction of energy-based devices (EBDs). Although the specific purpose of using EBDs in thyroid surgery is to achieve hemostasis, the mechanism through which EBDs achieve hemostasis differs from one devices to another (3).

Recent studies indicate that EBDs are used in 65.7% of thyroidectomy patients (1). Reported intraoperative advantages of EBDs include considerably decreased operative time, incision length and blood loss. Other clinically significant advantages of EBDs over conventional techniques include the superior postoperative outcomes of EBDs, e.g., reduced pain, wound drainage, neck hematoma, and hypocalcemia (1, 2, 5, 6).

In terms of RLN safety, however, EBDs have not proven superior to conventional devices used for thyroid surgery. For example, reported rates of RLN injury showed statistically inconsistent between EBDs and conventional devices (7). In fact, one 10-year meta-analysis reported that EBD use was associated with higher RLN paralysis rates (3). In another study, clinical outcomes of thyroidectomy were compared between 11,355 thyroidectomy patients treated with EBDs and a control group treated without EBDs. Compared to the non-EBD group, the EBD group had a significantly higher rate of hoarseness. However, the rate of severe hoarseness was significantly higher in the non-EBD group (1, 8, 9).

In another study, Liu et al. reported that the RLN palsy rate did not significantly differ between an EBD group and a clamp-and-tie group. However, the nerve injury mechanisms are significantly differed between the two groups. No patients in the clamp-and-tie group had thermal injury, whereas one-third of patients in the EBD group suffered thermal injury caused by lateral thermal spread in palsied RLNs (6).

## INTRAOPERATIVE NEUROMONITORING AND RLN THERMAL INJURY CAUSED BY EBDs

Intraoperative injury to the RLN can cause vocal cord paralysis. Symptoms may include hoarseness, choking, dysphagia and dysphonia in unilateral vocal cord paralysis, in addition, difficulty breathing may occur in cases of bilateral vocal cord paralysis (10–13). To reduce this major cause of morbidity after thyroid surgery, visual identification of RLN is the standard practice, and IONM facilitates this procedure (10, 14–16). Use of IONM not only enables the surgeons to evaluate RLN function in real time, but also to assess the mechanism of an impending or actual RLN injury and the appropriate surgical procedure for preventing or treating the injury (17–21). By elucidating the mechanism of iatrogenic RLN injury with IONM, many studies noted that traction and thermal injury are the first and second most common causes of RLN injury during thyroidectomy (5, 17, 22). Most intraoperative thermal injuries to the RLN result from thermal spread during use of high-temperature electrocautery devices and EBDs. Tissue contraction during EBD activation increases the risk of thermal injury because it reduces the distance from the RLN at which an EBD can be safely used (6). Thermal injury to the RLN often occurs unexpectedly when an EBD is activated or used for dissection. This type of injury usually is not only severe but irreversible (17).

In addition to the conventional uses of EBDs for tissue sealing, cutting, and hemostasis, surgeons have recently begun using EBDs for grasping and dividing tissue when dissection is performed near the RLN or even in direct contact with the RLN, especially in endoscopic procedures. As a results of technological advances in EBDs and the growing acceptance of surgical applications of EBDs, the increased incidence of thermal injury has emerged one of the main adverse events in thyroid surgery (23). Direct thermal burn injury can occur during or after activation of an EBD when the temperature of the blade is still high. Such injuries result from inadvertent contact between the blade and the skin or surrounding soft tissue, especially the RLN (24). Unlike direct thermal injury to the RLN, an indirect thermal injury to the RLN, which results from lateral thermal spread, is rarely visible to the naked eye. Therefore, animal experiments by using continuous IONM are needed for objective evaluation of the electrophysiology of RLN thermal injury and for establishing guidelines for safe use of EBDs, including minimum cooling time and safe distance between the EBD tip and the skin or surrounding soft tissue (**Figure 1**) (25, 26).

## ANIMAL STUDIES IN EBD SAFETY

Studies of EBD safety in the literature are typically performed in two stages: activation studies and cooling studies. Activation studies assess the distance from the RLN at which an EBD can be safely used without causing thermal injury; cooling studies assess the time (after activation) needed for the EBD tip or blade to cool sufficiently for use of the EBD in performing a dissection close to or in contact with the RLN (**Figure 2**).

### Activation Studies

The EBD is typically applied to RLN soft tissue at a distance starting from 5 mm and gradually decreased to 0 mm. Real-time

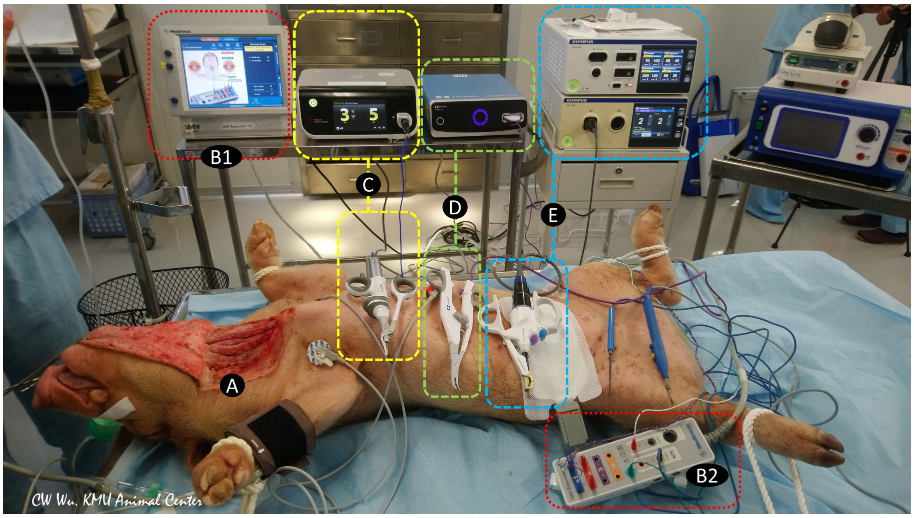



**FIGURE 1** | Animal models of continuous intraoperative neuromonitoring (cIONM) provide an objective platform for optimizing the safety parameters for various energy-based devices used for hemostasis and dissection near the recurrent laryngeal nerve (RLN) during thyroid surgery. **(A)** Preparation of porcine animal model by transverse incision and flap formation in neck skin. **(B1)** IONM monitoring system used for recording, monitoring, and analyzing real-time changes in laryngeal EMG. **(B2)** IONM interface box for connecting recording, stimulation, and ground electrodes. **(C)** Ultrasonic energy based device and energy generator. **(D)** Advanced biopolar energy based device and energy platform. **(E)** Hybrid energy based device (ultrasonic and bipolar energy) and multifunctional platform.

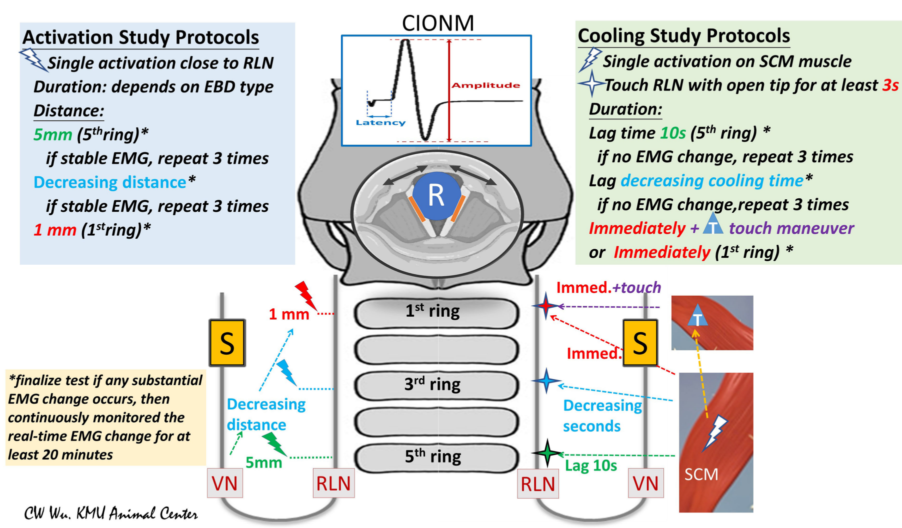



**FIGURE 2** | Flowchart of study protocols for using energy-based devices (EBDs). **(Left)** Activation Study Protocols: Tests were performed from the proximal to distal segments of the RLN. The distance from the tip of the EBD to the RLN was measured. In this study, the first test was performed at a distance of 5 mm from the fifth tracheal ring. If the EMG remained stable after three tests, further tests were performed at a shorter distance. If the EMG remained stable after repeated tests, further tests were performed at a distance of 1 mm or with the EBD tip in direct contact with the RLN. **(Right)** Cooling Study Protocol: Tests were performed on the RLN from the proximal to distal segment. After a single EBD activation on the SCM muscle, the operator touched the RLN with the tip of the open blade after varying cooling times. The fifth tracheal ring was touched after a cooling time of 10 seconds. If EMG remained stable in three tests, tests proceeded from the proximal RLN (fifth tracheal ring, green cross) to the distal RLN (first tracheal ring, red cross) after progressively decreasing cooling times. *asterisk: If a substantial EMG change was noted, the RLN experiment was considered complete, and EMG was continuously monitored for at least 20 minutes. T, touch maneuver: cooling by quickly touching surrounding tissue. S, Stimulation electrode for automatic periodic stimulation (APS) of vagus nerve (VN); R, Recording electrode on endotracheal tube for recording electromyography (EMG) signals evoked by vocal cord movement (black arrow); cIONM, continuous intraoperative neuromonitoring; RLN, recurrent laryngeal nerve; VN, vagus nerve; EBD, energy-based device; SCM, sternocleidomastoid; EMG, electromyography.

electrophysiologic electromyography (EMG) information is continuously recorded, compared and analyzed during varying durations of activation and under varying power settings. If a substantial EMG change occurs after any test, the RLN experiment is stopped, and real-time EMG is continuously recorded for 20 to 60 minutes to determine whether the injury is reversible (**Figure 2**, left) (5, 25, 27).

## Cooling Studies

After activation of the EBD on the sternocleidomastoid (SCM) muscle, surgeons touches the tip on the RLN after 10 seconds of waiting and cooling, then the cooling time gradually decreases to 0 seconds and observes the EMG for adverse changes. The "muscle touch maneuver" can be performed by touching the EBD tip/blade to the surrounding tissue right after activation. This maneuver offers ideal cooling effect by reducing the temperature immediately (**Figure 2**, right) (25).

# ELECTROCAUTERIES AND ENERGY-BASED DEVICES

## Monopolar Electrocautery

Electrocautery equipment is most commonly used in conventional thyroidectomy. In a monopolar electrocautery, current from the probe electrode passes through the patient to a return pad. This equipment is known for its lateral and vertical transmission and diffusion of electrical power into surrounding tissue. Since monopolar electrocautery rapidly generates temperatures exceeding 350°C, thermal spread in tissues is problematic (27–29). Wu et al. reported that safe use of monopolar electrocautery at 15 watts requires an activation distance of 5 mm and a cooling time of 1 second (25). However, the optimal safety parameters (i.e., activation distance and time) depend on the activation power use to on the tissue.

## Bipolar Electrocautery

In bipolar electrocautery, current only passes through tissue between two arms of a forceps-shaped electrode. Bipolar electrocautery is performed at a temperature significantly lower than that of monopolar electrocautery, and showed little difference of Celsius degree when compare to advanced bipolar EBDs (e.g., Ligasure) (28). An animal study indicated that, the safety parameters for bipolar electrocautery performed at 30 watts are an activation distance of 3 mm and a cooling time of 1 second (25).

## Advanced Bipolar EBDs

LigaSure, an advanced bipolar EBD, can seal vessels up to 7 mm in diameter (30, 31). The Ligasure Small Jaw (LSJ) and Ligasure Exact Dissector (LED) have curved jaws with bilateral symmetric blades coated with anti-adherent material to enable their use in performing fine-manipulation tasks (**Figure 3**). Reports of experiments performed using infrared cameras or thermosensors indicate that both devices operate at a temperature below 100°C (32–34).

**LigaSure Small Jaw (LSJ)** (Medtronic, Minneapolis, MN, USA)

The LSJ has an activation button with tactile feedback and a 16.5 mm long curved tip. According to Dionigi et al, the safe activation distance is 2 mm, and a 2-second interval or muscle touch maneuver is required for cooling (31).

**LigaSure Exact Dissector (LED)** (Medtronic, Minneapolis, MN, USA)

Compared to LSJ, the LED has a narrower jaw (2 mm) and a longer seal (20.6 mm). For sealing, the required activation time is


**FIGURE 3** | The LigaSure Exact Dissector (LED) (Medtronic, Mineapolis, MN, USA) is an advanced bipolar energy based device commonly used for open thyroid surgery. The finely curved symmetrical jaws have an anti-adherent nano-coating.

2 to 4 seconds, which is shorter than that of LSJ. In Huang et al. study, the safe activation distance was 1 mm, and the cooling study revealed no adverse EMG events after a 2-second cooling interval or after muscle touch maneuver (35).

## Ultrasonic EBDs

Ultrasonic EBDs deliver energy in the form of ultrasonic vibrations, which enable simultaneous cutting and coagulation. When a Harmonic device is used for transecting and sealing tissue, contact between the blade and the tissue pad of the device causes a rapid temperature increase.(**Figure 4**) A Harmonic device can seal vessels up to 7 mm in diameter. Notably, ultrasonic EBDs such as the Harmonic enable sealing at lower temperatures compared to monopolar electrocautery equipment (30, 36).

**Harmonic Focus (HF)** (Ethicon, Johnson and Johnson, Cincinnati, OH, USA)

The activation study in Wu et al. revealed no adverse EMG event at an activation distance of 1 mm and an activation time between 3 and 10 seconds. At a distance of 0 mm, EMG was stable in the first 3 seconds, but adverse EMG events occurred when activation time reached 4 seconds or longer. The cooling study revealed no adverse EMG event after a 10-second cooling period. When muscle touch maneuver was used for cooling, no adverse EMG events occurred after a 2-second cooling time (37).

**Harmonic Focus+ (HF+)** (Ethicon, Johnson and Johnson, Cincinnati, OH, USA)

Unlike the HF, the HF+ has Adaptive Tissue Technology, which increases precision in delivery of energy and reduces the time required for the device to reach its operating temperature (36). In the study, the HF+ did not cause significant thermal damage to the RLN at an activation distance of 1mm or even when the non-acting blade was activated while in direct contact with the nerve in the dry field. However, activation at a distance of 1 mm increased latency in some nerves whereas activation in direct contact revealed decreased amplitude in some nerves. In both cases, EMG changes recovered to baseline within 5-6 minutes (27).

**Harmonic ACE** (Ethicon, Johnson and Johnson, Cincinnati, OH, USA)

The Harmonic ACE is applicable in both endoscopic and open surgery. The device, 23cm length, 5.5mm diameter, can rotate 360 degrees. Kim et al. reported no adverse EMG events within 25 seconds after activation at a distance of 4 mm. At activation distances of 1-3 mm, however, shrinkage occurred in adjacent tissue within 6 to 25 seconds after activation. In some patients, activation resulted in adverse EMG events (38).

**Harmonic ACE+** (Ethicon, Johnson and Johnson, Cincinnati, OH, USA)

The Adaptive Tissue Technology used in the HF+ is also used in the Harmonic ACE+. This technology theoretically reduces thermal spread and transection time. Experiments showed that Harmonic ACE+ did not cause adverse EMG events within 20 seconds after activation at a distance of 1 mm from the RLN. When the HA+ was activated in direct contact with the RLN, however, adverse EMG events occurred after 6 seconds of activation (38).

**Sonicision** (Medtronic, Minneapolis, MN, USA)

Sonicision is an ultrasonic EBD that can perform vessel sealing and dissection in surgery. The device is cordless, which increases mobility and convenience. Since the device is available in lengths ranging from 13 to 48 cm, it can be used in either endoscopic or open surgery. According to Hayami et al., Sonicision can be safely used at a distance of 1 mm from the RLN (39).

## Hybrid EBDs (Ultrasonic and Bipolar EBDs)

**Thunderbeat (TB)** (Olympus Co Inc, Tokyo, Japan)

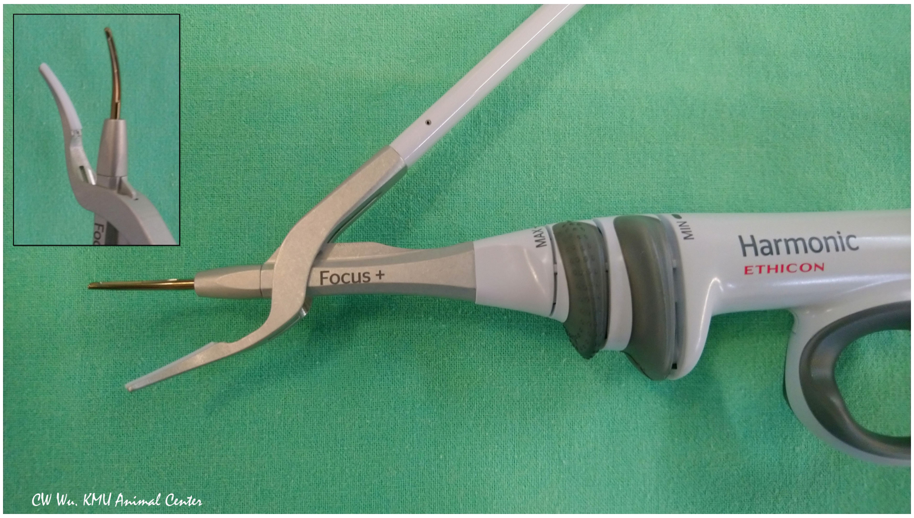



**FIGURE 4** | Ultrasonic energy based device. Harmonic Focus+ (HF+) (Ethicon, Johnson and Johnson, Cincinnati, OH, USA). The HF+ is widely used in open thyroid surgery. Its curved and tapered tip has bare blades on one side and a non-active tissue pad on the opposite side.

The TB integrates both ultrasonic and advanced bipolar energy. The curved probe is composed of aluminum and has a thin profile to aid release of residual heat after activation (**Figure 5**). Surgeons can use TB to coagulate, dissect and cut blood vessels 5-7 mm in diameter (4, 33). In Kwak et al. study, no adverse EMG events occurred when the TB was activated for less than 10 seconds at distances of 3 mm from the RLN. However, when the TB was activated for 8 seconds at a distance of 2 mm from the RLN, amplitude decreased (4).

## Ferromagnetic EBDs

Ferromagnetic EBDs are recently developed devices that enable hemostasis and dissection during thyroid surgery. Ferromagnetic EBDs generate pure thermal energy in response to a rapidly alternating magnetic field (40, 41).

**FMwand** (Domain Surgical, Salt Lake City, Utah)

The FMwand is a hemostatic dissecting scalpel with a dissecting loop. In Huang et al. study, no adverse EMG events occurred at distances of 2 mm or longer. Additionally, the cooling study revealed no adverse EMG events after a 1-second interval or after muscle touch maneuver (40).

**FMsealer** (Domain Surgical, Salt Lake City, Utah)

The FMsealer is a vessel sealing instrument that can seal vessels up to 7 mm in diameter. Compared to ultrasonic devices, FMsealer has a significantly lower peak temperature (92.1°C) and enables faster transection of tissue bundles (41). In their activation study, Huang et al. reported that the safe distance is 2 mm for a single 3-second activation. No adverse EMG events occurred after a 3-second cooling time or after muscle touch maneuver (40).

## DISCUSSION

Thyroid surgery is one of the most commonly performed endocrine surgical procedures, the risk of complications is high due to the anatomical structure and physiological function of the RLN. Symptoms after thyroid surgery may include dysphagia, dysphonia, aspiration, choking, and even dyspnea (10–13). The management of symptomatic patients varied case by case, from voice therapy, vocal fold injection, thyroplasty to tracheotomy. It is noteworthy that patients who underwent thyroidectomy without RLN injury may also suffered from dysphonia and dysphagia. However, most of the symptoms are transient with good prognosis (9, 11–13). Avoiding iatrogenic RLN injury is essential for voice and swallowing outcomes after thyroid surgery. Impaired RLN function and vocal fold movement are problematic complications that may lead to medicolegal litigation after thyroid surgery in the quality-of-life era (8, 9, 42, 43).

Because they are ideal for dissection and provide a hemostatic effect, EBDs are currently used in more than 60% of thyroid surgeries (1). However, the high temperatures generated by EBD blades raise the risk of unexpected iatrogenic RLN thermal injury. This article reviewed recently published medical literature relevant to safety parameters for EBD use in thyroid surgery. For various EBDs, **Table 1** summarizes the recent literature on optimal activation distances in terms of safety and cooling time. Surgeons should be familiar with the safety parameters of an EBD before using it in thyroid surgery and should follow standard procedures for hemostasis and dissection near the RLN to prevent iatrogenic RLN thermal injury and to improve the voice outcomes of patients.

**TABLE 1** | Summary of safety parameters of EBDs near the RLN during thyroid surgery.

| Device/Generator (Power) | Activation distance (activation time) | Cooling time | Reference (all by porcine model) |
|---|---|---|---|
| **Monopolar Electrocautery (15W)** | 5 mm (1 sec) | 1 sec | (25) |
| **Bipolar Electrocautery (30W)** | 3 mm (1 sec) | 1 sec | (25) |
| **Advanced Bipolar Energy Based Device** | | | |
| LigaSure Small Jaw (LSJ)/ ForceTriad energy platform (level2) | 2 mm (2-4 sec) | 2 sec or muscle touch (immediately) | (31) |
| LigaSure Exact Dissector (LED)/ ValleylabTM LS10 energy platform | 1 mm (2-4 sec) | 2 sec or muscle touch (immediately) | (35) |
| **Ultrasonic Energy BasedDevice** | | | |
| Harmonic Focus (HF)/ Ethicon Endo-Surgery Generator G11(level5) | 1 mm (3-10 sec) | 10 sec or muscle touch(2 sec) | (37) |
| Harmonic Focus+ (HF+)/ Ethicon Endo-Surgery Generator G11(level5) | 1 mm (4.7 ± 1.1sec) | | (27) |
| Harmonic ACE/ Ethicon Endo-Surgery Generator G11(level5) | 4 mm (10-25 sec) | | (38) |
| Harmonic ACE+/ Ethicon Endo-Surgery Generator G11(level5) | 1 mm (5-20 sec) | | (38) |
| Sonicision/ maximum power mode (55 kHz) | 1mm (1.5-2 sec) | | (39) |
| **Hybrid Energy Based Device (Ultrasonic and Bipolar Energy)** | | | |
| Thunderbeat (TB) | 3 mm (10 sec) | | (4) |
| **Ferromagnetic Energy Based Device** | | | |
| FMwand/ FMX G1 Generator (Max45) | 2 mm (3 sec) | 1 sec or muscle touch (immediately) | (35) |
| FMsealer/ FMX G1 Generator (Max3) | 2 mm (3 sec) | 1 sec or muscle touch (immediately) | (35) |

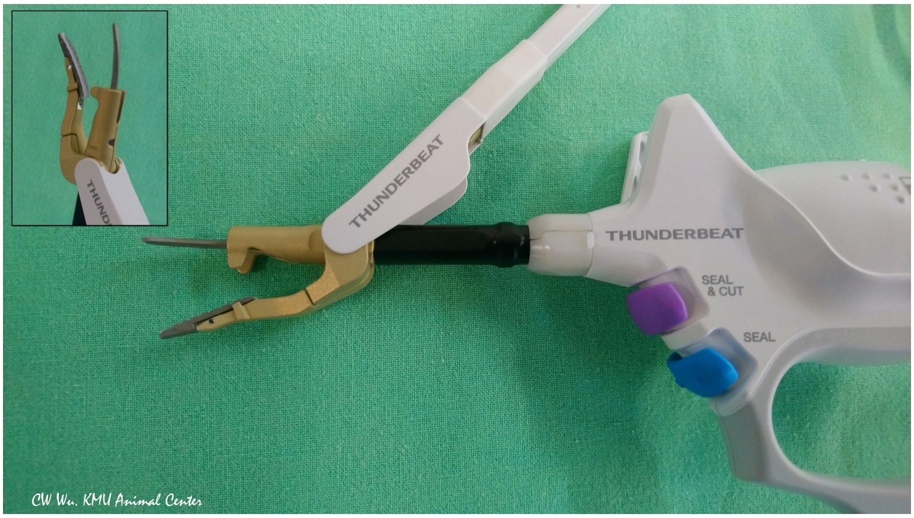



**FIGURE 5** | Hybrid energy based device (ultrasonic and bipolar energy). The Thunderbeat Open Fine Jaw (TB; Olympus Co Inc, Tokyo, Japan) has a thin, curved probe for fine dissection. The counter jaw enables its use for grasping tissue. The aluminum coating dissipates residual heat.

In the past two decades, IONM use in thyroid surgery has become well established and is increasingly accepted worldwide. Additionally, many studies have reported that continuous IONM by periodic vagal stimulation can be useful in high-risk procedure and enables corrective action to prevent RLN traction injuries (44–46). Unlike traction injury, however, thermal injury often occurs suddenly and unexpectedly. Since IONM may be inapplicable for early detection and prevention of thermal injuries, safe use of EBDs is more important than using IONM to identify thermal injuries retrospectively.

Recent experimental and clinical studies indicate that thermal injury to the RLN is more severe than mechanical injury (i.e., injury caused by traction, compression, etc.) to the RLN because thermal injury tends to cause irreversible changes in nerve function (17, 19). Additionally, visual identification of a thermal injury to the RLN is often difficult, and lateral thermal spread can occur even when the heat source does not make direct contact with the nerve (31, 37). Protein denaturation and RLN injuries occur at a temperature of 60°C (47). Thermal stimuli applied to the RLN at temperatures over 60°C can cause permanent functional damage to the endoneurium (19). Since most EBDs reach temperatures exceeding 60°C after activation, surgeons must carefully consider the risk of endoneurium injury, regardless of the EBD type used. Maximum activation temperatures of ultrasonic EBDs and hybrid devices (e.g. TB) may exceed 200°C, only lower to monopolar electrocautery which have a higher maximum activation temperature (> 350°C) (28, 29, 33, 39). Advanced bipolar EBDs, bipolar electrocautery and FMsealer have maximum activation temperatures ranging from 80 to 100°C (33, 41, 48). Therefore, surgeons should remain cognizant that using EBDs for dissection near the RLN can potentially cause thermal injury of varying severity, especially during endoscopic procedures in which the surgical field is limited and the EBDs is commonly used for dissection.

Different EBDs deliver energy through different mechanisms, and the high temperature generated by an EBD may not be proportional to the activation distance (32). Recent studies also indicate that advanced bipolar devices induce greater thermal spread compared to ultrasonic devices. However, the temperature of adjacent tissue affected by thermal spread reportedly remains below 30°C, which would not substantially change EMG (39, 48).

Notably, Hayami et al. argued that activating EBDs in the wet condition (e.g., after exposure to liquid content from tissue) generates high-temperature steam. Since the steam, hyperthermal liquid, or smog may cause thermal injury to the RLN, caution should be taken when operate in specific condition, and increasing the activation distance is essential (49, 50).

Long duration of EBDs use may cause tissue shrinkage or thermal injury (38). Temperatures potentially generated by EBDs increase as activation time increases. Heat production is slower in ultrasonic EBDs compared to electrocautery equipment. Ultrasonic EBDs, temperatures may reach 150 to 200°C when activation time exceeds 10 seconds (29, 33, 39).

Similarly, advanced bipolar EBDs reach much higher temperatures after a double activation compared to a single activation. Consequently, thermal injuries may occur when an advanced bipolar EBDs is not allowed to cool between activations (35).

For some EBDs, data for cooling time were unavailable and were not included in **Table 1**. Experiments using infrared cameras and thermo-sensors had elucidated this issue. According to the literature, the time required for ultrasonic EBDs to cool to 60°C is almost two-fold longer than that for advanced bipolar EBDs (32–34). The surgeons may opt to perform muscle touch maneuver if the surgeons concludes that the long cooling time for an EBD during surgery would raise the risk of an extended surgical time. For ultrasonic EBDs, the recommended minimum duration of the muscle touch maneuver is 2 seconds (37).

This article reviewed relevant medical literature on the safety parameters for use of EBDs in thyroid surgery, including minimum safe distance from the RLN and the cooling duration of EBDs. Applying continuous IONM in animal experiments is an ideal method to establish the safety parameters of newly launched EBDs (51). Notably, all reviewed studies were animal studies, and all used porcine models of the RLN since experimentally inducing RLN injury in a human patient would violate ethical guidelines. Recommended distances for safe use of EBDs slightly differed among some studies, possibly due to differences in the mechanical properties of tissue specimens (e.g. wet versus dry condition), differences in experimental animal species, and differences in instrument settings and methodologies. Neural and tissue characteristics may differ even when the same animal model is used (37, 49). Therefore, data obtained in animal experiments should be applied cautiously to human patients (30). Future large observational clinical studies are needed for further verification of the findings of this study.

## CONCLUSION

In conclusion, energy-based device (EBD) in thyroidectomy yields many superior outcomes, including considerable reduction of operative time, incision length, blood loss, and post-operative pain. One major advantage is significantly lowered rate of postoperative neck hematoma and postoperative hypocalcemia. To avoid an inadvertent iatrogenic RLN thermal injury caused by EBDs, standard procedures for safe use of these advanced medical devices must be developed and implemented. Many studies agree that animal models are ideal for experiments in continuous IONM because they provide objective data that can be used for electrophysiological evaluation of RLN thermal injury and for development of safety parameters for newly developed EBDs.

In general, conventional electrocautery generates higher temperature and wider thermal spread range, but when applying EBDs near the RLN adequate activation distance and cooling time are still required to avoid inadvertent thermal injury. Understanding EBD safety parameters and following standard procedures for using EBDs in thyroid surgery can improve safety and surgical outcomes, especially in voice quality and vocal cord mobility.

## AUTHOR CONTRIBUTIONS

JJ-W, TY-H, and CW-W conceived and designed the study. Administrative support was obtained by CH-L, LF-W. Provision of study materials by IC-L, PY-C, HC-C, HY-C, HY-T, YC-L and G-D. had collected and assembled the data. Data analysis and interpretation was done by FY-C, TY-H, CW-W. All authors were participated in manuscript writing and final approval of manuscript.

## FUNDING

This study was supported by grants from Kaohsiung Medical University Hospital (KMUH109-9M44), Kaohsiung Municipal Siaogang Hospital/Kaohsiung Medical University Research Center grants (KMHK-DK (C)110009, I-109-04, H-109-05, I-108-02) and Ministry of Science and Technology (MOST 108-2628-B-037-006, MOST 109-2628-B-037-014, MOST 110-2314-B-037-104-MY2, MOST 110-2314-B-037-120), Taiwan.

## ACKNOWLEDGMENTS

The authors would like to thank all authors of the papers included in this study, as well as participants in the contributing studies.

## REFERENCES

1. Moran K, Grigorian A, Elfenbein D, Schubl S, Jutric Z, Lekawa M, et al. Energy Vessel Sealant Devices Are Associated With Decreased Risk of Neck Hematoma After Thyroid Surgery. *Updates Surg* (2020) 72(4):1135–41. doi: 10.1007/s13304-020-00776-9
2. Canu GL, Medas F, Podda F, Tatti A, Pisano G, Erdas E, et al. Thyroidectomy With Energy-Based Devices: Surgical Outcomes and Complications—Comparison Between Harmonic Focus, Ligasure Small Jaw and Thunderbeat Open Fine Jaw. *Gland Surg* (2020) 9(3):721. doi: 10.21037/gs.2020.03.31
3. Garas G, Okabayashi K, Ashrafian H, Shetty K, Palazzo F, Tolley N, et al. Which Hemostatic Device in Thyroid Surgery? A Network Meta-Analysis of Surgical Technologies. *Thyroid* (2013) 23(9):1138–50. doi: 10.1089/thy.2012.0588
4. Kwak HY, Dionigi G, Kim D, Lee HY, Son GS, Lee JB, et al. Thermal Injury of the Recurrent Laryngeal Nerve by THUNDERBEAT During Thyroid Surgery: Findings From Continuous Intraoperative Neuromonitoring in a Porcine Model. *J Surg Res* (2016) 200(1):177–82. doi: 10.1016/j.jss.2015.06.066
5. Dionigi G, Wu C-W, Kim H-Y, Liu X, Liu R, Randolph GW, et al. Safety of Energy Based Devices for Hemostasis in Thyroid Surgery. *Gland Surg* (2016) 5(5):490. doi: 10.21037/gs.2016.09.01
6. Liu C-H, Wang C-C, Wu C-W, Lin Y-C, Lu I, Chang P-Y, et al. Comparison of Surgical Complications Rates Between Ligasure Small Jaw and Clamp-and-Tie Hemostatic Technique in 1,000 Neuro-Monitored Thyroidectomies. *Front Endocrinol* (2021) 12:313. doi: 10.3389/fendo.2021.638608
7. Pacilli M, Tartaglia N, Gerundo A, Pavone G, Fersini A, Ambrosi A. Energy Based Vessel Sealing Devices in Thyroid Surgery: A Systematic Review to Clarify the Relationship With Recurrent Laryngeal Nerve Injuries. *Medicina* (2020) 56(12):651. doi: 10.3390/medicina56120651
8. Huang T-Y, Yu W-HV, Chiang F-Y, Wu C-W, Fu S-C, Tai A-S, et al. How the Severity and Mechanism of Recurrent Laryngeal Nerve Dysfunction During Monitored Thyroidectomy Impact on Postoperative Voice. *Cancers* (2021) 13(21):5379. doi: 10.3390/cancers13215379
9. Christakis I, Klang P, Talat N, Galata G, Schulte K-M. Long-Term Quality of Voice Is Usually Acceptable After Initial Hoarseness Caused by a Thyroidectomy or a Parathyroidectomy. *Gland Surg* (2019) 8(3):226. doi: 10.21037/gs.2018.09.02

10. Schneider R, Randolph GW, Dionigi G, Wu CW, Barczynski M, Chiang FY, et al. International Neural Monitoring Study Group Guideline 2018 Part I: Staging Bilateral Thyroid Surgery With Monitoring Loss of Signal. *Laryngoscope* (2018) 128 Suppl 3:S1–17. doi: 10.1002/lary.27359
11. Yu W-HV, Wu C-W. Speech Therapy After Thyroidectomy. *Gland Surg* (2017) 6(5):501. doi: 10.21037/gs.2017.06.06
12. Borel F, Tresallet C, Hamy A, Mathonnet M, Lifante J-C, Brunaud L, et al. Self-Assessment of Voice Outcomes After Total Thyroidectomy Using the Voice Handicap Index Questionnaire: Results of a Prospective Multicenter Study. *Surgery* (2020) 167(1):129–36. doi: 10.1016/j.surg.2019.05.090
13. Borel F, Christou N, Marret O, Mathonnet M, Caillard C, Bannani S, et al. Long-Term Voice Quality Outcomes After Total Thyroidectomy: A Prospective Multicenter Study. *Surgery* (2018) 163(4):796–800. doi: 10.1016/j.surg.2017.09.023
14. Wu CW, Dionigi G, Barczynski M, Chiang FY, Dralle H, Schneider R, et al. International Neuromonitoring Study Group Guidelines 2018: Part II: Optimal Recurrent Laryngeal Nerve Management for Invasive Thyroid Cancer-Incorporation of Surgical, Laryngeal, and Neural Electrophysiologic Data. *Laryngoscope* (2018) 128 Suppl 3:S18–s27. doi: 10.1002/lary.27360
15. Wu CW, Randolph GW, Barczyński M, Schneider R, Chiang FY, Huang TY, et al. Training Courses in Laryngeal Nerve Monitoring in Thyroid and Parathyroid Surgery- the INMSG Consensus Statement. *Front Endocrinol (Lausanne)* (2021) 12:705346. doi: 10.3389/fendo.2021.705346
16. Feng AL, Puram SV, Singer MC, Modi R, Kamani D, Randolph GW. Increased Prevalence of Neural Monitoring During Thyroidectomy: Global Surgical Survey. *Laryngoscope* (2020) 130(4):1097–104. doi: 10.1002/lary.28210
17. Dionigi G, Wu CW, Kim HY, Rausei S, Boni L, Chiang FY. Severity of Recurrent Laryngeal Nerve Injuries in Thyroid Surgery. *World J Surg* (2016) 40(6):1373–81. doi: 10.1007/s00268-016-3415-3
18. Wu CW, Lee KD, Tae K, Ji YB, Kim SU, Lee HS, et al. Recurrent Laryngeal Nerve (RLN) Injury in Thyroid Surgery: Lessons Learned From the Intraoperative Neural Monitoring (IONM). *Int J Head Neck Sci* (2017) 1 (1):19–26. doi: 10.6696/IJHNS.2017.0101.04
19. Wu CW, Dionigi G, Sun H, Liu X, Kim HY, Hsiao PJ, et al. Intraoperative Neuromonitoring for the Early Detection and Prevention of RLN Traction Injury in Thyroid Surgery: A Porcine Model. *Surgery* (2014) 155(2):329–39. doi: 10.1016/j.surg.2013.08.015
20. Randolph GW, Dralle H, Abdullah H, Barczynski M, Bellantone R, Brauckhoff M, et al. Electrophysiologic Recurrent Laryngeal Nerve Monitoring During Thyroid and Parathyroid Surgery: International Standards Guideline Statement. *Laryngoscope* (2011) 121 Suppl 1:S1–16. doi: 10.1002/lary.21119
21. Chiang FY, Lu IC, Kuo WR, Lee KW, Chang NC, Wu CW. The Mechanism of Recurrent Laryngeal Nerve Injury During Thyroid Surgery–the Application of Intraoperative Neuromonitoring. *Surgery* (2008) 143(6):743–9. doi: 10.1016/j.surg.2008.02.006
22. Dionigi G, Alesina PF, Barczynski M, Boni L, Chiang FY, Kim HY, et al. Recurrent Laryngeal Nerve Injury in Video-Assisted Thyroidectomy: Lessons Learned From Neuromonitoring. *Surg Endosc* (2012) 26(9):2601–8. doi: 10.1007/s00464-012-2239-y
23. Dionigi G. Energy Based Devices and Recurrent Laryngeal Nerve Injury: The Need for Safer Instruments. *Langenbecks Arch Surg* (2009) 394(3):579–80; author reply 81-6. doi: 10.1007/s00423-008-0454-8
24. Lee E, Tong JY, Pasick LJ, Benito DA, Joshi A, Thakkar PG, et al. Complications Associated With Energy-Based Devices During Thyroidectomy From 2010–2020. *World J Otorhinolaryngology-Head Neck Surg* (2021). doi: 10.1016/j.wjorl.2021.04.008
25. Wu C-W, Huang T-Y, Chen H-C, Chen H-Y, Tsai T-Y, Chang P-Y, et al. Intra-Operative Neural Monitoring of Thyroid Surgery in a Porcine Model. *JoVE* (2019) 144):e57919. doi: 10.3791/57919
26. Wu C-W, Randolph GW, Lu I-C, Chang P-Y, Chen Y-T, Hun P-C, et al. Intraoperative Neural Monitoring in Thyroid Surgery: Lessons Learned From Animal Studies. *Gland Surg* (2016) 5(5):473–80. doi: 10.21037/gs.2016.09.06
27. Chávez KV, Barajas EM, Soroa F, Gamboa-Dominguez A, Ordóñez S, Pantoja JP, et al. Safety Assessment of the Use of Ultrasonic Energy in the Proximity of the Recurrent Laryngeal Nerve in a Porcine Model. *Am J Surg* (2018) 215 (1):186–90. doi: 10.1016/j.amjsurg.2017.04.013
28. Sutton P, Awad S, Perkins A, Lobo D. Comparison of Lateral Thermal Spread Using Monopolar and Bipolar Diathermy, the Harmonic Scalpel™ and the Ligasure™. *J Br Surg* (2010) 97(3):428–33. doi: 10.1002/bjs.6901
29. Kinoshita T, Kanehira E, Omura K, Kawakami K, Watanabe Y. Experimental Study on Heat Production by a 23.5-Khz Ultrasonically Activated Device for Endoscopic Surgery. *Surg Endoscopy* (1999) 13(6):621–5. doi: 10.1007/s004649901055
30. Bakkar S, Papavramidis TS, Aljarrah Q, Materazzi G, Miccoli P. Energy-Based Devices in Thyroid Surgery—An Overview. *Gland Surg* (2020) 9(Suppl 1):S14. doi: 10.21037/gs.2019.08.05
31. Dionigi G, Chiang FY, Kim HY, Randolph GW, Mangano A, Chang PY, et al. Safety of Ligasure in Recurrent Laryngeal Nerve Dissection-Porcine Model Using Continuous Monitoring. *Laryngoscope* (2017) 127(7):1724–9. doi: 10.1002/lary.26271
32. Smith CT, Zarebczan B, Alhefdhi A, Chen H. Infrared Thermographic Profiles of Vessel Sealing Devices on Thyroid Parenchyma. *J Surg Res* (2011) 170 (1):64–8. doi: 10.1016/j.jss.2011.03.005
33. Seehofer D, Mogl M, Boas-Knoop S, Unger J, Schirmeier A, Chopra S, et al. Safety and Efficacy of New Integrated Bipolar and Ultrasonic Scissors Compared to Conventional Laparoscopic 5-Mm Sealing and Cutting Instruments. *Surg Endoscopy* (2012) 26(9):2541–9. doi: 10.1007/s00464-012-2229-0
34. Kim FJ, Chammas M, Gewehr E, Morihisa M, Caldas F, Hayacibara E, et al. Temperature Safety Profile of Laparoscopic Devices: Harmonic ACE (ACE), Ligasure V (LV), and Plasma Trisector (PT). *Surg endoscopy* (2008) 22 (6):1464–9. doi: 10.1007/s00464-007-9650-9
35. Huang T-Y, Lin Y-C, Tseng H-Y, Dionigi G, Kim H-Y, Lu I-C, et al. Safety of Ligasure Exact Dissector in Thyroidectomy With Continuous Neuromonitoring: A Porcine Model. *Gland Surg* (2020) 9(3):702. doi: 10.21037/gs.2020.03.17
36. Broughton D, Welling AL, Monroe EH, Pirozzi K, Schulte JB, Clymer JW. Tissue Effects in Vessel Sealing and Transection From an Ultrasonic Device With More Intelligent Control of Energy Delivery. *Med Devices* (2013) 6:151. doi: 10.2147/MDER.S51663
37. Wu CW, Chai YJ, Dionigi G, Chiang FY, Liu X, Sun H, et al. Recurrent Laryngeal Nerve Safety Parameters of the H Armonic F Ocus During Thyroid Surgery: Porcine Model Using Continuous Monitoring. *Laryngoscope* (2015) 125(12):2838–45. doi: 10.1002/lary.25412
38. Kim HK, Chai YJ, Lee HY, Kim HY, Dionigi G. Comparing the Safety of Harmonic ACE and ACE+ Around the Recurrent Laryngeal Nerve in Swine Models. *Ann Surg Treat Res* (2018) 94(6):285–90. doi: 10.4174/astr.2018.94.6.285
39. Hayami M, Watanabe M, Mine S, Imamura Y, Okamura A, Yuda M, et al. Lateral Thermal Spread Induced by Energy Devices: A Porcine Model to Evaluate the Influence on the Recurrent Laryngeal Nerve. *Surg Endoscopy* (2019) 33(12):4153–63. doi: 10.1007/s00464-019-06724-y
40. Huang TY, Lin YC, Tseng HY, Dionigi G, Kim HY, Chai YJ, et al. Safety Parameters of Ferromagnetic Device During Thyroid Surgery: Porcine Model Using Continuous Neuromonitoring. *Head Neck* (2020) 42(10):2931–40. doi: 10.1002/hed.26334
41. Chen J, Jensen CR, Manwaring PK, Glasgow RE. Validation of a Laparoscopic Ferromagnetic Technology-Based Vessel Sealing Device and Comparative Study to Ultrasonic and Bipolar Laparoscopic Devices. *Surg Laparoscopy Endoscopy* (2017) 27(2):e12. doi: 10.1097/SLE.0000000000000385
42. Dralle H, Lorenz K, Machens A. Verdicts on Malpractice Claims After Thyroid Surgery: Emerging Trends and Future Directions. *Head Neck* (2012) 34(11):1591–6. doi: 10.1002/hed.21970
43. Gualniera P, Scurria S, Mondello C, Asmundo A, Sapienza D, Gianlorenzo D. Narrative Review of Proving the Causal Link of Recurrent Laryngeal Nerve Injury and Thyroidectomy: A Medico Legal Appraisal. *Gland Surg* (2020) 9 (5):1564–72. doi: 10.21037/gs-20-203
44. Dionigi G, Donatini G, Boni L, Rausei S, Rovera F, Tanda ML, et al. Continuous Monitoring of the Recurrent Laryngeal Nerve in Thyroid Surgery: A Critical Appraisal. *Int J Surg* (2013) 11(Suppl)1:S44–6. doi: 10.1016/S1743-9191(13)60014-X
45. Schneider R, Przybyl J, Hermann M, Hauss J, Jonas S, Leinung S. A New Anchor Electrode Design for Continuous Neuromonitoring of the Recurrent Laryngeal Nerve by Vagal Nerve Stimulations. *Langenbecks Arch Surg* (2009) 394(5):903–10. doi: 10.1007/s00423-009-0503-y

46. Phelan E, Schneider R, Lorenz K, Dralle H, Kamani D, Potenza A, et al. Continuous Vagal IONM Prevents Recurrent Laryngeal Nerve Paralysis by Revealing Initial EMG Changes of Impending Neuropraxic Injury: A Prospective, Multicenter Study. *Laryngoscope* (2014) 124(6):1498–505. doi: 10.1002/lary.24550
47. Lin YC, Dionigi G, Randolph GW, Lu IC, Chang PY, Tsai SY, et al. Electrophysiologic Monitoring Correlates of Recurrent Laryngeal Nerve Heat Thermal Injury in a Porcine Model. *Laryngoscope* (2015) 125(8): E283–E90. doi: 10.1002/lary.25362
48. Hruby GW, Marruffo FC, Durak E, Collins SM, Pierorazio P, Humphrey PA, et al. Evaluation of Surgical Energy Devices for Vessel Sealing and Peripheral Energy Spread in a Porcine Model. *J Urol* (2007) 178(6):2689–93. doi: 10.1016/j.juro.2007.07.121
49. Hayami M, Watanabe M, Mine S, Imamura Y, Okamura A, Yuda M, et al. Steam Induced by the Activation of Energy Devices Under a Wet Condition may Cause Thermal Injury. *Surg Endoscopy* (2020) 34(5):2295–302. doi: 10.1007/s00464-019-07312-w
50. Yu X, Liu C, Yan M, Gong W, Wang Y. Hyperthermal Liquid, Spray, and Smog may be Potential Risk Factors for Recurrent Laryngeal Nerve Thermal Injury During Thyroid Surgeries. *Endocrine* (2021) 72(1):198–207. doi: 10.1007/s12020-020-02451-w
51. Prasad A, Durrant J, Smeak DD, Newman JG. The Thermal Safety Profile of a New Bipolar Vessel Sealing Device for Thyroid Surgery. *Surg Technol Int* (2021) 39:sti39/1501. doi: 10.52198/21.STI.39.SO1501

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Publisher's Note:** All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Endocrinology

ORIGINAL RESEARCH
published: 30 November 2021
doi: 10.3389/fendo.2021.755231

# Prognostic Indicators of Non-Transection Nerve Injury and Vocal Fold Motion Impairment After Thyroid Surgery – Correlation Between Intraoperative Neuromonitoring Findings and Perioperative Voice Parameters

***Tzu-Yen Huang*** [1,2,3]***, Wing-Hei Viola Yu*** [1]***, Feng-Yu Chiang*** [4,5]***, Che-Wei Wu*** [1,6]***, Shih-Chen Fu*** [7,8]***, An-Shun Tai*** [7,8]***, Yi-Chu Lin*** [1]***, Hsin-Yi Tseng*** [1]***, Ka-Wo Lee*** [1,9] ***and Sheng-Hsuan Lin*** [7,8,10,11]*

*[1] International Thyroid Surgery Center, Department of Otolaryngology-Head and Neck Surgery, Kaohsiung Medical University Hospital, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan, [2] Department of Biological Science and Technology, National Yang Ming Chiao Tung University, Hsinchu, Taiwan, [3] Department of Biological Science and Technology, National Chiao Tung University, Hsinchu, Taiwan, [4] Department of Otolaryngology-Head and Neck Surgery, E-Da Hospital, Kaohsiung, Taiwan, [5] School of Medicine, College of Medicine, I-Shou University, Kaohsiung, Taiwan, [6] Department of Otolaryngology-Head and Neck Surgery, Kaohsiung Municipal Siaogang Hospital, Kaohsiung Medical University Hospital, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan, [7] Institute of Statistics, National Yang Ming Chiao Tung University, Hsinchu, Taiwan, [8] Institute of Statistics, National Chiao Tung University, Hsinchu, Taiwan, [9] Department of Otolaryngology-Head and Neck Surgery, Kaohsiung Municipal Tatung Hospital, Kaohsiung Medical University Hospital, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan, [10] Institute of Data Science and Engineering, National Yang Ming Chiao Tung University, Hsinchu, Taiwan, [11] Institute of Data Science and Engineering, National Chiao Tung University, Hsinchu, Taiwan*

OPEN ACCESS

***Edited by:***
*Paolo Miccoli, University of Pisa, Italy*

***Reviewed by:***
*Gabriele Materazzi, University of Pisa, Italy*
*Erivelto Martinho Volpi, Centro de referencia no ensino do diagnóstico por imagem (CETRUS), Brazil*

****Correspondence:***
*Sheng-Hsuan Lin*
*shenglin@nctu.edu.tw*

***Specialty section:***
*This article was submitted to Thyroid Endocrinology, a section of the journal Frontiers in Endocrinology*

***Received:*** *08 August 2021*
***Accepted:*** *15 November 2021*
***Published:*** *30 November 2021*

***Citation:***
*Huang T-Y, Yu W-HV, Chiang F-Y, Wu C-W, Fu S-C, Tai A-S, Lin Y-C, Tseng H-Y, Lee K-W and Lin S-H (2021) Prognostic Indicators of Non-Transection Nerve Injury and Vocal Fold Motion Impairment After Thyroid Surgery – Correlation Between Intraoperative Neuromonitoring Findings and Perioperative Voice Parameters. Front. Endocrinol. 12:755231. doi: 10.3389/fendo.2021.755231*

**Objectives:** In patients with recurrent laryngeal nerve (RLN) injury after thyroid surgery, unrecovered vocal fold motion (VFM) and subjective voice impairment cause extreme distress. For surgeons, treating these poor outcomes is extremely challenging. To enable early treatment of VFM impairment, this study evaluated prognostic indicators of non-transection RLN injury and VFM impairment after thyroid surgery and evaluated correlations between intraoperative neuromonitoring (IONM) findings and perioperative voice parameters.

**Methods:** 82 adult patients had postoperative VFM impairment after thyroidectomy were enrolled. Demographic characteristics, RLN electromyography (EMG), and RLN injury mechanism were compared. Multi-dimensional voice program, voice range profile and Index of voice and swallowing handicap of thyroidectomy (IVST) were administered during I-preoperative; II-immediate, III-short-term and IV-long-term postoperative periods. The patients were divided into R/U Group according to the VFM was recovered/unrecovered 3 months after surgery. The patients in U Group were divided into U1/U2 Group according to total IVST score change was <4 and ≥4 during period-IV.

**Results:** Compared to R Group (42 patients), U Group (38 patients) had significantly more patients with EMG >90% decrease in the injured RLN (p<0.001) and thermal injury as the RLN injury mechanism (p=0.002). Voice parameter impairments were more severe in U Group compared to R Group. Compared to U1 group (19 patients), U2 Group (19 patients) had a significantly larger proportion of patients with EMG decrease >90% in the injured RLN (p=0.022) and thermal injury as the RLN injury mechanism (p=0.017). A large pitch range decrease in period-II was a prognostic indicator of a moderate/severe long-term postoperative subjective voice impairment.

**Conclusion:** This study is the first to evaluate correlations between IONM findings and voice outcomes in patients with VFM impairment after thyroid surgery. Thyroid surgeons should make every effort to avoid severe type RLN injury (e.g., thermal injury or injury causing EMG decrease >90%), which raises the risk of unrecovered VFM and moderate/severe long-term postoperative subjective voice impairment. Using objective voice parameters (e.g., pitch range) as prognostic indicators not only enables surgeons to earlier identify patients with low voice satisfaction after surgery, and also enable implementation of interventions sufficiently early to maintain quality of life.

**Keywords: thyroid surgery, intraoperative neuromonitoring (IONM), vocal fold motion, recurrent laryngeal nerve (RLN), index of voice and swallowing handicap of thyroidectomy (IVST), subjective/objective voice analysis**

## INTRODUCTION

Recurrent laryngeal nerve (RLN) injury during thyroid surgery is the most common etiology of vocal fold motion (VFM) impairment (1) and morbidity after this procedure and a leading cause of medico-legal litigation after thyroid surgery (2). To avoid RLN injury during thyroid surgery, adjunct use of intraoperative neuromonitoring (IONM) has gained widespread use for identifying the RLN early in thyroid surgery and for elucidating nerve injury mechanism (3–6). The incidence of RLN paralysis may be underestimated if VFM is not routinely examined (7). Previous works report that permanent RLN palsy occurs in 1–3% of thyroid surgeries and that temporary RLN palsy occurs in 1.4-38% of these procedures (8, 9). For comprehensive evaluation of RLN function before and after thyroid surgery, current practice guidelines recommend performing pre- and post-operative laryngofiberscopy routinely (6, 10).

Patients who had a RLN injury during thyroid surgery are expected to have VFM impairment after surgery and may also experience severe dysphonia, dyspnea, and aspiration (11). In patients with temporary RLN palsy caused by a non-transection RLN injury, Chiang et al. (12) reported that VFM usually recovers within 3 days to 4 months (mean, 30.7 days) after surgery. However, the course of VFM recovery depends on the nerve injury mechanism (13). Thermal injuries are associated with a long recovery time and severe histological disturbance in the endoneurium whereas mechanical injuries are associated with distorted epineuria and perineuria (13, 14). After RLN injury, natural neuromuscular compensation mechanisms may yield outcomes that are acceptable to the patient, including RLN function outcomes and voice outcomes (15). However, early assessment of voice performance is important for deciding subsequent voice intervention (16). There is evidence that voice interventions 3 months after RLN injury can greatly improve voice outcome after thyroid surgery (10, 17, 18).

Impaired VFM after thyroid surgery is considered evidence of RLN injury. Unrecovered VFM and subjective voice impairment degrade quality of life and satisfaction with treatment, which causes extreme distress in patients. For surgeons, treating these poor outcomes is also extremely challenging. To enable early identification and treatment of VFM impairment and to improve patient satisfaction with surgery outcomes, this study evaluated prognostic indicators of non-transection RLN injury and VFM impairment after thyroid surgery. Correlations between IONM findings and perioperative voice parameters were also investigated.

## MATERIALS AND METHODS

The subjects of this study were adult patients who had received IONM-assisted primary thyroid surgery by "IONM team" at a single institution (Kaohsiung Medical University Hospital, Taiwan) from June, 2013, to June, 2019. All patients had normal and symmetric VFM before surgery and had VFM impairment within 2 weeks after surgery. The total number of surgeries performed in this period was 1033, and the number of surgeries without VFM impairment was 951. The analysis included 82 (7.9%) patients after exclusion of one oral cancer patient who had received cancer surgery combined with lateral neck dissection and one nasopharyngeal carcinoma patient who had received radiation therapy in the neck region. The flowchart in **Figure 1** depicts the procedure for inclusion and exclusion of

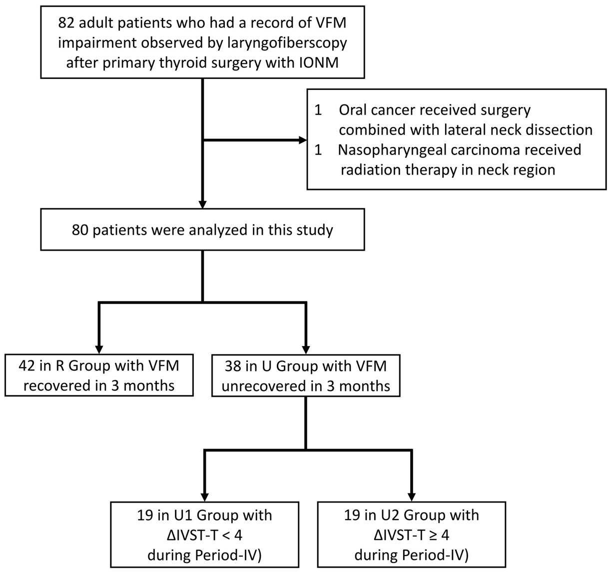



**FIGURE 1** | Flow diagram for inclusion and exclusion of patients. VFM, vocal fold motion; IONM, intraoperative neuromonitoring; IVST, Index of Voice and Swallowing Handicap of Thyroidectomy.

patients in this study. Ethical approval of this study was obtained from the Kaohsiung Medical University Hospital Institutional Review Board (KMUHIRB-E(I)-20200359). In all patients, vagus nerve function and RLN function were routinely evaluated using the standard four-step vagus nerve and RLN stimulation (V1-R1-R2-V2) procedure under IONM and the evoked electromyography (EMG) amplitudes were obtained and recorded (3, 19). The RLN EMG decrease was defined and calculated as the decrease in the EMG amplitude of the post-dissection R2 signal from the EMG amplitude of the pre-dissection R1 signal. No patient who had received bilateral thyroidectomy in this study had RLN signal >50% decreases on both sides. All exposed RLNs, including injury mechanisms (transection, mechanical, or thermal), were documented by photograph. Mechanical injury was classified as type 1 (segmental injury) or type 2 (global injury) according to the criteria proposed by Chiang et al. (3) and the INMSG (6). All patients received surgery by "IOINM team" routinely received a VFM survey. Laryngofiberscopy was documented by video in all patients before surgery and within 2 weeks after surgery. All patients with VFM impairment 2 weeks after surgery underwent additional monthly examinations until VFM recovery. Patients were divided into two groups according to VFM recovery: a recovered VFM group (R Group) and an unrecovered VFM group (U Group). The R Group criterion was laryngofiberscopic evidence of VFM impairment recovery within 3 months after thyroidectomy; the U group criterion was persistent VFM impairment more than 3 months after thyroidectomy. Patient information, including gender, age, surgery type (unilateral versus bilateral), and pathology results (benign versus malignant) was recorded and compared between groups.

## Objective and Subjective Voice Analysis

All patients underwent both subjective and objective voice analyses in four periods: period-I (preoperative period, within 2 months before surgery), period-II (immediate postoperative period, median duration of 3 days, range of 1-7 days), period-III (short-term postoperative period, median duration of 12 days, range of 7-30 days), and period-IV (long-term postoperative period, median duration of 40 days, range of 30-90 days).

All objective voice analyses in all subjects were performed by a single experienced speech-language pathologist (WHV. Y) using the Multidimensional Voice Program (model 5105, version 3.1.7; KayPENTAX, USA) and the Voice Range Profile (model 4326, version 3.3.0; KayPENTAX, USA). Multidimensional Voice Program analyses included mean fundamental frequency (mean F0), jitter, shimmer and noise-to-harmonic ratio whereas Voice Range Profile analyses included maximum pitch frequency (Fmax), minimum pitch frequency (Fmin), and pitch range (PR). The PR was defined as the number of semitones between Fmax and Fmin.

All preoperative and postoperative subjective voice analyses were performed using the 10-item Index of Voice and Swallowing Handicap of Thyroidectomy (IVST) (**Supplemental Table 1**), which provides an index of the main symptoms observed in the patient. Each item in this subjective assessment is scored from 0-2 (never, sometimes, and always), respectively. The two domains of the IVST are the voice domain (IVST-V; items 1-7; score range 0-14) and the swallowing domain (IVST-S; items 8-10; score range 0-6). Thus, the score range for the total IVST (IVST-T) is 0 to 20.

The equation for calculating postoperative change in objective voice analysis data was $\Delta = (B - A)/A$, and the equation for calculating postoperative change in subjective voice analysis data was $\Delta = B - A$, where A and B are preoperative and postoperative values, respectively.

Long-term postoperative subjective voice impairment was also evaluated in patients with unrecovered VFM (U Group). The U group was divided into patients with no/mild subjective voice impairment (ΔIVST-T < 4) in Period-IV (U1 Group) and patients with moderate/severe subjective voice impairment (ΔIVST-T ≥ 4) in Period-IV (U2 Group).

## Statistical Analysis

To analyze the variables, independent t test and Pearson chi-square test were performed using R software (version-3.4). A two-tailed p value less than 0.05 was considered statistically significant.

# RESULTS

## Demographic Characteristics of R Group and U Group

**Table 1** compares the 42 (52.5%) patients in R Group and the 38 (47.5%) patients in U Group. Age, gender, surgical extent, and pathology results did not significantly differ between groups. The proportions of patients with <50%, 50-90%, >90% EMG decreases in the injured RLN were 0.0%, 83.3%, and 16.7% in

**TABLE 1** | Demographic characteristics of Recovered VFM Group (R Group) and Unrecovered VFM Group (U Group).

| | R Group | U Group | p value |
|---|---|---|---|
| Number (%) | 42 (52.5%) | 38 (47.5%) | |
| Age (mean ± SD) | 50.7 ± 13.7 | 52.7 ± 12.4 | 0.497 |
| Gender | | | 0.073 |
| Male (%) | 11 (26.2%) | 5 (13.2%) | |
| Female (%) | 31 (73.8%) | 33 (86.8%) | |
| Surgical extent | | | 0.086 |
| Unilateral (%) | 7 (16.7%) | 1 (2.6%) | |
| Bilateral (%) | 35 (83.3%) | 37 (97.4%) | |
| Pathology | | | 0.069 |
| Benign (%) | 24 (57.1%) | 14 (36.8%) | |
| Malignant (%) | 18 (42.9%) | 24 (73.2%) | |
| EMG decrease in the injured RLN | | | <0.001 |
| <50% decreased (%) | 0 (0.0%) | 0 (0.0%) | |
| 50-90% decreased (%) | 35 (83.3%) | 17 (44.7%) | |
| >90% decreased(%) | 7 (16.7%) | 21 (55.3%) | |
| RLN Injury mechanism and type | | | 0.002 |
| Transection (%) | 0 (0.0%) | 0 (0.0%) | |
| Mechanical (%) | 42 (100.0%) | 30 (78.9%) | |
| Type 1 | 33 | 27 | |
| Type 2 | 9 | 3 | |
| Thermal (%) | 0 (0.0%) | 8 (21.1%) | |
| Subjective voice impairment during period-IV | | | 0.028* |
| No/Mild (ΔIVST-T <4) (%) | 31 (73.8%) | 19 (50.0%) | |
| Moderate/Severe (ΔIVST-T ≥4) (%) | 11 (26.2%) | 19 (50.0%) | |
| RLN reinnervation or nerve grafting | 0 (0.0%) | 0 (0.0%) | |

*VFM, vocal fold motion; SD, standard deviation; EMG, electromyography; RLN, recurrent laryngeal nerve; IVST, Index of Voice and Swallowing Handicap of Thyroidectomy; IVST-T, Total IVST score; period IV, Long-term postoperative period (range of 30-90 days).*
**p value <0.05, showed significant difference.*

R Group, respectively; the corresponding proportions in U Group were 0.0%, 44.7%, and 55.3%, respectively. That is, the proportions of patients with >90% EMG decreases were significantly larger in U Group compared to R Group (p<0.001).

No patients had transection injury in either the R Group or the U Group. All 42 (100.0%) patients in the R Group had mechanical injury (type 1 in 33 patients and type 2 in 9 patients). Among the 38 patients in U Group, 30 (78.9%) patients had mechanical injury, 27 had type 1 injury, 3 had type 2 injury; and 8 (21.1%) had thermal injury. The percentage of patients with thermal injury was significantly higher in U Group compared to R Group (p=0.002). The proportions of patients with no/mild (ΔIVST-T <4) and moderate/severe (ΔIVST-T ≥4) subjective voice impairment in period-IV were 73.8% and 26.2% in R Group, respectively, versus 50.0% and 50.0% in U Group, respectively. In period-IV, U group also had significantly more patients with moderate/severe subjective voice impairment compared to R Group (p=0.028). No patients in this study had received RLN reinnervation or nerve grafting.

## Voice Parameter Changes (Δ) Associated With Different VFM Outcomes

In **Supplemental Table 2**, the detailed voice parameters, voice parameter changes (Δ), and p values are compared between R Group and U Group in each follow-up period. Voice parameter comparisons between the two groups revealed significant differences in preoperative Fmax and preoperative PR. Postoperative parameters did not significantly differ. To minimize the influence of preoperative differences, voice parameter changes (Δ) were calculated and compared. In period-IV the U group had a ΔIVST-T score of 7.1 ± 6.8.

**Figure 2** compares voice parameter changes (Δ) between the R Group and the U Group in each follow-up period. Due to large standard deviations, the two groups did not significantly differ in objective or subjective voice parameters in all follow-up periods. However, U Group showed larger impairments of voice parameters compared to R Group, especially in ΔFmax, ΔPR, ΔJitter, ΔIVST-T, ΔIVST-V, and ΔIVST-S.

## Demographic Characteristics and Objective Voice Parameter Changes (Δ) in U Group According to Severity of Subjective Voice Impairment in Long-Term Postoperative Period

To evaluate the wide range of subjective voice impairment within U Group, **Table 2** shows the demographic characteristics of the U1 Group (no/mild subjective voice impairment) and U2 Group (moderate/severe subjective voice impairment). Compared to the U1 Group the U2 Group had significantly larger proportions of patients with EMG decrease >90% in the injured RLN (p=0.022) and patients with thermal injury as the primary RLN injury mechanism (p=0.017). **Figure 3** compares objective voice parameter changes (Δ) in the U1 Group and U2 Group in each follow-up period. In all postoperative periods, impairments in objective voice parameters were much larger in U2 Group compared to the U1 group. In period-II, ΔPR significantly p=0.007) differed between the U1 and U2 groups. In period-III, ΔFmax (p=0.013) and ΔPR (p=0.004) differed between the U1 and

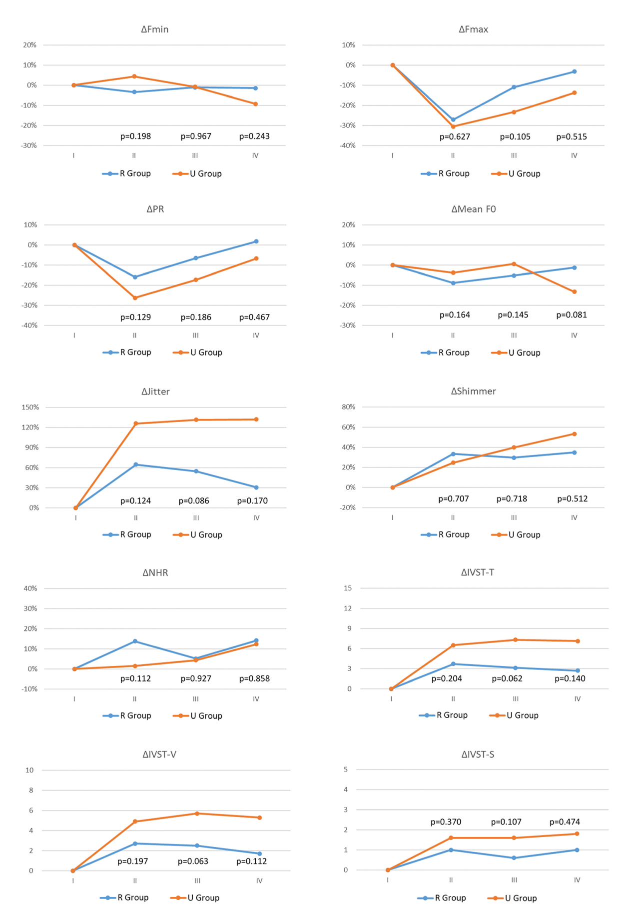



**FIGURE 2** | Voice parameter changes (Δ) with different vocal cord movement (VFM) outcomes: R Group (Blue line) and U Group (Red line). Fmax, Maximum pitch frequency; Fmin, Minimum pitch frequency; PR, Pitch range; Mean F0, mean fundamental frequency; NHR, noise-to-harmonic ratio; IVST, Index of Voice and Swallowing Handicap of Thyroidectomy; IVST-T, Total IVST score; IVST-V, IVST score of voice domain score; IVST-S, IVST score of swallowing domain. period I, Preoperative period (within 2 months before surgery); period II, Immediate postoperative period (median duration of 3 days; range of 1-7 days); period III, Short-term postoperative period (median duration of 12 days; range of7-30 days); period IV, Long-term postoperative period (median duration of 40 days, range of 30-90 days). The equation for calculating postoperative change in objective voice analysis (Fmax, Fmin, PR, Mean F0, Jitter, Shimmer, NHR) data was Δ= (B - A)/A, the unit is %; the equation for calculating postoperative change in subjective voice analysis (IVST-T, IVST-V, IVST-S) data was Δ= B – A, the unit is score. Where A and B are preoperative and postoperative values, respectively. The preoperative Δ is 0 in all the voice parameter. p value <0.05, showed significant difference.

U2 groups; ΔJitter and ΔShimmer were larger in U2 Group compared to U1 Group. In period-IV, ΔPR (p=0.006) also significantly differed between groups; ΔFmax, ΔJitter, and ΔShimmer were larger in U2 Group compared to U1 Group.

## DISCUSSION

This study is the first to investigate correlations between IONM findings and voice outcomes in patients with impaired VFM after thyroid surgery. This analysis showed that, compared to the R Group, the U Group (particularly the U2 Group) had larger proportions of patients with EMG decrease >90% in the injured RLN and patients with thermal injury as the RLN injury mechanism (**Tables 1**, **2**). Voice parameter changes were much larger in the U Group compared to the R Group, but the change did not reach statistical significance (**Figure 2**). A large pitch range decrease in period-II is a prognostic indicator of moderate/severe long-term postoperative subjective voice impairment (**Figure 3**). Therefore, surgeons should make every effort to avoid severe type RLN injury during thyroid surgery and should utilize voice analysis to enable early identification of patients who may be experiencing distress and low satisfaction caused by poor surgical outcomes and to enable early initiation of intervention therapy to maintain quality of life in these patients.

The EMG data in revealed four interesting findings regarding injury mechanisms and postoperative VFM outcomes (**Table 1**). 1) No patient with EMG <50% decrease had postoperative asymmetric VFM. This finding indicates that preserving RLN function during surgery is the key factor in VFM preservation after surgery. Accurately recording all data for asymmetric VFM before surgery is also essential for avoiding misjudgment of vocal cord function and potential legal liability (20). 2) Patients with EMG 50-90% decrease in the injured RLN may not achieve total recovery from asymmetric VFM. Using continuous IONM can minimize complications by avoiding surgical procedures that can cause mechanical injury (21). Continuous IONM prevents most mechanical injuries with visually intact RLN, thereby enabling modification of injury-causing surgical procedures in 80% of cases (22). The advancement of continuous IONM technology can make a breakthrough in VFM evaluation after thyroidectomy (23). 3) All patients with thermal RLN injury in this study had unrecovered VFM (U Group). RLN thermal injury is difficult to be detected visually and the risk of permanent palsy is high, surgeons should maintain vigilance in modern thyroid surgery that increases the use of energy-based devices (24). Compared to relatively mild mechanical injuries, thermal injuries sustained during surgery may require earlier voice intervention (25) performed under comprehensive postoperative laryngofiberscopy and voice analysis. 4) The R Group and the U Group in this study did not significantly differ in Type 1 and Type 2 mechanical injury. In severe Type 2 (global) mechanical injury, VFM may have chance to be unrecovered.

In current study, patients in U group had higher proportion of malignant pathologic report than patients in R group (73.2% vs. 42.9%). For malignant disease, surgeons tend to dissect a longer segment in proximal end of RLN and perform central neck dissection; and tend to dissect the most distal end of RLN near laryngeal entry to decrease the tissue remnant in malignant disease. According to a large international registry database study with 1,000 RLNs at risks enrolled, the abnormal RLN trajectory (23%) was higher than surgeon expected, and 34% of RLN with loss of signal following an abnormal trajectory, for instance, fixed/splayed/entrapped RLN at the ligament of Berry,

**TABLE 2 |** Demographic characteristic of patients in U Group with different subjective voice outcomes during long-term postoperative period (Period-IV).

| | U1 Group (ΔIVST-T < 4 during Period-IV) | U2 Group (ΔIVST-T ≥ 4 during Period-IV) | p value |
|---|---|---|---|
| Case number | 19 patients (50.0%) | 19 patients (50.0%) | |
| Age | 50.5 ± 10.9 | 54.9 ± 11.8 | 0.240 |
| Gender | | | 0.150 |
| Male (%) | 4 (21.1%) | 1 (5.3%) | |
| Female (%) | 15 (78.8%) | 18 (94.7%) | |
| Surgical extent | | | 0.311 |
| Unilateral (%) | 1 (5.3%) | 0 (0.0%) | |
| Bilateral (%) | 18 (94.7%) | 19 (100.0%) | |
| Pathology | | | 0.179 |
| Benign (%) | 5 (26.3%) | 9 (47.4%) | |
| Malignant (%) | 14 (73.7%) | 10 (52.6%) | |
| EMG decrease in the injured RLN | | | 0.022* |
| 50-90% decreased (%) | 12 (63.2%) | 5 (26.3%) | |
| >90% decreased (%) | 7 (36.8%) | 14 (73.7%) | |
| RLN injury mechanism | | | 0.017* |
| Mechanical (%) | 18 (94.7%) | 12 (63.2%) | |
| Thermal (%) | 1 (5.3%) | 7 (36.8%) | |

*IVST, Index of Voice and Swallowing Handicap of Thyroidectomy; IVST-T, Total IVST score; EMG, electromyography; RLN, recurrent laryngeal nerve.*
*Period IV (range of 30-90 days).*
**p value <0.05, showed significant difference.*

extensive RLN dissection, cases of cancer invasion or when lateral lymph node dissection (26). In this manner, the risk of RLN mechanical and thermal injury rate can be higher in malignant disease.

Some of the patients who revealed asymmetric VFM under laryngofiberscopy still had good subjective voice performance, which has been mentioned previously (27, 28). Reiter et al. (29) reported that voice parameters did not significantly differ between patients with and patients without recovery from vocal cord paralysis at the end of a 12-month follow up. In the current study, the R Group and the U Group did not significantly differ in objective or subjective voice parameters in all follow-up periods. However, U Group had much larger impairments compared to R Group, especially in ΔFmax, ΔPR, ΔJitter, ΔIVST-T, ΔIVST-V, and ΔIVST-S in **Figure 2**. The likely explanation for the lack of significant between-group differences was the large within-group differences in subjective voice outcomes. As **Table 2** indicates, the U1 and U2 Groups significantly differed in the incidence of severe RLN injury (i.e., EMG >90% decrease in injured RLN) and in RLN injury mechanism (thermal injury). Therefore, thyroid surgeons should make every effort to avoid severe type RLN injury. In the literature, several technical maneuvers had been reported for rescuing RLN function, including intravenous steroid (30), nimodipine (31), cold dextrose solution irrigation (32), etc., but the effectiveness of these methods remain uncertain. Besides of RLN factors, sufficient neuromuscular compensation plays an important role in reducing voice impairment after thyroid surgery (15, 33). Therefore, for good long-term postoperative voice outcomes after thyroid surgery, surgeons should prioritize restoration of neuromuscular compensation. Achieving the maximum neuromuscular compensation requires a multidisciplinary approach, especially with the participation of a speech-language pathologist to perform speech and dysphagia therapy (34). Other advanced interventions such as augmentation laryngoplasty and nerve reinnervation also have important rehabilitative roles in patients with voice recovery failure (35, 36).

In many institutions, the clinical practice environment may not include a thyroid surgeon with a laryngology background and may not have well-established procedures for routine cooperation between surgeons and speech-language pathologists (34). Under these conditions, compensation for voice impairment after thyroid surgery may not occur until long after surgery, which complicates detection of complications and other outcomes. Inadequate personnel and practices such as these may also mislead surgeons to believe that follow-up laryngofiberscopy and voice analysis are unnecessary. Early identification of voice impairment caused by VFM asymmetry can reduce the number of patient consultations needed to address psychological distress caused by poor voice outcomes and related concerns. It is worth mentioning that the voice impairment related to external branch of superior laryngeal nerve (EBSLN) injury is less significant than that of iatrogenic RLN injury. However, the stable EBSLN IONM (37) and careful analysis of high-pitched voice change (16) after thyroidectomy will largely improve life quality of the patients.

In terms of screening and interpreting voice outcomes, subjective voice analysis using IVST still has advantages over objective voice analysis. First, since a normal range of objective voice parameters has not been established, objective voice analysis requires time-consuming calculations of voice parameter changes (Δ) in individual patients whereas subjective voice analysis avoids this limitation. Second, for classifying patients with a wide range of long-term postoperative subjective voice impairments, e.g., the U Group in this study, IVST-T is simpler and more acceptable than objective voice parameters. Nevertheless, comprehensive objective voice analysis is still preferable for collecting and analyzing detailed voice data and for using these data as prognostic indicators of subjective voice impairment (**Figure 3**). Third, in patients with vocal cord paralysis, change in voice quality and loudness are


**FIGURE 3** | Objective voice parameter changes (Δ) with different subjective voice outcomes during long-term postoperative period (Period-IV): U1 Group (Blue line, ΔIVST-T< 4 during Period-IV) and U2 Group (Red line, ΔIVST-T ≥ 4 during Period-IV). The abbreviations of objective/subjective voice parameters, the definition of follow-up periods (I/II/III/IV), and the equation for calculating postoperative change in objective voice analysis are same in **Figure 2**. The preoperative Δ is 0 in all the voice parameter. p value <0.05, showed significant difference.

among the most common complaints (38). Since objective voice recording method was used in the current study, loudness adjustments were made during recording, which limited objective assessments of loudness changes. Such changes could only be represented by IVST scores.

Several limitations of this study should be mentioned. First, demographic characteristics that may affect preoperative objective voice parameters differed between R Group and U Group. Future research may investigate novel preoperative objective voice parameters with less demographic variation and define "normal" ranges for such parameters. Second, no system for classifying nerve reinnervation or grafting has been established. Therefore, future works should consider how to account for the wide variation in nerve function outcomes after these procedures. Last, a longer observation time (e.g., 1 year) may be needed to observe voice compensation processes. However, the current data were sufficient for initial identification of trends in voice parameter changes after thyroidectomy. A future long-term post-thyroidectomy voice study should discuss and compare voice interventions (e.g., voice therapy, augmentation laryngoplasty, and medialization thyroplasty) and their effects.

## CONCLUSION

This study is the first to evaluate correlations between IONM findings and voice outcomes in patients with VFM impairment after thyroid surgery. In addition to assessing EMG status and RLN injury mechanisms, thyroid surgeons should routinely include laryngofiberscopy and subjective/objective voice analyses as standard tools for evaluation and diagnosis before and after thyroid surgery. Thyroid surgeons should also make every effort to avoid severe type (EMG >90% decrease, thermal-related) RLN injury, which is associated with a high risk of unrecovered VFM and with a high risk of moderate-to-severe long-term postoperative subjective voice impairment. Using objective voice parameters (e.g., pitch range) as prognostic indicators only enables surgeons to earlier identify patients who have low voice satisfaction after surgery, it also enables early implementation of intervention therapy (e.g., speech therapy, augmentation laryngoplasty, and nerve reinnervation), which can maximize neuromuscular compensation in these patients and maintain their quality of life.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author.

## ETHICS STATEMENT

Ethical approval of this study was obtained from the Kaohsiung Medical University Hospital Institutional Review Board (KMUHIRB-E(I)-20200359). The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

Supervision – F-YC, C-WW, K-WL, and S-HL. Materials – T-YH, W-HY, F-YC, and C-WW. Data Collection and Processing – T-YH, W-HY, and S-HL. Analysis and Interpretation- T-YH, S-CF, A-ST, and S-HL. Literature Search - T-YH, W-HY, Y-CL, H-YT, and S-HL. Writing Manuscript – All authors. All authors have read and agreed to the published version of the manuscript.

## FUNDING

This study was supported by grants from Kaohsiung Medical University Hospital, Kaohsiung Medical University (KMUH109-9M44), Kaohsiung Municipal Siaogang Hospital/Kaohsiung Medical University Research Center grants (KMHK-DK(C) 110009, I-109-04, H-109-05, I-108-02), and Ministry of Science and Technology (MOST 108-2628-B-037-006, MOST 109-2628-B-037-014, MOST 110-2636-B-009-008, MOST 110-2314-B-037-104-MY2, MOST 110-2314-B-037-120), Taiwan.

## ACKNOWLEDGMENTS

The authors would like to thank all authors of the papers included in this study, as well as participants in the contributing studies.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2021.755231/full#supplementary-material

## REFERENCES

1. Rosenthal LHS, Benninger MS, Deeb RH. Vocal Fold Immobility: A Longitudinal Analysis of Etiology Over 20 Years. *Laryngoscope* (2007) 117 (10):1864–70. doi: 10.1097/MLG.0b013e3180de4d49
2. Dralle H, Lorenz K, Machens A. Verdicts on Malpractice Claims After Thyroid Surgery: Emerging Trends and Future Directions. *Head Neck* (2012) 34(11):1591–6. doi: 10.1002/hed.21970
3. Chiang FY, Lu IC, Kuo WR, Lee KW, Chang NC, Wu CW. The Mechanism of Recurrent Laryngeal Nerve Injury During Thyroid Surgery–the Application of Intraoperative Neuromonitoring. *Surgery* (2008) 143(6):743–9. doi: 10.1016/j.surg.2008.02.006
4. Snyder SK, Lairmore TC, Hendricks JC, Roberts JW. Elucidating Mechanisms of Recurrent Laryngeal Nerve Injury During Thyroidectomy and Parathyroidectomy. *J Am Coll Surg* (2008) 206(1):123–30. doi: 10.1016/j.jamcollsurg.2007.07.017
5. Chiang FY, Lee KW, Chen HC, Chen HY, Lu IC, Kuo WR, et al. Standardization of Intraoperative Neuromonitoring of Recurrent Laryngeal Nerve in Thyroid Operation. *World J Surg* (2010) 34(2):223–9. doi: 10.1007/s00268-009-0316-8
6. Randolph GW, Dralle H, Abdullah H, Barczynski M, Bellantone R, Brauckhoff M, et al. Electrophysiologic Recurrent Laryngeal Nerve Monitoring During Thyroid and Parathyroid Surgery: International Standards Guideline Statement. *Laryngoscope* (2011) 121 Suppl 1:S1–16. doi: 10.1002/lary.21119
7. Jeannon JP, Orabi A, Bruch G, Abdalsalam H, Simo R. Diagnosis of Recurrent Laryngeal Nerve Palsy After Thyroidectomy: A Systematic Review. *Int J Clin Pract* (2009) 63(4):624–9. doi: 10.1111/j.1742-1241.2008.01875.x
8. Leow C, Webb A. The Lateral Thyroid Ligament of Berry. *Int Surg* (1998) 83 (1):75–8.
9. Yang S, Zhou L, Lu Z, Ma B, Ji Q, Wang Y. Systematic Review With Meta-Analysis of Intraoperative Neuromonitoring During Thyroidectomy. *Int J Surg* (2017) 39:104–13. doi: 10.1016/j.ijsu.2017.01.086
10. Chandrasekhar SS, Randolph GW, Seidman MD, Rosenfeld RM, Angelos P, Barkmeier-Kraemer J, et al. Clinical Practice Guideline: Improving Voice Outcomes After Thyroid Surgery. *Otolaryngology—Head Neck Surg* (2013) 148(6_suppl):S1–S37. doi: 10.1177/0194599813487301
11. Crumley RL. Unilateral Recurrent Laryngeal Nerve Paralysis. *J voice* (1994) 8 (1):79–83. doi: 10.1016/S0892-1997(05)80323-6
12. Chiang F-Y, Wang L-F, Huang Y-F, Lee K-W, Kuo W-R. Recurrent Laryngeal Nerve Palsy After Thyroidectomy With Routine Identification of the Recurrent Laryngeal Nerve. *Surgery* (2005) 137(3):342–7. doi: 10.1016/j.surg.2004.09.008
13. Dionigi G, Wu C-W, Kim HY, Rausei S, Boni L, Chiang F-Y. Severity of Recurrent Laryngeal Nerve Injuries in Thyroid Surgery. *World J Surg* (2016) 40(6):1373–81. doi: 10.1007/s00268-016-3415-3
14. Wu CW, Dionigi G, Sun H, Liu X, Kim HY, Hsiao PJ, et al. Intraoperative Neuromonitoring for the Early Detection and Prevention of RLN Traction Injury in Thyroid Surgery: A Porcine Model. *Surgery* (2014) 155(2):329–39. doi: 10.1016/j.surg.2013.08.015
15. Dewan K, Vahabzadeh-Hagh A, Soofer D, Chhetri DK. Neuromuscular Compensation Mechanisms in Vocal Fold Paralysis and Paresis. *Laryngoscope* (2017) 127(7):1633–8. doi: 10.1002/lary.26409
16. Huang T-Y, Yu W-HV, Chiang F-Y, Wu C-W, Fu S-C, Tai A-S, et al. Correlation Between Objective and Subjective High-Pitched Voice Impairment in Patients After Thyroid Surgery. *Front Endocrinol* (2021) 12:788878(1514). doi: 10.3389/fendo.2021.788878
17. Friedman AD, Burns JA, Heaton JT, Zeitels SM. Early Versus Late Injection Medialization for Unilateral Vocal Cord Paralysis. *Laryngoscope* (2010) 120 (10):2042–6. doi: 10.1002/lary.21097
18. Yung KC, Likhterov I, Courey MS. Effect of Temporary Vocal Fold Injection Medialization on the Rate of Permanent Medialization Laryngoplasty in Unilateral Vocal Fold Paralysis Patients. *Laryngoscope* (2011) 121(10):2191–4. doi: 10.1002/lary.21965
19. Chiang F-Y, Lu I-C, Chen H-C, Chen H-Y, Tsai C-J, Hsiao P-J, et al. Anatomical Variations of Recurrent Laryngeal Nerve During Thyroid Surgery: How to Identify and Handle the Variations With Intraoperative Neuromonitoring. *Kaohsiung J Med Sci* (2010) 26(11):575–83. doi: 10.1016/S1607-551X(10)70089-9
20. Heuer RJ, Sataloff RT, Emerich K, Rulnick R, Baroody M, Spiegel JR, et al. Unilateral Recurrent Laryngeal Nerve Paralysis: The Importance of "Preoperative" Voice Therapy. *J voice* (1997) 11(1):88–94. doi: 10.1016/S0892-1997(97)80028-8
21. Dionigi G, Donatini G, Boni L, Rausei S, Rovera F, Tanda ML, et al. Continuous Monitoring of the Recurrent Laryngeal Nerve in Thyroid Surgery: A Critical Appraisal. *Int J Surg* (2013) 11:S44–S6. doi: 10.1016/S1743-9191(13)60014-X
22. Schneider R, Randolph GW, Barczynski M, Dionigi G, Wu C-W, Chiang F-Y, et al. Continuous Intraoperative Neural Monitoring of the Recurrent Nerves in Thyroid Surgery: A Quantum Leap in Technology. *Gland Surg* (2016) 5 (6):607. doi: 10.21037/gs.2016.11.10
23. Kim DH, Kim SW, Hwang SH. Intraoperative Neural Monitoring for Early Vocal Cord Function Assessment After Thyroid Surgery: A Systematic Review and Meta-Analysis. *World J Surg* (2021) 45(11):3320–7. doi: 10.1007/s00268-021-06225-x
24. Liu C-H, Wang C-C, Wu C-W, Lin Y-C, Lu I, Chang P-Y, et al. Comparison of Surgical Complications Rates Between LigaSure Small Jaw and Clamp-And-Tie Hemostatic Technique in 1,000 Neuro-Monitored Thyroidectomies. *Front Endocrinol* (2021) 12:313. doi: 10.3389/fendo.2021.638608
25. Leclerc A-A, Smith LJ. Early Management of Unilateral Vocal Fold Paralysis. In: Amin M, Johnson M, (eds). *Decision Making in Vocal Fold Paralysis* (2019) 29–39. doi: 10.1007/978-3-030-23475-1_3
26. Liddy W, Wu C-W, Dionigi G, Donatini G, Giles Senyurek Y, Kamani D, et al. Varied RLN Course Is Associated With Increased Risk of Nerve Dysfunction During Thyroidectomy: Results of the Surgical Anatomy of the RLN in Thyroid Surgery (SAR) Study, an International Multicenter Prospective Anatomic and Electrophysiologic Study of 1000 Monitored Nerves at Risk From the International Neural Monitoring Study Group (INMSG). *Thyroid* (2021) 31(11):1730–40. doi: 10.1089/thy.2021.0155
27. Christakis I, Klang P, Talat N, Galata G, Schulte K-M. Long-Term Quality of Voice Is Usually Acceptable After Initial Hoarseness Caused by a Thyroidectomy or a Parathyroidectomy. *Gland Surg* (2019) 8(3):226. doi: 10.21037/gs.2018.09.02
28. Sorensen JR, Printz T, Iwarsson J, Grøntved ÅM, Døssing H, Hegedüs L, et al. The Impact of Post-Thyroidectomy Paresis on Quality of Life in Patients With Nodular Thyroid Disease. *Otolaryngology–Head Neck Surg* (2019) 161 (4):589–97. doi: 10.1177/0194599819855379
29. Reiter R, Heyduck A, Hoffmann TK, Brosch S, Buchberger MA, Schorer K, et al. Quality of Voice and Prognostic Markers for the Recovery of Vocal Fold Paralysis After Thyroid Surgery. *Ann Otol Rhinol Laryngol* (2019) 128 (12):1104–10. doi: 10.1177/0003489419858629
30. Wang L-F, Lee K-W, Kuo W-R, Wu C-W, Lu S-P, Chiang F-Y. The Efficacy of Intraoperative Corticosteroids in Recurrent Laryngeal Nerve Palsy After Thyroid Surgery. *World J Surg* (2006) 30(3):299–303. doi: 10.1007/s00268-005-0399-9
31. Hydman J, Björck G, Persson JK, Zedenius J, Mattsson P. Diagnosis and Prognosis of Iatrogenic Injury of the Recurrent Laryngeal Nerve. *Ann Otol Rhinol Laryngol* (2009) 118(7):506–11. doi: 10.1177/000348940911800709
32. Chung SR, Baek JH, Choi YJ, Lee JH. Management Strategy for Nerve Damage During Radiofrequency Ablation of Thyroid Nodules. *Int J Hyperthermia* (2019) 36(1):203–9. doi: 10.1080/02656736.2018.1554826
33. Borel F, Christou N, Marret O, Mathonnet M, Caillard C, Bannani S, et al. Long-Term Voice Quality Outcomes After Total Thyroidectomy: A

Prospective Multicenter Study. *Surgery* (2018) 163(4):796–800. doi: 10.1016/j.surg.2017.09.023
34. Wu C-W, Hao M, Tian M, Dionigi G, Tufano RP, Kim HY, et al. Recurrent Laryngeal Nerve Injury With Incomplete Loss of Electromyography Signal During Monitored Thyroidectomy—Evaluation and Outcome. *Langenbeck's Arch Surg* (2017) 402(4):691–9. doi: 10.1007/s00423-016-1381-8
35. Lee SW, Kim JW, Chung CH, Mok JO, Shim SS, Koh YW, et al. Utility of Injection Laryngoplasty in the Management of Post-Thyroidectomy Vocal Cord Paralysis. *Thyroid* (2010) 20(5):513–7. doi: 10.1089/thy.2009.0397
36. Lee SW, Park KN. A Long-Term Comparative Prospective Study Between Reinnervation and Injection Laryngoplasty. *Laryngoscope* (2018) 128(8):1893–7. doi: 10.1002/lary.27140
37. Zhang D, Pino A, Caruso E, Dionigi G, Sun H. Neural Monitoring in Thyroid Surgery Is Here to Stay. *Gland Surg* (2020) 9(Suppl 1):S43. doi: 10.21037/gs.2019.10.24
38. Siu J, Tam S, Fung K. A Comparison of Outcomes in Interventions for Unilateral Vocal Fold Paralysis: A Systematic Review. *Laryngoscope* (2016) 126(7):1616–24. doi: 10.1002/lary.25739

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Publisher's Note:** All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Endocrinology

POLICY AND PRACTICE REVIEWS
published: 07 December 2021
doi: 10.3389/fendo.2021.795281



**Edited by:**
Paolo Miccoli,
University of Pisa, Italy

**Reviewed by:**
Pietro Giorgio Calo',
University of Cagliari, Italy
Erivelto Martinho Volpi,
Centro de referencia no ensino do diagnóstico por imagem (CETRUS), Brazil

***Correspondence:**
Gianlorenzo Dionigi
gianlorenzo.dionigi@unimi.it

**†ORCID:**
Che-Wei Wu
orcid.org/0000-0003-1052-5348
Tzu-Yen Huang
orcid.org/0000-0002-5044-0325
Marcin Barczyński
orcid.org/0000-0001-6062-1851
Rick Schneider
orcid.org/0000-0002-2244-4791
Amanda Silver Karcioglu
orcid.org/0000-0002-1358-774X
Gianlorenzo Dionigi
orcid.org/0000-0003-0864-6087

**Specialty section:**
This article was submitted to Thyroid Endocrinology, a section of the journal Frontiers in Endocrinology

**Received:** 14 October 2021
**Accepted:** 08 November 2021
**Published:** 07 December 2021

**Citation:**
Wu C-W, Huang T-Y, Randolph GW, Barczyński M, Schneider R, Chiang F-Y, Silver Karcioglu A, Wojtczak B, Frattini F, Gualniera P, Sun H, Weber F, Angelos P, Dralle H and Dionigi G (2021) Informed Consent for Intraoperative Neural Monitoring in Thyroid and Parathyroid Surgery – Consensus Statement of the International Neural Monitoring Study Group. Front. Endocrinol. 12:795281. doi: 10.3389/fendo.2021.795281

# Informed Consent for Intraoperative Neural Monitoring in Thyroid and Parathyroid Surgery – Consensus Statement of the International Neural Monitoring Study Group

*Che-Wei Wu[1,2†], Tzu-Yen Huang[1†], Gregory W. Randolph[3], Marcin Barczyński[4†], Rick Schneider[5†], Feng-Yu Chiang[6], Amanda Silver Karcioglu[3†], Beata Wojtczak[7], Francesco Frattini[8], Patrizia Gualniera[9], Hui Sun[10], Frank Weber[11], Peter Angelos[12], Henning Dralle[11] and Gianlorenzo Dionigi[13,14*†] on behalf of the International Neural Monitoring Study Group (INMSG)*

[1] Department of Otorhinolaryngology-Head and Neck Surgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan, [2] Center for Liquid Biopsy and Cohort Research, and Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan, [3] Department of Otolaryngology, Harvard Medical School, Boston, MA, United States, [4] Department of Endocrine Surgery, Third Chair of General Surgery, Jagiellonian University Medical College, Krakow, Poland, [5] Department of Visceral, Vascular and Endocrine Surgery, University Hospital Halle, Martin-Luther-University, Halle-Wittenberg, Germany, [6] Department of Otolaryngology, E-Da Hospital, School of Medicine, College of Medicine, I-Shou University, Kaohsiung, Taiwan, [7] Department of General, Minimally Invasive and Endocrine Surgery, Wroclaw Medical University, Wroclaw, Poland, [8] Department of Surgery, Ospedale di Circolo, ASST, Settelaghi, Varese, Italy, [9] Forensics Division, Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Messina, Italy, [10] Division of Thyroid Surgery, China-Japan Union Hospital of Jilin University, Changchun, China, [11] Department of General, Visceral and Transplantation Surgery, University of Duisburg-Essen, Essen, Germany, [12] Department of Surgery and MacLean Center for Clinical Medical Ethics, The University of Chicago, Chicago, IL, United States, [13] Division of Surgery, Istituto Auxologico Italiano IRCCS, Milan, Italy, [14] Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy

In the past decade, the use of intraoperative neural monitoring (IONM) in thyroid and parathyroid surgery has been widely accepted by surgeons as a useful technology for improving laryngeal nerve identification and voice outcomes, facilitating neurophysiological research, educating and training surgeons, and reducing surgical complications and malpractice litigation. Informing patients about IONM is not only good practice and helpful in promoting the efficient use of IONM resources but is indispensable for effective shared decision making between the patient and surgeon. The International Neural Monitoring Study Group (INMSG) feels complete discussion of IONM in the preoperative planning and patient consent process is important in all patients undergoing thyroid and parathyroid surgery. The purpose of this publication is to evaluate the impact of IONM on the informed consent process before thyroid and parathyroid surgery and to review the current INMSG consensus on evidence-based consent. The objective of this consensus statement, which outlines general and specific considerations as well as recommended criteria for informed consent for the use of IONM, is to assist surgeons and patients in the processes of informed consent and shared decision making before thyroid and parathyroid surgery.

**Keywords: intraoperative neural monitoring, thyroid surgery, parathyroid surgery, informed consent, shared-decision making, international neural monitoring study group, voice**

## INTRODUCTION

Over the last 20 years, there has been a clear trend in thyroid and parathyroid surgery in the use of intraoperative neural monitoring (IONM) to support identification and dissection of the recurrent laryngeal nerve (RLN), facilitate assessment of vocal cord (VC) function and voice outcomes, neurophysiological research, surgical education and training, and medico-legal issues related to loss of VC function (1–15). According to Dralle et al., 70,000 patients received monitored thyroid and parathyroid surgery per year in Germany (16). The contribution of IONM technology has led over time to significant improvement in quality in neck endocrine surgery (17, 18). Current IONM technology enables the monitoring of the external branch of the superior laryngeal nerve (EBSLN) (19–24), real-time monitoring of RLN function by continuous intraoperative nerve monitoring (C-IONM) (25–32) *via* the vagal nerve, and RLN or EBSLN monitoring during endoscopic/robotic surgeries (33–40).

Research in IONM often oversimplifies neuromonitoring equipment and related technological innovations as mere instruments for optimizing RLN identification and preservation during surgery. IONM should not be just considered as a tool for reduction in RLN injury rates, but rather as technology that affords a more comprehensive understanding of RLN function during surgery. Therefore, more integrated and improved information should be offered to patients before surgery (16, 41). Neuromonitoring studies strongly suggest that informing patients about IONM is not only a good practice, it is indispensable for effective shared decision making between the patient and the surgeon and for promoting productive and efficient use of IONM and non-IONM resources (42).

The International Neural Monitoring Study Group (INMSG) (www.inmsg.org) has been at the forefront of IONM technology and procedural adoption since the introduction of neural monitoring in thyroid and parathyroid surgery. The INMSG acknowledges the important supportive roles of IONM in preoperative planning and patient consent in thyroid and parathyroid surgery. The purposes of this paper are to analyze the impact of IONM on the informed consent process and to discuss the existing evidence-based INMSG consensus on informed consent involving the use of IONM.

The studies included in this review were retrieved by a comprehensive Medline search for articles pertaining to informed consent in thyroid surgery. The search was expanded by adding related texts and articles developed from reference lists, personal contacts, conference proceedings, and co-author bibliographies. Focused Medline searches regarding specific aspects of IONM informed consent were done as needed to address any gaps in knowledge. This consensus statement also outlines general and specific considerations and distinguishes essential recommended standard elements of informed consent to IONM to assist surgeons in the clinical decision-making process for the surgical management of thyroid and parathyroid disease.

## GENERAL CONSIDERATIONS

### International Comparison of IONM Availability and Cost

International comparisons are needed to track IONM use in different healthcare systems, to highlight areas of strength and weakness, and to identify factors that may impede or accelerate adoption of this technology (43–45). The introduction and adoption of IONM varies among different health organizations and different regions (**Figure 1**). For example, while IONM is common in Germany, where it is utilized by over 70% of surgeons, it is utilized in only in a minority of cases in the UK (24%) and Italy (14%) (5, 46–48). In the United States of America (USA), where data for IONM use are widely available, IONM use is increasing (6, 9). Surveys of the American Association of Endocrine Surgeons members found an increase in use of IONM from 7% to 37% between 2001 and 2007 (9). Surveys have also revealed disparities in the distribution of IONM use throughout the USA; e.g., most (69%) of surgeons who use IONM practice in the Northeastern USA (6). In other countries, particularly developing countries, access to IONM technology remains limited (43).

Several factors influence the adoption of IONM technology. High cost of IONM equipment is perhaps the greatest barrier to IONM adoption, particularly in publicly funded healthcare institutions (43). IONM costs vary widely by country and reach as high as €800 per procedure (44), and the consumable medical supplies for IONM may be self-pay items in some regions. Thus, depending on the country and its healthcare system, the technology may be deemed unaffordable.

The wide variation in IONM availability and cost apparently results from intrinsic differences in healthcare systems (i.e., public *versus* private) and differences in health insurance coverage (43). These differences inevitably contribute to non-uniform modalities and structures of informed consent and patient information. For this reason, IONM cost and availability issues mentioned above should be carefully considered when obtaining informed consent. Additional international research is needed to understand better the

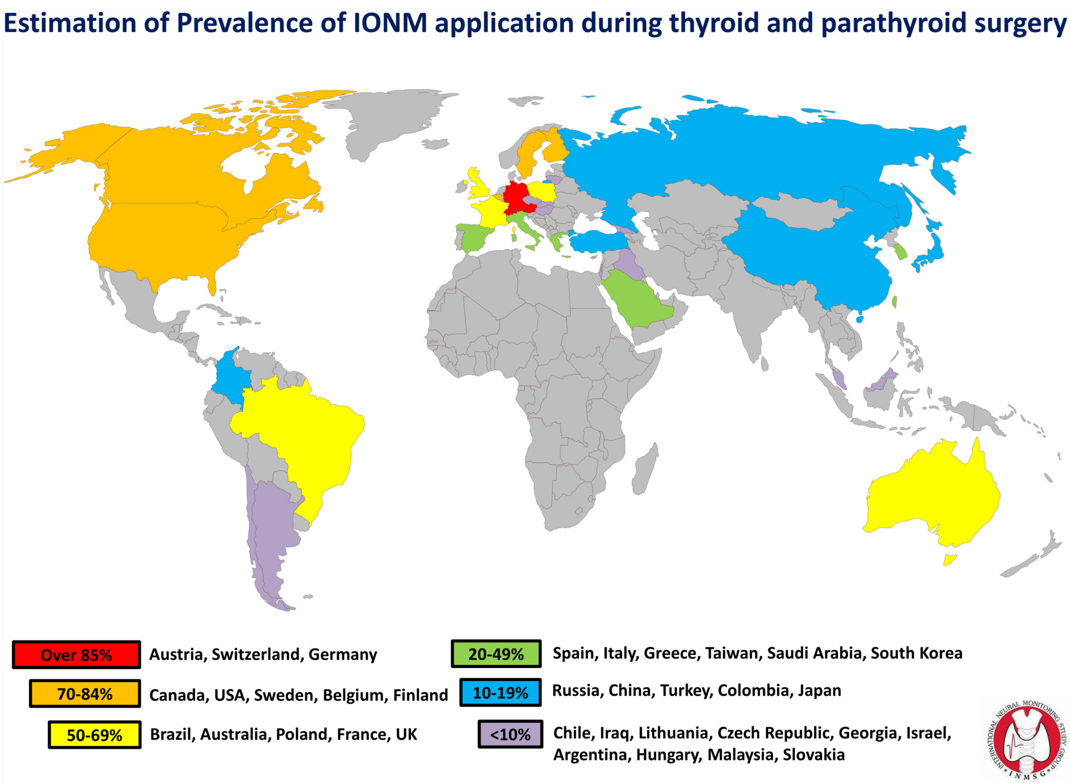



**FIGURE 1** | IONM use estimation by country (Source: First World Congress Of Neural Monitoring In Thyroid And Parathyroid Surgery. 17-19, September 2015, Kraków, Poland. http://ionmworldcongress.com/- courtesy of Inomed Medizintechnik GmbH, Emmendingen Germany. World map by www.freeworldmaps.net.).

relationships among IONM strategies, health-care organizations, and the informed consent process.

## Sources of IONM Information

Patients obtain health information from various sources (e.g., TV, radio, newspaper, magazines, the Internet, and personal contacts) to supplement the information provided by their healthcare professionals (49, 50). The time and manner in which individuals use supplemental information depends on various socioeconomic factors, including race, education, income, health literacy, and health status (49, 50).

Patients as well as relatives/friends of patients use the Internet as a source of information about an illness, including therapies, side effects, and new surgical procedures. According to data from an Italian survey, 6 out of 10 internet users considered internet searches an acceptable substitute for consultation with family doctors (50). In the 2,300 online questionnaires completed in this survey, 58% of the respondents replied that when they experienced a health problem, they first searched for information online. Demographic characteristics associated with use of the Internet to search for health-related news and information include female gender, young age, and medium to high socio-economic level.

Since traditional media (i.e., television, radio, etc.) provide limited information about IONM, in 2015 INMSG established a website specifically for providing IONM information (www.inmsg.org). Nevertheless, Ferrari C. et al. reported that, for the general public, internet information about IONM during thyroid surgery, is too specific, too difficult to understand, and too difficult to access (51). The authors analyzed IONM-related websites available to the general public that specifically discussed thyroid surgery. Most websites (64%) were associated with scientific publications. Most websites (91%) were in English, and only 19% of the websites provided multilingual information (including English) or in were written in other languages. The authors rated 58% of the sites as "excellent-to-good" and 42% as "fair-to-poor". The median Flesch Reading Ease Score was 49.6; the median Flesch-Kincaid Grade Level was 13.85 (51). Internet information regarding IONM thus is not only inadequate for properly educating patients, but potentially misleading as most websites tend to present only the benefits of the technology. Patients who would like to understand IONM technology need improved access and quality of online resources and information on IONM. Treating physicians also serve as another valuable source of IONM information for patients and are expected to provide detailed and reliable information and counseling in the benefits as well as limitations of current IONM systems (50).

## IONM Curriculum and Responsibility for Monitoring

Before implementing IONM in practice, surgeons should have completed relevant surgical training and should be able to address common complications (1, 4, 52). IONM procedures are maximized with a well-trained team. As routine use of IONM increases, surgeons should include nerve monitoring courses in their curriculum to ensure competency (**Figure 2**).

The need for ongoing professional education training to acquire and maintain knowledge and expertise in current IONM technologies and applications will also contribute to progressive improvement of pre-operative information given to patients. Patients must be adequately informed of the experience of the surgeon and/or surgical team in performing the proposed surgical intervention. Surgeons have four main responsibilities in an IONM-assisted surgical procedure (**Figure 2**):

### (A) Technical Responsibilities

Using and setting up IONM equipment correctly and understanding the inherent properties of the system to avoid inaccurate baseline setup (e.g., confirming proper muscle relaxation type/dosage, correct electrode placement with low impedance, etc.) (1).

### (B) Interpretive Responsibilities

Surgeons should be able to distinguish between true and artifactual responses and perform appropriate troubleshooting to identify and correct the issue at hand (52).

### (C) Information Responsibilities

The surgeon has a duty to provide patients with accurate and relevant IONM information, including its benefits and limitations. When providing information to the patient, the surgeon must consider many factors, including education level, emotional state, and ability to understand the content of the discussion. In all cases, further information requests by the patient must be satisfied. However, information related specifically to IONM technology may be limited to those elements that the patient's culture and psychological condition are able to understand and accept, to avoid superfluous clarification and discussion of data and technical aspects of the procedure which are not of benefit to the patient.

### (D) Documentation Responsibilities

The surgeon is responsible for carefully reviewing and documenting the information, including patient's thyroid history, preoperative radiologic imaging, pre-operative symptoms, pre- and postoperative laryngeal examination, detailed surgical or operative report with intraoperative RLN findings, and surgical complications if any.

Electromyographical (EMG) muscle action potential recording and documentation is possible with all modern IONM devices (1, 10). IONM converts muscle activity into recorded EMG signals, which are often possible to print out (1). Such information provides the surgeon with a summary of relevant information collected during the operation (i.e., artifact signal, amplitude decline, and latency increase) and may be of interest for patients seeing to understand the use of IONM (1, 10, 16). Documentation of IONM use during thyroid and parathyroid surgery can include time-traceable measures of EMG amplitude, latency, waveform morphology, and magnitude of stimulating current. EMG curves provide proof of intact nerve function.

Monitoring nerves during surgical procedures may potentially reduce the medico-legal liability of the surgeon as well as the economic losses of the patient, healthcare system, and insurance companies. Recorded nerve signals are also important for early determination of whether voice changes are RLN-related (1, 4, 10, 16). From a medico-legal perspective, recording and documenting the muscle action potential is recommended at the beginning (V1; R1) and at the end of the resection (V2; R2) for each side of resection. Additionally, documentation included in the medical record should, at minimum, include V2 stimulation after thyroidectomy is

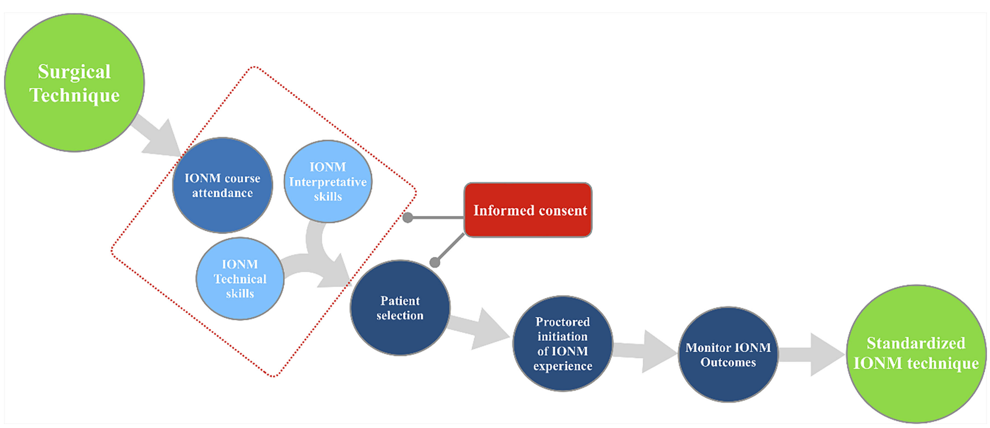



**FIGURE 2** | Standardization of IONM during thyroid and parathyroid surgery. IONM specific informed consent is an essential topic to be discussed during formal INMSG courses. Informed consent must be offered to all patients in whom IONM is utilized.

completed on the first side, which indicates that thyroidectomy can safely proceed on the contralateral side (13, 46, 53, 54).

## Is IONM Evidence-Based?

Evidence of the benefit of IONM is limited to class II and class III studies, the same evidence level generally applied to other technologies and clinical practices in thyroid surgery (52, 55, 56). In studies that have investigated IONM use in other surgical procedures (including spinal surgery, vascular surgery, and brain surgery), even highly accredited investigations (e.g., Cochrane reviews) have not provided class I evidence that IONM improves safety (57, 58). Meta-analyses have reported no conclusive evidence of the superiority or inferiority of IONM over visual nerve identification for any outcome measures (52, 59–65) (**Table 1**).

**TABLE 1 |** Summary of meta-analysis articles on the topic of RLN palsy after thyroid surgery with and without use of IONM.

| Author | Year | Journal | Studies included in meta-analysis | Bibliographic database | NAR | T. Palsy with IONM (%) | P. Palsy with IONM (%) | T. Palsy without IONM (%) | P. Palsy without IONM (%) | *p* value | Conclusion |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Dralle H | 2008 | World J Surg (52) | 6 with and without IONM | Medline | 19290 with IONM 6671 without IONM | 2.7 | 0.8 | 2.8 | 0.9 | 0.45 (T.) 0.30 (P.) | IONM does not result in lower postoperative RLN palsy rates compared with RLN dissection alone. Visual identification remains the basis for nerve protection. |
| | | | 10 with IONM only | Medline | 7374 with IONM | 3.7 | 0.7 | NA | NA | NA | |
| Rulli F | 2014 | Acta Otorhinolaryngol Ital (64) | 8 | PubMed and Ovid, and the Cochrane Library database | Total 5257 | NA | NA | NA | NA | 0.035 (T.) 0.235 (P.) | IONM prevents transient injury. No advantage was found in permanent injuries. |
| Pisanu A | 2014 | J Surg Res (65) | 20 | Embase, Medline, Cochrane, PubMed, and Google Scholar databases | 24038 with IONM 11475 without IONM | 2.62 | 0.79 | 2.72 | 0.92 | 0.552 (T.) 1.000 (P.) | Using IONM or not showed no statistically significant difference in the incidence of RLN palsy. |
| Lombardi CP | 2016 | Surgery (63) | 14 (4 RCTs) | PubMed, Scopus, and CENTRAL | 25814 with IONM 15929 without IONM | NA | 0.7 | NA | 0.9 | 0.071 (P.) | IONM does not prevent permanent nerve palsy. |
| Sun W | 2017 | Clin Endocrinol (60) | 9 | PubMed, SCIE and Wan Fang databases | 1109 with IONM 1327 without IONM | 3.98 | 1.26 | 6.63 | 2.78 | 0.227 (T.) 0.031 (P.) | Significant effect of IONM in preventing permanent RLN palsy. |
| Yang S | 2017 | Inter J Surg (61) | 24 (4 RCTs) | PubMed, Embase, and the Cochrane library | 8668 with IONM 8535 without IONM | 1.82 | 0.67 | 2.58 | 1.07 | <0.001 (T.) 0.005 (P.) | Benefits of reducing RLN palsy rate by using IONM. Using IONM may improve the outcome by reducing amount of residual thyroid tissue. |
| Wong KP | 2017 | Inter J Surg (62) | 10 | Pubmed, Medline, Embase and CENTRAL | 6155 with IONM 4460 without IONM | 2.4 | 1.3 | 3.9 | 1.6 | 0.016 (T.) 0.104 (P.) | Use of IONM during high-risk thyroidectomy decreases the rate of RLN palsy. IONM should be recommended during re-operation or thyroidectomy for malignancy. |
| Cirocchi R | 2019 | Cochrane Database Syst Rev (59) | 5 RCTs | CENTRAL, Medline, Embase, ICTRP Search Portal and ClinicalTrials.gov | 1451 with IONM 1444 without IONM | 2.2 | 0.7 | 3.6 | 0.9 | 0.09 (T.) 0.54 (P.) | No evidence for the superiority or inferiority of IONM over visual nerve identification alone on any of the outcomes measured. |

*RLN, recurrent laryngeal nerve; IONM, intraoperative nerve monitoring; NAR, nerves at risk; T. palsy, Transient RLN palsy; P. palsy, Permanent RLN palsy; RCT, randomized controlled trial; CENTRAL, Cochrane Central Register of Controlled Trials; NA, not assessable.*

Class I studies in the use of IONM in thyroid surgery are not possible for at least two reasons (52, 55–65). First, the likelihood of IONM use in preventing a transient RLN deficit is so low that a controlled study that randomly assigned patients to a control group or a monitored group would be arduous (52). Moreover, the incidence of permanent RLN complications is even lower. Thus, IONM use would be aimed at further reducing the incidence of a complication that already has a low incidence (52). An adequately powered study would be laborious as the number of patients needed would likely exceed the number of patients possible to enroll in multi-institutional studies (52).

Accordingly, future perceptions of the benefit of IONM will continue to be based on its good clinical outcomes, historical control studies, and cost-benefit evaluations (66). Therefore, in our opinion during the informed consent process, telling patients that IONM is adequately evidence-based in reducing RLN paralysis is misleading and unethical.

## IONM and Malpractice Claims of Nerve Palsy

Malpractice claims related to thyroid and parathyroid surgery are costly and time-consuming (67). All permanent and transient consequences of thyroid surgery constituted malpractice claims and the RLN injury or palsy is the leading cause (10, 67–69). Dralle et al. (10) reported nearly 60% of 75 malpractice claims between 1995 and 2010 involved RLN palsy (21 unilateral and 22 bilateral), with a 45% tracheostomy rate for bilateral palsy. They noted that IONM has become the subject of pleading in 4 of 7 malpractice claims involving unilateral or bilateral RLN palsy since 2007. In none of these cases did IONM follow international standards, resulting in 3 plaintiff verdicts. In addition, Gartland et al. (67) found that bilateral RLN injury, accounting for up 18% of 128 malpractice suits in the US, was predictive of plaintiff verdicts (OR 3.58, P=0.03) on multivariable regression analysis.

The growing appreciation that standardized IONM can prevent bilateral RLN palsies after signal loss on the initial side of resection may become increasingly relevant to malpractice litigation (10). An informed consent detailing the strengths and weaknesses of IONM, including the need to change operative treatment plans in the event of LOS, may serve as a line of defense in the event of litigation (11, 70, 71).

# DEFINING THE STANDARD OF IONM INFORMED CONSENT

## Purpose of Informed Consent in Thyroid Surgery

Before undergoing IONM-assisted thyroid surgery, the patient must be adequately informed of the purpose and nature of the endocrine intervention as well as its potential benefits and risks (72). A dedicated form for written informed consent for thyroid or parathyroid surgery should include the following information: type of surgery, objectives of surgery, consequences of thyroidectomy or parathyroidectomy, risk and benefits of declining thyroidectomy or parathyroidectomy, alternative procedures (active surveillance, thermal ablation, etc.), and possible risks of thyroidectomy or parathyroidectomy (73, 74). The extent of informed consent for IONM-assisted thyroidectomy or parathyroidectomy depends on the purpose and context (i.e., legal, ethical, administrative, documentation and knowledge).

## Target Population and Timing

Informed consent must be obtained from a patient (or appropriate guardian or healthcare proxy) referred for IONM-assisted thyroid surgery. Whenever possible, informed consent should be obtained from the patient (or guardian) well in advance of the intervention to allow for adequate time for reflection. Ideally, the patient should be briefed on IONM in the planning stage of the intervention (75).

## Counseling Specifically Related to IONM

Although the criteria for adequate informed consent may differ by country and by hospital, in our opinion, the consent process should always include discussion of (a) IONM limitations (IONM accuracy, technical failure, etc.) and (b) IONM consequences (i.e. possible staged thyroidectomy) (76–78) (**Figure 3**).

### IONM Limitations

As with any intraoperative technology, we believe it is important to explain to the patient as part of informed consent that the IONM has limitation and may fail. IONM false-positive rates, surgeon IONM inexperience, and technical failures are the main reasons IONM may provide unreliable results (1, 2). According to the literature, device malfunction or false IONM results may occur in 1% to 13% of procedures (1, 2, 79, 80).

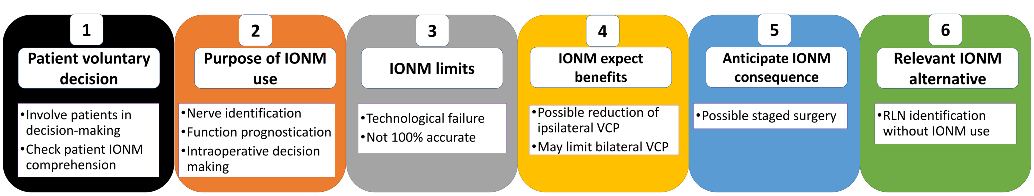



**FIGURE 3** | IONM Informed Consent. Diagram showing key information of the preoperative encounter and IONM informed consent process. It is necessary to document the parties involved in the informed-consent process.

### Staged Thyroidectomy

Before consenting to bilateral thyroidectomy with IONM, the patient should be advised that a staged thyroidectomy may be needed. As IONM use increases, an adaptation of the staged strategy will be necessary. The patient should be advised that a such a staged strategy is neuromonitoring-dependent. In the event of intraoperative signal failure during the first operated side, a 2-step procedure is advised in order to avoid the catastrophic effects of bilateral RLN paresis (74).

Pre-surgery planning for the second side in cases of prior aborted total thyroidectomy or bilateral parathyroidectomy should include three surgical options for addressing the contralateral side with intact RLN function:

(1) No contralateral resection at initial surgery with LOS in cases of bilateral goiter, Graves' disease, or low risk thyroid carcinoma (differentiated and medullary thyroid carcinomas) with the aim of 2-stage completion surgery after verification of recovery of nerve function on the initial side.

(2) Contralateral subtotal lobe resection keeping the dissection plane ventral to the RLN plane in cases of benign goiter thus maintaining a safety distance to the nerve with the aim of avoiding a second operation, because of patient´s co-morbidities.

(3) Total thyroidectomy as planned for advanced thyroid carcinomas (including undifferentiated thyroid carcinomas) with the aim of immediate postoperative radioactive iodine therapy.

## IONM Informed Consent Documentation

As in all complex medical technologies, the possibility of technological failure should be discussed with the patient pre-operatively during informed consent. As noted above, the surgeon should also discuss that a staged thyroidectomy might be indicated if the initial side shows evidence of LOS. The informed consent form should state the limitations of IONM and the procedure for LOS on the first-side during thyroidectomy as follows:

### For IONM Limitations

"As with all technologies applied in surgery, IONM technology can also fail in accuracy".

### For Staged Thyroidectomy

"During thyroid surgery we are using a device to assess the function of the RLN in real-time. When there is a loss of signal and possible loss function of the RLN on the first side of dissection (dominant side), we stop the procedure to possibly prevent bilateral VC palsy. This would result in a possible second surgery or staged thyroidectomy."

## Practical Implementation Advice: Improving the IONM Informed Consent Process

The informed consent process should only be implemented if the patient has capacity to consent or has an appropriate surrogate decision maker. To ensure that the informed consent discussion is understood by the patient or surrogate, the language used in the discussion should target the appropriate level of health literacy. Surgeons should be prepared to provide additional information when requested by patients and/or surrogates. Some thyroid clinics may opt to provide informational brochures or videos. The use of multimedia technology (e.g., videos of surgical procedures, computer animations, and graphics), in addition to traditional forms of printed or hand-produced material, may reduce inconsistencies in the amount of information assimilated by patients with different education levels and may improve the quality of the informed consent process (81).

# SPECIAL CONSIDERATIONS

## EBSLN Monitoring

In addition to RLN paralysis, another important consequence of thyroidectomy is the possible change in voice quality and projection due to EBSLN paresis. The EBSLN is vulnerable to damage in patients with a large goiter, a thyroid tumor of the superior pole, a short neck, or lower lying nerves such as Cernea types 2a and 2b (20, 21, 82). Recent reports indicate that IONM aids in EBSLN identification and preservation in both conventional and endoscopic thyroidectomy (19, 21, 24, 39, 83–85). In the opinion of the authors, the benefits of IONM on EBSLN preservation is still nascent. However, discussion of the potential for EBSLN paralysis may be especially relevant in certain patients, such as voice professionals, where discussion of the utility (and limitations) of EBSLN monitoring may be important, if not required.

## Exception to IONM Informed Consent

The surgeon has a professional responsibility to provide the patient with IONM information that is accurate, relevant and commensurate with the health literacy of the patient. To reiterate, suggesting that IONM use is adequately evidence-based in reducing RLN palsies is inappropriate, since data in the literature are still insufficient to support this claim. We believe that certain issues (particularly technological issues) can be excluded from the IONM informed consent discussion. Examples include:

- The availability, difference and options of IONM systems (86, 87) and recording EMG tube, (i.e. post-cricoid or anterior laryngeal electrodes) (88–94).
- The availability, difference and options of I-IONM stimulating probe or dissectors (34, 40, 95–99).
- The availability, difference and options of C-IONM stimulation electrodes, and the surgical approach of C-IONM placement electrode on the vagus nerve (26, 100–103).

## IONM in the Case of Preoperative Nerve Palsy

Although preoperative vocal cord palsy is often associated with RLN invasion by advanced thyroid malignancy, it may also be associated with benign conditions that result in compression or stretching or in inflammation (Hashimoto's or Riedel's infiltration) with a reported incidence of 0.2 to 1% (104–106). A detectable EMG signal in the case of vocal cord palsy may indicate residual neural function in the form of retained electrical conductivity (14). In benign condition, some studies (107, 108) suggest that a short duration of vocal cord palsy increases the probability of postoperative recovery of vocal cord function and that IONM is helpful for mapping a severely displaced and compressed RLN such as in the case of a large substernal goiter (108). In Kamani et al., recognizable RLN electrophysiologic activity was preserved in over 50% of cases with preoperative vocal cord dysfunction. In addition, malignant invasion of the RLN was associated with preoperative vocal cord paralysis in only 50% (109). In Lorenz et al., 41 of 285 patients (14%) with preoperative vocal cord palsy had a detectable EMG signal. If the RLN is preserved during surgery, and if the malignancy has not directly invaded the RLN, functional recovery is reported as high as 38% to 89% (110).

The postoperative outcome of the paralyzed RLN and its management determine what strategy will be appropriate for managing the RLN if contralateral surgery is required (14). Therefore, patients with preoperative vocal cord palsy should be informed of the benefits of IONM. Additionally, patients who consent to use IONM must be adequately informed of surgical strategies for intraoperative RLN management.

### Patients Who Refuse IONM

The surgeon must not perform any diagnostic-therapeutic-surgical procedure without the consent of a validly informed patient. Depending on the country and its healthcare system, the cost of IONM consumable medical supplies may be unaffordable by patients without insurance coverage (111). The surgeon must desist from any IONM use in the case of explicit refusal of IONM by a patient capable of understanding. In their decades of experience in IONM, however, INMSG Board members have seldom encountered a patient who refused IONM.

### In the Event of Unavailable IONM Technology

The IONM technology may be unavailable or not utilized in the following scenarios:

(i). The patient has given written consent to IONM, but the IONM device is currently unavailable or malfunctioned preoperatively at the institution. The thyroid intervention can be rescheduled or referred to another center where IONM is available.

(ii). The patient has signed IONM informed consent, however the device has malfunctioned intraoperatively. In the event of intraoperative IONM device breakdown, the thyroid intervention continues without IONM. This possibility should be discussed preoperatively with the patient (i.e., IONM limitations - see above) and disclosed post-operatively to the patient.

### IONM in Clinical Research

It should be emphasized that large and rapid technological advances in IONM have broadened the framework of possible alternatives in IONM procedures. Therefore, the inherent risks and benefits of the IONM procedure proposed for the patient must be clearly explained and supported with documentation, which may include opinions in the literature on the proposed IONM modality. The experience and case history of the IONM team must also be clearly explained.

For researchers, prior review and approval from the local institutional review board (IRB) or independent ethics committee (IEC) is mandatory before performing clinical research in IONM. The IRB/IEC is responsible for reviewing the research proposal and ensuring that informed consent procedures are adequately and ethically implemented without jeopardizing the rights, safety, and well-being of the human subjects.

## LIMITATIONS OF THE INMSG CONSENSUS

The INMSG, a multidisciplinary international group established in 2006, comprises surgeons, laryngologists, voice and laryngeal electromyography specialists, anesthesiologists, and researchers who have extensive experience in thyroid and parathyroid neural IONM and have previously published multiple manuscripts and guidelines related to RLN and EBSLN monitoring (1, 4, 13–15, 19). Although we hope that this consensus statement identifies high-quality studies that provide a strong quantitative base of evidence for the above recommendations for informed consent to IONM, the resulting bibliography reflects a bias within the literature toward thyroid surgery and much of the quantitative literature on this topic is descriptive in nature. Informed consent is primarily a legal, ethical and administrative concept; although often informed by data, the standards of scholarship in law and ethics focus on the strength of analytical argument rather than the weight of empirical data. Therefore, we sought to synthesize the available knowledge on this subject by referencing empirical data as needed and summarizing relevant arguments that are particularly prevalent, persuasive or insightful.

## CONCLUSION

Improving voice outcomes after thyroid and parathyroid surgery is an important issue in the quality-of-life era. Surgical use of IONM has gained widespread acceptance in the international community as a useful technique for reducing possible RLN and EBSLN injury in these procedures. This INMSG consensus statement outlines the general and specific considerations regarding the surgical use of IONM and provides essential recommended standard elements of informed consent for the use of IONM thereby assisting surgeons and patients in the informed consent process and in shared decision making prior to thyroid or parathyroid surgery.

## AUTHOR CONTRIBUTIONS

All authors have made a substantial contribution to the concept of the article, drafted and revised the article critically for important intellectual content. All authors have read and agreed to the published version of the manuscript.

## FUNDING

This study was supported by grants from Kaohsiung Medical University Hospital, Kaohsiung Medical University (KMUH109-9M44), Kaohsiung Municipal Siaogang Hospital/Kaohsiung

Medical University Research Center grants (KMHK-DK(C) 110009, I-109-04, H-109-05, I-108-02), and Ministry of Science and Technology (MOST 110-2314-B-037-104-MY2, MOST 110-2314-B-037-120), Taiwan.

## REFERENCES

1. Randolph GW, Dralle H, Abdullah H, Barczynski M, Bellantone R, Brauckhoff M, et al. Electrophysiologic Recurrent Laryngeal Nerve Monitoring During Thyroid and Parathyroid Surgery: International Standards Guideline Statement. *Laryngoscope* (2011) 121(Suppl 1):S1–16. doi: 10.1002/lary.21119
2. Dionigi G, Bacuzzi A, Barczynski M, Biondi A, Boni L, Chiang FY, et al. Implementation of Systematic Neuromonitoring Training for Thyroid Surgery. *Updates Surg* (2011) 63(3):201–7. doi: 10.1007/s13304-011-0098-z
3. Dionigi G, Barczynski M, Chiang FY, Dralle H, Duran-Poveda M, Iacobone M, et al. Why Monitor the Recurrent Laryngeal Nerve in Thyroid Surgery? *J Endocrinol Invest* (2010) 33(11):819–22. doi: 10.1007/bf03350349
4. Wu CW, Randolph GW, Barczyński M, Schneider R, Chiang FY, Huang TY, et al. Training Courses in Laryngeal Nerve Monitoring in Thyroid and Parathyroid Surgery- The INMSG Consensus Statement. *Front Endocrinol (Lausanne)* (2021) 12:705346. doi: 10.3389/fendo.2021.705346
5. Dionigi G, Lombardi D, Lombardi CP, Carcoforo P, Boniardi M, Innaro N, et al. Intraoperative Neuromonitoring in Thyroid Surgery: A Point Prevalence Survey on Utilization, Management, and Documentation in Italy. *Updates Surg* (2014) 66(4):269–76. doi: 10.1007/s13304-014-0275-y
6. Marti JL, Holm T, Randolph G. Universal Use of Intraoperative Nerve Monitoring by Recently Fellowship-Trained Thyroid Surgeons is Common, Associated With Higher Surgical Volume, and Impacts Intraoperative Decision-Making. *World J Surg* (2016) 40(2):337–43. doi: 10.1007/s00268-015-3238-7
7. Dionigi G, Bacuzzi A, Boni L, Rovera F, Dionigi R. What is the Learning Curve for Intraoperative Neuromonitoring in Thyroid Surgery? *Int J Surg (London England)* (2008) 6(Suppl 1):S7–12. doi: 10.1016/j.ijsu.2008.12.023
8. Ho Y, Carr MM, Goldenberg D. Trends in Intraoperative Neural Monitoring for Thyroid and Parathyroid Surgery Amongst Otolaryngologists and General Surgeons. *Eur Arch Oto-Rhino-Laryngology Off J Eur Fed Oto-Rhino-Laryngological Societies (EUFOS) affiliated German Soc Oto-Rhino-Laryngology - Head Neck Surg* (2013) 270(9):2525–30. doi: 10.1007/s00405-013-2359-6
9. Sturgeon C, Sturgeon T, Angelos P. Neuromonitoring in Thyroid Surgery: Attitudes, Usage Patterns, and Predictors of Use Among Endocrine Surgeons. *World J Surg* (2009) 33(3):417–25. doi: 10.1007/s00268-008-9724-4
10. Dralle H, Lorenz K, Machens A. Verdicts on Malpractice Claims After Thyroid Surgery: Emerging Trends and Future Directions. *Head Neck* (2012) 34(11):1591–6. doi: 10.1002/hed.21970
11. Angelos P. Ethical and Medicolegal Issues in Neuromonitoring During Thyroid and Parathyroid Surgery: A Review of the Recent Literature. *Curr Opin Oncol* (2012) 24(1):16–21. doi: 10.1097/CCO.0b013e32834cd596
12. Angelos P. Recurrent Laryngeal Nerve Monitoring: State of the Art, Ethical and Legal Issues. *Surg Clinics North America* (2009) 89(5):1157–69. doi: 10.1016/j.suc.2009.06.010
13. Schneider R, Randolph GW, Dionigi G, Wu CW, Barczynski M, Chiang FY, et al. International Neural Monitoring Study Group Guideline 2018 Part I: Staging Bilateral Thyroid Surgery With Monitoring Loss of Signal. *Laryngoscope* (2018) 128(Suppl 3):S1–s17. doi: 10.1002/lary.27359
14. Wu CW, Dionigi G, Barczynski M, Chiang FY, Dralle H, Schneider R, et al. International Neuromonitoring Study Group Guidelines 2018: Part II: Optimal Recurrent Laryngeal Nerve Management for Invasive Thyroid Cancer-Incorporation of Surgical, Laryngeal, and Neural Electrophysiologic Data. *Laryngoscope* (2018) 128(Suppl 3):S18–27. doi: 10.1002/lary.27360
15. Schneider R, Randolph G, Dionigi G, Barczyński M, Chiang FY, Triponez F, et al. Prospective Study of Vocal Fold Function After Loss of the Neuromonitoring Signal in Thyroid Surgery: The International Neural Monitoring Study Group's POLT Study. *Laryngoscope* (2016) 126(5):1260–6. doi: 10.1002/lary.25807
16. Dralle H, Schneider R, Lorenz K, Phuong NT, Sekulla C, Machens A. Vocal Cord Paralysis After Thyroid Surgery: Current Medicolegal Aspects of Intraoperative Neuromonitoring. *Der Chirurg; Z fur alle Gebiete der Operativen Medizen* (2015) 86(7):698–706. doi: 10.1007/s00104-015-0033-9
17. Dralle H, Weber F. Modern Endocrine Surgery - Striving for a Better Quality of Life. *Best Pract Res Clin Endocrinol Metab* (2019) 33(4):101345. doi: 10.1016/j.beem.2019.101345
18. Dralle H. Impact of Modern Technologies on Quality of Thyroid Surgery. *Langenbecks Arch Surg* (2006) 391(1):1–3. doi: 10.1007/s00423-005-0012-6
19. Barczynski M, Randolph GW, Cernea CR, Dralle H, Dionigi G, Alesina PF, et al. External Branch of the Superior Laryngeal Nerve Monitoring During Thyroid and Parathyroid Surgery: International Neural Monitoring Study Group Standards Guideline Statement. *Laryngoscope* (2013) 123(Suppl 4): S1–14. doi: 10.1002/lary.24301
20. Dionigi G, Kim HY, Randolph GW, Wu CW, Sun H, Liu X, et al. Prospective Validation Study of Cernea Classification for Predicting EMG Alterations of the External Branch of the Superior Laryngeal Nerve. *Surg Today* (2016) 46 (7):785–91. doi: 10.1007/s00595-015-1245-9
21. Iwata AJ, Liddy W, Barczyński M, Wu CW, Huang TY, Van Slycke S, et al. Superior Laryngeal Nerve Signal Attenuation Influences Voice Outcomes in Thyroid Surgery. *Laryngoscope* (2021) 131(6):1436–42. doi: 10.1002/lary.29413
22. Wu CW, Randolph GW, Lu IC, Chang PY, Chen YT, Hun PC, et al. Intraoperative Neural Monitoring in Thyroid Surgery: Lessons Learned From Animal Studies. *Gland Surg* (2016) 5(5):473–80. doi: 10.21037/gs.2016.09.06
23. Liddy W, Barber SR, Cinquepalmi M, Lin BM, Patricio S, Kyriazidis N, et al. The Electrophysiology of Thyroid Surgery: Electrophysiologic and Muscular Responses With Stimulation of the Vagus Nerve, Recurrent Laryngeal Nerve, and External Branch of the Superior Laryngeal Nerve. *Laryngoscope* (2017) 127(3):764–71. doi: 10.1002/lary.26147
24. Barczynski M, Konturek A, Stopa M, Honowska A, Nowak W. Randomized Controlled Trial of Visualization *Versus* Neuromonitoring of the External Branch of the Superior Laryngeal Nerve During Thyroidectomy. *World J Surg* (2012) 36(6):1340–7. doi: 10.1007/s00268-012-1547-7
25. Schneider R, Randolph GW, Barczynski M, Dionigi G, Wu C-W, Chiang F-Y, et al. Continuous Intraoperative Neural Monitoring of the Recurrent Nerves in Thyroid Surgery: A Quantum Leap in Technology. *Gland Surg* (2016) 5(6):607–16. doi: 10.21037/gs.2016.11.10
26. Mangano A, Kim HY, Wu CW, Rausei S, Hui S, Xiaoli L, et al. Continuous Intraoperative Neuromonitoring in Thyroid Surgery: Safety Analysis of 400 Consecutive Electrode Probe Placements With Standardized Procedures. *Head Neck* (2016) 38(Suppl 1):E1568–74. doi: 10.1002/hed.24280
27. Dionigi G, Chiang FY, Hui S, Wu CW, Xiaoli L, Ferrari CC, et al. Continuous Intraoperative Neuromonitoring (C-IONM) Technique With the Automatic Periodic Stimulating (APS) Accessory for Conventional and Endoscopic Thyroid Surgery. *Surg Technol Int* (2015) 26:101–14.
28. Phelan E, Schneider R, Lorenz K, Dralle H, Kamani D, Potenza A, et al. Continuous Vagal IONM Prevents Recurrent Laryngeal Nerve Paralysis by Revealing Initial EMG Changes of Impending Neuropraxic Injury: A Prospective, Multicenter Study. *Laryngoscope* (2014) 124(6):1498–505. doi: 10.1002/lary.24550
29. Schneider R, Randolph GW, Sekulla C, Phelan E, Thanh PN, Bucher M, et al. Continuous Intraoperative Vagus Nerve Stimulation for Identification of Imminent Recurrent Laryngeal Nerve Injury. *Head Neck* (2013) 35 (11):1591–8. doi: 10.1002/hed.23187
30. Schneider R, Machens A, Randolph G, Kamani D, Lorenz K, Dralle H. Impact of Continuous Intraoperative Vagus Stimulation on Intraoperative Decision Making in Favor of or Against Bilateral Surgery in Benign Goiter. *Best Pract Res Clin Endocrinol Metab* (2019) 33(4):101285. doi: 10.1016/j.beem.2019.06.001
31. Zhang D, Wang T, Zhao Y, Sun H, Pino A, Kim HY, et al. Pre-Prototype Stimulating and Recording Endotracheal Tube for Continuous Monitoring of the Recurrent Laryngeal Nerve During Thyroid Surgery. *J Invest Surg* (2021) 34(9):1033–43. doi: 10.1080/08941939.2020.1734693

32. Schneider R, Machens A, Sekulla C, Lorenz K, Elwerr M, Dralle H. Superiority of Continuous Over Intermittent Intraoperative Nerve Monitoring in Preventing Vocal Cord Palsy. *Br J Surg* (2021) 108(5):566–73. doi: 10.1002/bjs.11901
33. Zhang D, Sun H, Tufano R, Caruso E, Dionigi G, Kim HY. Recurrent Laryngeal Nerve Management in Transoral Endoscopic Thyroidectomy. *Oral Oncol* (2020) 108:104755. doi: 10.1016/j.oraloncology.2020.104755
34. Zhang D, Li S, Dionigi G, Zhang J, Wang T, Zhao Y, et al. Stimulating and Dissecting Instrument for Transoral Endoscopic Thyroidectomy: Proof of Concept Investigation. *Surg endoscopy* (2020) 34(2):996–1005. doi: 10.1007/s00464-019-06936-2
35. Zhang D, Wu C-W, Wang T, Zhao Y, Kim HY, Pino A, et al. Drawbacks of Neural Monitoring Troubleshooting Algorithms in Transoral Endoscopic Thyroidectomy. *Langenbeck's Arch Surg* (2021) 406(7):2433–40. doi: 10.1007/s00423-021-02217-6
36. Ji YB, Jeong JH, Wu CW, Chiang FY, Tae K. Neural Monitoring of the External Branch of the Superior Laryngeal Nerve During Transoral Thyroidectomy. *Laryngoscope* (2021) 131(2):E671–e6. doi: 10.1002/lary.28883
37. Ji YB, Ko SH, Song CM, Sung ES, Lee BJ, Wu CW, et al. Feasibility and Efficacy of Intraoperative Neural Monitoring in Remote Access Robotic and Endoscopic Thyroidectomy. *Oral Oncol* (2020) 103:104617. doi: 10.1016/j.oraloncology.2020.104617
38. Huang TY, Lin YC, Tseng HY, Kim HY, Dionigi G, Lu IC, et al. Full Percutaneous Intraoperative Neuromonitoring Technique in Remote Thyroid Surgery: Porcine Model Feasibility Study. *Head Neck* (2021) 43(2):505–13. doi: 10.1002/hed.26500
39. Dionigi G, Kim HY, Wu CW, Lavazza M, Materazzi G, Lombardi CP, et al. Neuromonitoring in Endoscopic and Robotic Thyroidectomy. *Updates Surg* (2017) 69(2):171–9. doi: 10.1007/s13304-017-0442-z
40. Dionigi G, Wu CW, Tufano RP, Rizzo AG, Anuwong A, Sun H, et al. Monitored Transoral Endoscopic Thyroidectomy *via* Long Monopolar Stimulation Probe. *J Vis Surg* (2018) 4:24. doi: 10.21037/jovs.2017.12.25
41. Rawlings A, Sillin L, Shadduck P, McDonald M, Crookes P, MacFadyen B Jr, et al. Informed Consent: A Shared Decision-Making Process That Creates a New Professional Obligation for Care. *Surg endoscopy* (2020) 34(11):4713–6. doi: 10.1007/s00464-020-07970-1
42. Wehrmann D, Green GE, Weatherwax KJ, Shuman AG. Navigating the Informed Consent Process When Using Innovative Surgery. *Otolaryngology–Head Neck Surg Off J Am Acad Otolaryngology-Head Neck Surg* (2020) 162(2):177–80. doi: 10.1177/0194599819897067
43. Sun H, Kim HY, Carcoforo P, Dionigi G. Cost and Training are Diffusion Patterns Limits for Neural Monitoring in Thyroid Surgery. *Gland Surg* (2019) 8(4):334–5. doi: 10.21037/gs.2018.11.08
44. Dionigi G, Bacuzzi A, Boni L, Rausei S, Rovera F, Dionigi R. Visualization *Versus* Neuromonitoring of Recurrent Laryngeal Nerves During Thyroidectomy: What About the Costs? *World J Surg* (2012) 36(4):748–54. doi: 10.1007/s00268-012-1452-0
45. Wang T, Kim HY, Wu CW, Rausei S, Sun H, Pergolizzi FP, et al. Analyzing Cost-Effectiveness of Neural-Monitoring in Recurrent Laryngeal Nerve Recovery Course in Thyroid Surgery. *Int J Surg (London England)* (2017) 48:180–8. doi: 10.1016/j.ijsu.2017.10.003
46. Dralle H, Sekulla C, Lorenz K, Thanh PN, Schneider R, Machens A. Loss of the Nerve Monitoring Signal During Bilateral Thyroid Surgery. *Br J Surg* (2012) 99(8):1089–95. doi: 10.1002/bjs.8831
47. Hopkins C, Khemani S, Terry RM, Golding-Wood D. How We do it: Nerve Monitoring in ENT Surgery: Current UK Practice. *Clin Otolaryngol Off J ENT-UK ; Off J Netherlands Soc Oto-Rhino-Laryngology Cervico-Facial Surg* (2005) 30(2):195–8. doi: 10.1111/j.1365-2273.2004.00933.x
48. Godballe C, Madsen AR, Sørensen CH, Schytte S, Trolle W, Helweg-Larsen J, et al. Risk Factors for Recurrent Nerve Palsy After Thyroid Surgery: A National Study of Patients Treated at Danish Departments of ENT Head and Neck Surgery. *Eur Arch oto-rhino-laryngology Off J Eur Fed Oto-Rhino-Laryngological Societies (EUFOS) affiliated German Soc Oto-Rhino-Laryngology - Head Neck Surg* (2014) 271(8):2267–76. doi: 10.1007/s00405-013-2767-7
49. Cutilli CC. Seeking Health Information: What Sources do Your Patients Use? *Orthopedic Nurs* (2010) 29(3):214–9. doi: 10.1097/NOR.0b013e3181db5471
50. di Giacomo P, Ricci FL, Bocchi L. Integrated Multimedia Medical Data Agent in E-Health. *Stud Health Technol Inf* (2006) 121:70–3.
51. Ferrari CC, Spampatti S, Leotta A, Rausei S, Rovera F, Boni L, et al. Web-Based Information on Intraoperative Neuromonitoring in Thyroid Surgery. *Int J Surg (London England)* (2013) 11 Suppl 1:S40–1. doi: 10.1016/s1743-9191(13)60012-6
52. Dralle H, Sekulla C, Lorenz K, Brauckhoff M, Machens A. Intraoperative Monitoring of the Recurrent Laryngeal Nerve in Thyroid Surgery. *World J Surg* (2008) 32(7):1358–66. doi: 10.1007/s00268-008-9483-2
53. Dionigi G, Frattini F. Staged Thyroidectomy: Time to Consider Intraoperative Neuromonitoring as Standard of Care. *Thyroid* (2013) 23(7):906–8. doi: 10.1089/thy.2013.0004
54. Wu CW, Sun H, Zhang G, Kim HY, Catalfamo A, Portinari M, et al. Staged Thyroidectomy: A Single Institution Perspective. *Laryngoscope Investig Otolaryngol* (2018) 3(4):326–32. doi: 10.1002/lio2.171
55. Barczynski M, Konturek A, Cichon S. Randomized Clinical Trial of Visualization *Versus* Neuromonitoring of Recurrent Laryngeal Nerves During Thyroidectomy. *Br J Surg* (2009) 96(3):240–6. doi: 10.1002/bjs.6417
56. Anuwong A, Kim HY, Dionigi G. Neural Monitoring in Thyroid Surgery: Is it Evidence-Based? Is it Cost-Effective? *World J Surg* (2016) 40(11):2829–30. doi: 10.1007/s00268-016-3513-2
57. Fehlings MG, Brodke DS, Norvell DC, Dettori JR. The Evidence for Intraoperative Neurophysiological Monitoring in Spine Surgery: Does it Make a Difference? *Spine* (2010) 35(9 Suppl):S37–46. doi: 10.1097/BRS.0b013e3181d8338e
58. Sala F. Intraoperative Neurophysiology is Here to Stay. *Child's nervous system ChNS* (2010) 26(4):413–7. doi: 10.1007/s00381-010-1090-5
59. Cirocchi R, Arezzo A, D'Andrea V, Abraha I, Popivanov GI, Avenia N, et al. Intraoperative Neuromonitoring *Versus* Visual Nerve Identification for Prevention of Recurrent Laryngeal Nerve Injury in Adults Undergoing Thyroid Surgery. *Cochrane Database Syst Rev* (2019) 1(1):Cd012483. doi: 10.1002/14651858.CD012483.pub2
60. Sun W, Liu J, Zhang H, Zhang P, Wang Z, Dong W, et al. A Meta-Analysis of Intraoperative Neuromonitoring of Recurrent Laryngeal Nerve Palsy During Thyroid Reoperations. *Clin Endocrinol* (2017) 87(5):572–80. doi: 10.1111/cen.13379
61. Yang S, Zhou L, Lu Z, Ma B, Ji Q, Wang Y. Systematic Review With Meta-Analysis of Intraoperative Neuromonitoring During Thyroidectomy. *Int J Surg (London England)* (2017) 39:104–13. doi: 10.1016/j.ijsu.2017.01.086
62. Wong KP, Mak KL, Wong CK, Lang BH. Systematic Review and Meta-Analysis on Intra-Operative Neuro-Monitoring in High-Risk Thyroidectomy. *Int J Surg (London England)* (2017) 38:21–30. doi: 10.1016/j.ijsu.2016.12.039
63. Lombardi CP, Carnassale G, Damiani G, Acampora A, Raffaelli M, De Crea C, et al. "The Final Countdown": Is Intraoperative, Intermittent Neuromonitoring Really Useful in Preventing Permanent Nerve Palsy? Evidence From a Meta-Analysis. *Surgery* (2016) 160(6):1693–706. doi: 10.1016/j.surg.2016.06.049
64. Rulli F, Ambrogi V, Dionigi G, Amirhassankhani S, Mineo TC, Ottaviani F, et al. Meta-Analysis of Recurrent Laryngeal Nerve Injury in Thyroid Surgery With or Without Intraoperative Nerve Monitoring. *Acta Otorhinolaryngologica Italica Organo Ufficiale Della Societa Italiana di Otorinolaringologia e Chirurgia Cervico-Facciale* (2014) 34(4):223–9.
65. Pisanu A, Porceddu G, Podda M, Cois A, Uccheddu A. Systematic Review With Meta-Analysis of Studies Comparing Intraoperative Neuromonitoring of Recurrent Laryngeal Nerves *Versus* Visualization Alone During Thyroidectomy. *J Surg Res* (2014) 188(1):152–61. doi: 10.1016/j.jss.2013.12.022
66. Al-Qurayshi Z, Kandil E, Randolph GW. Cost-Effectiveness of Intraoperative Nerve Monitoring in Avoidance of Bilateral Recurrent Laryngeal Nerve Injury in Patients Undergoing Total Thyroidectomy. *Br J Surg* (2017) 104(11):1523–31. doi: 10.1002/bjs.10582
67. Gartland RM, Bloom JP, Parangi S, Hodin R, DeRoo C, Stephen AE, et al. A Long, Unnerving Road: Malpractice Claims Involving the Surgical Management of Thyroid and Parathyroid Disease. *World J Surg* (2019) 43(11):2850–5. doi: 10.1007/s00268-019-05102-y
68. Singer MC, Iverson KC, Terris DJ. Thyroidectomy-Related Malpractice Claims. *Otolaryngology–Head Neck Surg* (2012) 146(3):358–61. doi: 10.1177/0194599811430898

69. Choi S, Shin S, Lee W, Choi SM, Kang SW. Medicolegal Lessons Learned From Thyroidectomy-Related Lawsuits: An Analysis of Judicial Precedents in South Korea From 1998 to 2019. *Gland Surg* (2020) 9(5):1286–97. doi: 10.21037/gs-20-398
70. Demontis R, Pittau MR, Maturo A, Petruzzo P, Calò G. Medico Legal Aspects on Neuromonitoring in Thyroid Surgery: Informed Consent on Malpractice Claims. *Il Giornale di Chirurgia* (2017) 38(3):149–54. doi: 10.11138/gchir/2017.38.3.149
71. Verzeletti A, Vassalini M, Bin P, Lancini L, Restori M, De Ferrari F. Malpractice Claims Related to Recurrent Laryngeal Nerve Injury: Forensic Remarks Regarding 15 Cases. *Egyptian J Forensic Sci* (2016) 6(4):501–4. doi: 10.1016/j.ejfs.2016.04.001
72. Ferguson BD, Angelos P. Ethical and Legal Considerations of Patients Audio Recording, Videotaping, and Broadcasting Physician Encounters. *JAMA Surg* (2021) 156(2):119–20. doi: 10.1001/jamasurg.2020.2968
73. Ronen O, Robbins KT, Olsen KD, Shaha AR, Randolph GW, Nixon IJ, et al. Case for Staged Thyroidectomy. *Head Neck* (2020) 42(10):3061–71. doi: 10.1002/hed.26393
74. Tran DK, Angelos P. How Should Shared Decision Making Be Taught? *AMA J ethics* (2020) 22(5):E388–94. doi: 10.1001/amajethics.2020.388
75. Angelos P, O'Connor M. Responsibilities and Expectations: Considerations of Disclosure of Overlapping Operations. *Ann Surg* (2020) 271(6):1016–7. doi: 10.1097/sla.0000000000003756
76. Angelos P. Informed Consent Requires The Patient Have The Opportunity To Be Informed. *Ann Thorac Surg* (2019) 108(6):1611–2. doi: 10.1016/j.athoracsur.2019.08.010
77. Angelos P. Interventions to Improve Informed Consent: Perhaps Surgeons Should Speak Less and Listen More. *JAMA Surg* (2020) 155(1):13–4. doi: 10.1001/jamasurg.2019.3796
78. Skowron KB, Angelos P. Surgical Informed Consent Revisited: Time to Revise the Routine? *World J Surg* (2017) 41(1):1–4. doi: 10.1007/s00268-016-3715-7
79. Langerman A, Siegler M, Angelos P. Intraoperative Decision Making: The Decision to Perform Additional, Unplanned Procedures on Anesthetized Patients. *J Am Coll Surgeons* (2016) 222(5):956–60. doi: 10.1016/j.jamcollsurg.2016.02.011
80. Stack BCJr., Angelos P. The Ethics of Disclosure and Counseling of Patients With Thyroid Cancer. *JAMA otolaryngology– Head Neck Surg* (2015) 141 (11):957–8. doi: 10.1001/jamaoto.2015.2419
81. Michalski A, Stopa M, Miśkowiak B. Use of Multimedia Technology in the Doctor-Patient Relationship for Obtaining Patient Informed Consent. *Med Sci Monitor Int Med J Exp Clin Res* (2016) 22:3994–9. doi: 10.12659/msm.894147
82. Cernea CR, Ferraz AR, Nishio S, Dutra AJr., Hojaij FC, dos Santos LR. Surgical Anatomy of the External Branch of the Superior Laryngeal Nerve. *Head Neck* (1992) 14(5):380–3. doi: 10.1002/hed.2880140507
83. Mangano A, Lianos GD, Boni L, Kim HY, Roukos DH, Dionigi G. Intraoperative Neuromonitoring of the External Branch of the Superior Laryngeal Nerve During Thyroidectomy: The Need for Evidence-Based Data and Perioperative Technical/Technological Standardization. *TheScientificWorldJournal* (2014) 2014:692365. doi: 10.1155/2014/692365
84. Wu CW, Liu X, Barczynski M, Kim HY, Dionigi G, Sun H, et al. Optimal Stimulation During Monitored Thyroid Surgery: EMG Response Characteristics in a Porcine Model. *Laryngoscope* (2017) 127(4):998–1005. doi: 10.1002/lary.26141
85. Naytah M, Ibrahim I, da Silva S. Importance of Incorporating Intraoperative Neuromonitoring of the External Branch of the Superior Laryngeal Nerve in Thyroidectomy: A Review and Meta-Analysis Study. *Head Neck* (2019) 41 (6):2034–41. doi: 10.1002/hed.25669
86. Pino A, Frattini F, Sun H, Zhang D, Makay O , Rausei S, et al. An Improved Recurrent Laryngeal Nerve-Monitoring Device: Technical Note for NIM Vital™. *Surg Technol Int* (2021) 38:109–24. doi: 10.52198/21.STI.38.GS1443
87. Pino A, Wu CW, Kim HY, Frattini F, Sun H, Zhang D, et al. C2 Xplore® for Intermittent and Continuous Laryngeal Nerve Monitoring: Technical Note. *Surg Technol Int* (2021) 38:145–50. doi: 10.52198/21.Sti.38.Gs1442
88. Barber SR, Liddy W, Kyriazidis N, Cinquepalmi M, Lin BM, Modi R, et al. Changes in Electromyographic Amplitudes But Not Latencies Occur With Endotracheal Tube Malpositioning During Intraoperative Monitoring for Thyroid Surgery: Implications for Guidelines. *Laryngoscope* (2017) 127 (9):2182–8. doi: 10.1002/lary.26392
89. Chiang F-Y, Lu IC, Chang P-Y, Dionigi G, Randolph GW, Sun H, et al. Comparison of EMG Signals Recorded by Surface Electrodes on Endotracheal Tube and Thyroid Cartilage During Monitored Thyroidectomy. *Kaohsiung J Med Sci* (2017) 33(10):503–9. doi: 10.1016/j.kjms.2017.06.014
90. Liddy W, Lawson BR, Barber SR, Kamani D, Shama M, Soylu S, et al. Anterior Laryngeal Electrodes for Recurrent Laryngeal Nerve Monitoring During Thyroid and Parathyroid Surgery: New Expanded Options for Neural Monitoring. *Laryngoscope* (2018) 128(12):2910–5. doi: 10.1002/lary.27362
91. Wu CW, Chiang FY, Randolph GW, Dionigi G, Kim HY, Lin YC, et al. Feasibility of Intraoperative Neuromonitoring During Thyroid Surgery Using Transcartilage Surface Recording Electrodes. *Thyroid* (2018) 28 (11):1508–16. doi: 10.1089/thy.2017.0680
92. Wu CW, Chiang FY, Randolph GW, Dionigi G, Kim HY, Lin YC, et al. Transcutaneous Recording During Intraoperative Neuromonitoring in Thyroid Surgery. *Thyroid* (2018) 28(11):1500–7. doi: 10.1089/thy.2017.0679
93. Lee HS, Oh J, Kim SW, Jeong YW, Wu CW, Chiang FY, et al. Intraoperative Neuromonitoring of Recurrent Laryngeal Nerve During Thyroidectomy With Adhesive Skin Electrodes. *World J Surg* (2020) 44(1):148–54. doi: 10.1007/s00268-019-05208-3
94. Huang TY, Kim HY, Dionigi G, Lu IC, Chang PY, Chiang FY, et al. Laryngeal Neural Monitoring During Pediatric Thyroid Cancer Surgery-Is Transcartilage Recording a Preferable Method? *Cancers (Basel)* (2021) 13 (16):4051–62. doi: 10.3390/cancers13164051
95. Wu CW, Liu X, Barczynski M, Kim HY, Dionigi G, Sun H, et al. Optimal Stimulation During Monitored Thyroid Surgery: EMG Response Characteristics in a Porcine Model. *Laryngoscope* (2017) 127(4):998–1005. doi: 10.1002/lary.26141
96. Abt NB, Puram SV, Kamani D, Modi R, Randolph GW. Neuromonitored Thyroid Surgery: Optimal Stimulation Based on Intraoperative EMG Response Features. *Laryngoscope* (2020) 130(12):E970–5. doi: 10.1002/lary.28613
97. Oh MY, Lee J-M, Lee M-h, Choi HS, Kim J, Hwang K-T, et al. Application of Patch Stimulator for Intraoperative Neuromonitoring During Thyroid Surgery: Maximizing Surgeon's Convenience. *Gland Surg* (2021) 10 (8):2378–85. doi: 10.21037/gs-21-327
98. Chiang FY, Lu IC, Chang PY, Sun H, Wang P, Lu XB, et al. Stimulating Dissecting Instruments During Neuromonitoring of RLN in Thyroid Surgery. *Laryngoscope* (2015) 125(12):2832–937. doi: 10.1002/lary.25251
99. Kim J, Moon HJ, Chai YJ, Lee JM, Hwang KT, Wu CW, et al. Feasibility of Attachable Ring Stimulator for Intraoperative Neuromonitoring During Thyroid Surgery. *Int J Endocrinol* (2020) 2020:5280939. doi: 10.1155/2020/5280939
100. Kim HY, Chai YJ, Barczynski M, Makay Ö, Wu C-W, Rizzo AG, et al. Technical Instructions for Continuous Intraoperative Neural Monitoring in Thyroid Surgery. *J Endocr Surg* (2018) 18(1):61–78. doi: 10.16956/jes.2018.18.1.61
101. Schneider R, Przybyl J, Hermann M, Hauss J, Jonas S, Leinung S. A New Anchor Electrode Design for Continuous Neuromonitoring of the Recurrent Laryngeal Nerve by Vagal Nerve Stimulations. *Langenbecks Arch Surg* (2009) 394(5):903–10. doi: 10.1007/s00423-009-0503-y
102. Lamadé W, Ulmer C, Rieber F, Friedrich C, Koch KP, Thon KP. New Backstrap Vagus Electrode for Continuous Intraoperative Neuromonitoring in Thyroid Surgery. *Surg Innovation* (2011) 18(3):206–13. doi: 10.1177/1553350611409955
103. Sinclair CF, Téllez MJ, Ulkatan S. Noninvasive, Tube-Based, Continuous Vagal Nerve Monitoring Using the Laryngeal Adductor Reflex: Feasibility Study of 134 Nerves at Risk. *Head Neck* (2018) 40(11):2498–506. doi: 10.1002/hed.25377
104. Chiang FY, Lin JC, Lee KW, Wang LF, Tsai KB, Wu CW, et al. Thyroid Tumors With Preoperative Recurrent Laryngeal Nerve Palsy: Clinicopathologic Features and Treatment Outcome. *Surgery* (2006) 140 (3):413–7. doi: 10.1016/j.surg.2006.02.006

105. Holl-Allen RT. Laryngeal Nerve Paralysis and Benign Thyroid Disease. *Arch Otolaryngol (Chicago Ill 1960)* (1967) 85(3):335–7. doi: 10.1001/archotol.1967.00760040337018
106. Rowe-Jones JM, Rosswick RP, Leighton SE. Benign Thyroid Disease and Vocal Cord Palsy. *Ann R Coll Surgeons Engl* (1993) 75(4):241–4.
107. Worgan D, Saunders S, Jones J. Recurrent Laryngeal Nerve Paralysis and the non-Malignant Thyroid. *J laryngology otology* (1974) 88(4):375–8. doi: 10.1017/s0022215100078816
108. Wang JJ, Lu IC, Chang PY, Wu CW, Wang LF, Huang TY, et al. Peculiar Anatomic Variation of Recurrent Laryngeal Nerve and EMG Change in a Patient With Right Substernal Goiter and Pre-Operative Vocal Cord Palsy-Case Report. *Gland Surg* (2020) 9(3):802–5. doi: 10.21037/gs.2020.03.36
109. Kamani D, Darr EA, Randolph GW. Electrophysiologic Monitoring Characteristics of the Recurrent Laryngeal Nerve Preoperatively Paralyzed or Invaded With Malignancy. *Otolaryngology–Head Neck Surg* (2013) 149 (5):682–8. doi: 10.1177/0194599813504735
110. Lorenz K, Abuazab M, Sekulla C, Schneider R, Nguyen Thanh P, Dralle H. Results of Intraoperative Neuromonitoring in Thyroid Surgery and Preoperative Vocal Cord Paralysis. *World J Surg* (2014) 38(3):582–91. doi: 10.1007/s00268-013-2402-1
111. Al-Qurayshi Z, Randolph GW, Alshehri M, Kandil E. Analysis of Variations in the Use of Intraoperative Nerve Monitoring in Thyroid Surgery. *JAMA Otolaryngol–Head Neck Surg* (2016) 142(6):584–9. doi: 10.1001/jamaoto.2016.0412

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Publisher's Note:** All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Endocrinology

ORIGINAL RESEARCH
published: 10 February 2022
doi: 10.3389/fendo.2022.817476

# A Surgeon-Centered Neuromuscular Block Protocol Improving Intraoperative Neuromonitoring Outcome of Thyroid Surgery

*I-Cheng Lu*[1,2], *Chiung-Dan Hsu*[1], *Pi-Ying Chang*[3], *Sheng-Hua Wu*[2,3], *Tzu-Yen Huang*[2,4], *Yi-Chu Lin*[4], *How-Yun Ko*[4], *Gianlorenzo Dionigi*[5,6], *Young Jun Chai*[7], *Feng-Yu Chiang*[8], *Yi-Wei Kuo*[9*†] and *Che-Wei Wu*[2,4*†]

[1] Department of Anesthesiology, Kaohsiung Municipal Siaogang Hospital, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan, [2] Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan, [3] Department of Anesthesiology, Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan, [4] Department of Otorhinolaryngology, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan, [5] Division of General Surgery, Endocrine Surgery Section, Istituto Auxologico Italiano IRCCS (Istituto di ricovero e cura a carattere scientifico), Milan, Italy, [6] Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy, [7] Department of Surgery, Seoul National University College of Medicine, Seoul Metropolitan Government—Seoul National University Boramae Medical Center, Transdisciplinary Department of Medicine & Advanced Technology, Seoul National University Hospital, Seoul, South Korea, [8] Department of Otolaryngology, E-Da Hospital, I-Shou University, Kaohsiung, Taiwan, [9] Department of Anesthesiology, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan

OPEN ACCESS

**Edited by:**
*Loredana Pagano,*
*University of Turin, Italy*

**Reviewed by:**
*Erivelto Martinho Volpi,*
*Centro de referencia no ensino do diagnóstico por imagem (CETRUS), Brazil*
*Leonardo Rossi,*
*University of Pisa, Italy*

***Correspondence:**
*Yi-Wei Kuo*
*harry.k101@msa.hinet.net*
*Che-Wei Wu*
*cwwu@kmu.edu.tw*

*†These authors have contributed equally to this work*

**Specialty section:**
*This article was submitted to Thyroid Endocrinology, a section of the journal Frontiers in Endocrinology*

**Received:** 18 November 2021
**Accepted:** 11 January 2022
**Published:** 10 February 2022

**Citation:**
*Lu I-C, Hsu C-D, Chang P-Y, Wu S-H, Huang T-Y, Lin Y-C, Ko H-Y, Dionigi G, Chai YJ, Chiang F-Y, Kuo Y-W and Wu C-W (2022) A Surgeon-Centered Neuromuscular Block Protocol Improving Intraoperative Neuromonitoring Outcome of Thyroid Surgery. Front. Endocrinol. 13:817476. doi: 10.3389/fendo.2022.817476*

**Background:** Neuromuscular blocking agents provide muscular relaxation for tracheal intubation and surgery. However, the degree of neuromuscular block may disturb neuromuscular transmission and lead to weak electromyography during intraoperative neuromonitoring. This study aimed to investigate a surgeon-friendly neuromuscular block degree titrated sugammadex protocol to maintain both intraoperative neuromonitoring quality and surgical relaxation during thyroid surgery.

**Methods:** A total of 116 patients were enrolled into two groups and underwent elective thyroid surgery with intraoperative neuromonitoring. All patients followed a standardized intraoperative neuromonitoring protocol with continuous neuromuscular transmission monitoring and received 0.6 mg/kg rocuronium for tracheal intubation. Patients were allocated into two groups according to the degree of neuromuscular block when the anterior surface of the thyroid gland was exposed. The neuromuscular block degree was assessed by the train-of-four (TOF) count and ratio. Patients in group I received sugammadex 0.25 mg/kg for non-deep neuromuscular block degree (TOF count = 1~4). Patients in group II were administered sugammadex 0.5 mg/kg for deep neuromuscular block degree (TOF count = 0). The quality of the intraoperative neuromonitoring was measured using the $V_1$ electromyography (EMG) amplitude. An amplitude less than 500 μV and greater than 500 μV was defined as weak and satisfactory, respectively.

**Results:** The quality of the intraoperative neuromonitoring was not different between groups I and II (satisfactory/weak: 75/1 vs. 38/2, *P* = 0.14). The quality of surgical relaxation was acceptable after sugammadex injection and showed no difference between groups [55/76 (72.3%) in group I vs. 33/40 (82.5%) in group II, *P* = 0.23].

**Conclusions:** This surgeon-centered sugammadex protocol guided by neuromuscular block degree (0.5 mg/kg for deep block and 0.25 mg/kg for others) showed comparably high intraoperative neuromonitoring quality and adequate surgical relaxation. The results expanded the practicality of sugammadex for precise neuromuscular block management during monitored thyroidectomy.

**Keywords: intraoperative neuromonitoring (IONM), thyroid surgery, recurrent laryngeal nerve (RLN), neuromuscular block degree, sugammadex**

## INTRODUCTION

Intraoperative neuromonitoring (IONM) has gained increasing popularity during thyroid surgery in recent years. IONM is an adjunct tool for the identification and localization, detecting anatomical variations, differentiating mechanisms of injury, and predicting the postoperative function of the recurrent laryngeal nerve (RLN) (1–12). The goal of IONM is to diminish the occurrence of RLN injury and vocal cord paralysis associated with thyroid and parathyroid surgery.

Both good contact of surface electrodes (13–19) and adequate reversal of neuromuscular blockade (NMB) (20–27) are prerequisites for successful IONM of the RLN. For adequate relaxation to facilitate tracheal intubation and surgery, a profound or deep NMB is desirable. A proper reversal of the NMB is mandatory for functional IONM *via* evoked electromyogram (EMG) signals. Recently, sugammadex following rocuronium during anesthesia induction has been reported as an effective NMB regimen for successful IONM in animal and human clinical studies involving thyroid surgery (28–30).

Various sugammadex regimens have been reported. Low-dose sugammadex can enhance spontaneous neuromuscular functional recovery, while high-dose sugammadex can result in undesirable involuntary movement during surgery. In our previous report, sugammadex at a dose of 0.5 mg/kg induced NMB reversal from rocuronium 0.6 mg/kg and provided high-quality monitoring of the RLN for thyroid surgery (31). Chai et al. (32) demonstrated that sugammadex at either 1 or 2 mg/kg resulted in high-quality IONM. The bucking effect of sugammadex is dose-related, such that 2 mg/kg sugammadex was associated with up to 35% higher effects than 1 mg/kg sugammadex (32). However, the titration of sugammadex dosage according to the degree of NMB has not been investigated.

This study aimed to establish a surgeon-friendly protocol by titrating the sugammadex dose based on the degree of NMB before initial vagus nerve stimulation ($V_1$) to maintain both surgical relaxation and IONM quality during thyroid surgery. We hypothesized that sugammadex titrated at a dose of 0.25 mg/kg is effective for the reversal of rocuronium-induced moderate NMB and can provide effective IONM with sufficient surgical relaxation. We compared this protocol with 0.5 mg/kg sugammadex for deep NMB, which was routinely administered at our institution.

## METHODS

### Patient Data

This retrospective observational study was approved by the institutional review board of Kaohsiung Medical University Hospital [KMUHIRB-E(I)-20210070] and registered at ClinicalTrials.gov (NCT 04982185). Patients who underwent elective total thyroidectomy or total lobectomy with routine IONM were included between August 1, 2019, and July 31, 2020. Patients who met the following exclusion criteria were excluded from the study: age ≤20 years, American Society of Anesthesiologists (ASA) status of ≥4, vocal cord palsy, or previous thyroid surgery. All operations were performed by the same surgeon, and anesthesia was administered by two experienced anesthesiologists. The neuromonitoring setup, surgical procedures, and loss of signal algorithm followed the International Neural Monitoring Study Group Guidelines (1, 5, 11, 12).

### Anesthesia

Upon arrival at the operating room, each patient was placed under standard physiological monitoring (oximetry, electrocardiography, non-invasive blood pressure, and capnography). Before anesthesia induction, a donut pad beneath the neck was placed for thyroidectomy. An oral endotracheal tube with a 7.0- and 7.5-mm internal diameter was placed for female and male patients, respectively.

The NMB degree was continuously monitored by the train-of-four (TOF) count and ratio derived from the adductor pollicis muscle. Anesthetic depth was assessed using the response entropy (RE) or bispectral index (BIS). Anesthesia induction was initiated with fentanyl (1 μg/kg), lidocaine (1 mg/kg), and propofol (1.5–2 mg/kg). When loss of consciousness was identified, rocuronium (0.6 mg/kg) was administered to induce

NMB in all patients. When the maximum NMB was achieved, the anesthesiologist performed tracheal intubation using a Trachway video intubating stylet (Biotronic Instrument Enterprise Ltd., Tai Chung, Taiwan). The position of the endotracheal tube was confirmed by end-tidal $CO_2$ and auscultation.

Anesthesia was maintained with sevoflurane and propofol target-controlled infusion with an Orchestra™ infusion pump (Fresenius Vial, France). The effect-site concentration of propofol was maintained at 1–1.5 μg/ml. Two registered nurse anesthetists followed the standardized anesthesia regimen according to our institution's protocol and adjusted the inhaled sevoflurane concentration to maintain an entropy or BIS value between 40 and 60. A bolus of fentanyl 0.5 μg/kg was administered before the skin incision.

## Study Flowchart

The timing of sugammadex administration was decided by the surgeon after the initial surgical steps of subplatysmal flap creation and strap muscle separation to expose the anterior surface of the thyroid gland. Patients were allocated into two groups according to the degree of NMB before sugammadex administration. A TOF count of 0 was defined as deep NMB. A TOF count of 1–3 was defined as moderate neuromuscular block and 4 as recovery (33). Patients with non-deep NMB (group I) received sugammadex 0.25 mg/kg. Patients with deep NMB (group II) were administered sugammadex 0.5 mg/kg (**Figure 1**). All patients followed the standard anesthesia protocol for monitored thyroidectomy (**Table 1**).

## Surgical Techniques and Intraoperative Neuromonitoring Setup

A lower neck skin incision was made along the skin crease. Subcutaneous fat and platysma were divided, and a subplatysmal dissection was made above the incision up to the level of the thyroid cartilage. The fascia between the strap muscles was divided, and the anterior surface of the thyroid gland was exposed. After resection of the pyramidal lobe, a pair of subdermal electrodes (length, 12.0 mm; diameter, 0.4 mm; Medtronic, Jacksonville, FL) was inserted into the subperichondrium of the thyroid cartilage lamina on both sides (34). The thyroid cartilage electrodes were connected to the nerve integrity monitoring (NIM). The elicited EMG signals with electrode leads were documented as channels 1 and 2 simultaneously. The NIM system generated stimuli with a time window set to 50 ms and an amplitude scale set to 0.2 mV/division. The pulsed stimuli were 100 μs in duration and 4 Hz in frequency. Event capture was activated at a threshold of 100 μV. The intraoperative standardized IONM protocol routinely followed the departmental guidelines. The highest EMG amplitudes were recorded. $V_1$ signal represents vagal stimulation before dissection, $R_1$ signal represents RLN stimulation at first identification, $R_2$ signal represents RLN stimulation after complete dissection, and $V_2$ signal represents repeat vagal stimulation after resection of the thyroid.

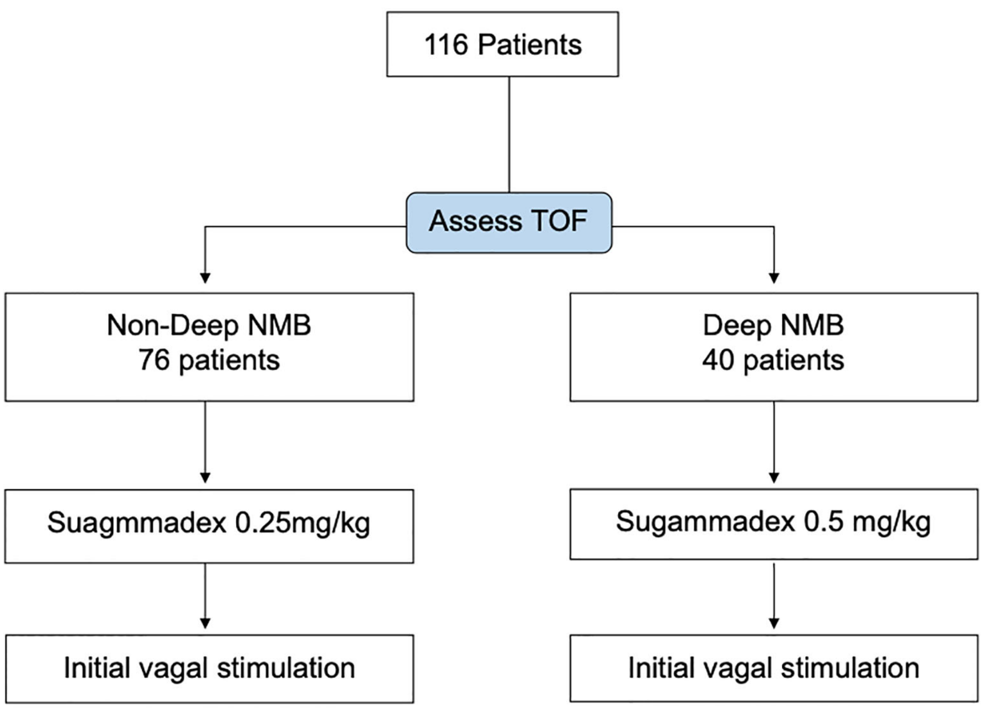



**FIGURE 1** | Study flowchart of the 116 consecutive patients, 40 with deep neuromuscular block (NMB) are reversed by sugammadex 0.5 mg/kg. Another 76 patients with moderate NMB or recovery are reversed by sugammadex 0.25 mg/kg. TOF, train of four.

**TABLE 1** | Departmental anesthesia protocol for intraoperative neuromonitoring during thyroid surgery.

| Time courses | Remarks |
|---|---|
| **Preoperative evaluation** | ASA physical status and upper airway management assessment |
| **Monitoring setup** | Standard physical/neuromuscular/anesthesia depth monitors |
| **Anesthesia induction** | |
| Induction | Fentanyl 1 μg/kg, lidocaine 1 mg/kg, and propofol 1.5–2 mg/kg |
| NMBA | Rocuronium 0.6 mg/kg |
| **Anesthesia maintenance** | Avoid NMBA |
| Inhaled anesthetic | Sevoflurane 1%–4% |
| Intravenous anesthetic | Propofol TCI, effect-site concentration: 1~1.5 μg/kg |
| Anesthesia depth | Entropy or BIS between 40 and 60 |
| Vasopressor | Ephedrine 8–10 mg if MAP reduction >20% mmHg |
| PONV prophylaxis | Dexamethasone 5 mg, avoid morphine |
| Inadequate relaxation | A bolus of fentanyl 0.5 μg/kg and propofol 20–30 mg |
| **Neural monitoring** | Low dose of sugammadex blockade |
| Placing TC electrodes | Sugammadex 0.5 mg/kg if TOF count = 0 (con)<br>Sugammadex 0.25 mg/kg if TOF count = 1–4 |
| $V_1$ and $V_2$ signal | EMG amplitude correlated with TOF ratio |
| **Anesthesia emergency** | |
| Extubation | Additional sugammadex up to 2.0 mg/kg<br>Extubation when spontaneous breath with TOF ratio >0.95 |
| Pain control | Parecoxib 40 mg or NSAID if not contraindicated<br>Fentanyl 0.5 μg/kg |
| **Postoperative visit** | Anesthesia adverse events and satisfaction |

*ASA, American Society of Anesthesiologists; NMBA, neuromuscular blocking agent; TCI, target-controlled infusion; MAP, mean arterial pressure; BIS, bispectral index; PONV, postoperative nausea vomiting; TC, thyroid cartilage; $V_1$ and $V_2$, initial and final vagal stimulation; TOF, train-of-four mode of neuromuscular transmission monitoring; EMG, electromyography; NSAID, non-steroidal anti-inflammatory drug.*

## Outcome Measures

The primary outcomes of this study were the quality of the IONM and EMG amplitude of the $V_1$ signal. The quality of IONM was measured using the obtained $V_1$ amplitude. Satisfactory and weak signal was defined as a $V_1$ amplitude of >500 μV and <500 μV, respectively. The secondary outcome was the quality of surgical relaxation. The quality of relaxation was assessed by the number of free periods without any intraoperative limb movement, coughing, and swallowing events. The data of NMB, anesthesia depth, hemodynamics, postoperative adverse events, and surgical outcomes were also recorded and analyzed. All patients received preoperative and postoperative video recordings of vocal cord mobility by flexible laryngofiberoscopy. When asymmetric cord movement was found postoperatively, a comparison with the preoperative recording was performed.

## Statistical Analysis

Continuous data were presented as mean ± standard deviation (SD) values, and nominal data are presented as number (%). The distribution of variables was tested using the Kolmogorov–Smirnov test. Statistical analysis of continuous variables with normal distribution between groups was compared using the unpaired t-test, while continuous variables without normal distribution were compared using the Mann–Whitney U test. All statistical tests were two-tailed. Categorical nominal variables were analyzed using the chi-square or Fisher exact test. Statistical significance was set at $P < 0.05$.

The sample size estimation was based on two similarly designed studies. To ensure adequate power for the study, a minimal sample size of 40 patients was used to measure the effect of 0.5 mg/kg sugammadex according to a previous study (31). One previous study showed satisfactory nerve monitoring ($V_1$ >500 μV) in 90% of patients when the vagus nerve was monitored after delivery of 1 mg/kg sugammadex (32). To establish a non-inferiority study in which 0.25 mg/kg sugammadex would not be less satisfactory, the case number required for the study was 38 patients per group with a 10% non-inferiority margin, an alpha of 0.05, and a beta of 0.2.

# RESULTS

A total of 116 patients (24 men and 92 women; aged 21–88 years) were included in this study (**Figure 1**). Detailed patient characteristics are shown in **Table 2**. All tracheal intubations were successful after the first attempt, and no intubation-related upper airway trauma was noted. There was no difference between the two groups in terms of demographic data, physical status, disease diagnosis, vasopressor use, and surgical relaxation. The number of patients with complete surgical relaxation was significantly lower after sugammadex injection [71 (93.4%) to 55 (72.3%) in group I, $P < 0.01$, vs. 39 (97.5%) to 33 (82.5%) in group II, $P = 0.03$]. Overall, 193 nerves were at risk, and only one nerve had intraoperative loss of signal. This was a cancer patient who had postoperative temporary RLN palsy who recovered after 4 weeks.

Key time intervals for anesthesia, operation, and neuromonitoring did not differ significantly between the groups (**Table 3**). The average time from anesthesia induction (rocuronium) to sugammadex injection was 46.0 (± 9.1) min in group I and 43.4 (± 9.3) min in group II ($P = 0.14$). The average time from the surgeon's request to administer sugammadex to initial

**TABLE 2 |** Patient characteristics of 116 patients receiving monitored thyroidectomy.

| | Group I (n = 76) | Group II (n = 40) | *P* value |
|---|---|---|---|
| Female gender | 62 (81.5%) | 30 (75%) | 0.71 |
| Age, mean (SD), years | 51.2 (13.4) | 55.6 (12.6) | 0.82 |
| Weight (kg) | 60.0 (11.5) | 57.8 (9.9) | 0.29 |
| Height (cm) | 159.8 (7.7) | 157.7 (7.3) | 0.14 |
| BMI (kg/m$^2$) | 23.4 (3.6) | 23.2 (3.5) | 0.79 |
| ASA status | | | |
| I | 2 (2.6%) | 1 (2.5%) | 0.89 |
| II | 56 (73.7%) | 31 (77.5%) | |
| III | 18 (23.7%) | 8 (20%) | |
| Diagnosis | | | 0.75 |
| Cancer | 30 (39.5%) | 16 (42.5%) | |
| Benign | 46 (60.5%) | 24 (57.5%) | |
| Vasopressor | 7 (9.2%) | 5 (12.5%) | 0.58 |
| Complete relaxation* | | | |
| Before sugammadex | 71 (93.4%) | 39 (97.5%) | 0.35 |
| After sugammadex | 55 (72.3%) | 33 (82.5%) | 0.23 |
| Nerve at risk (n) | 122 | 71 | |
| RLN signal loss# | 1 (0.8%) | 0 (0%) | 0.44 |
| Temporary palsy | 1 (0.8%) | 0 (0%) | 0.44 |
| Permanent palsy | 0 (0%) | 0 (0%) | 1.0 |

*ASA status, American Society of Anesthesiologists Physical Status classification system; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); *Without any one event of limb movement, coughing, or swallowing; #signal loss was defined as an EMG amplitude decrease of more than 50% of the baseline value.*

vagal stimulation was as short as 5.4 (± 2.1) min in group I and 5.1 (± 2.1) min in group II ($P$ = 0.48).

With respect to IONM quality, all patients showed a positive $V_1$ signal after sugammadex. The $V_1$ EMG amplitude was greater than 500 μV in most patients. There was no significant difference between the groups (satisfactory/weak: 75/1 in group I and 38/2 in group II, $P$ = 0.23). The EMG amplitude and NMB degree were compared at $V_1$ and $V_2$ stimulations between the two groups. At the $V_1$ time point, group I demonstrated a higher EMG amplitude [1,926 (± 806) vs. 1,616 (± 939), $P$ = 0.06] and a higher TOF ratio [36 (± 28) vs. 30 (± 32), $P$ = 0.29] than group II, but the difference was not statistically significant (**Table 3**). Both the mean EMG amplitude and TOF ratio at the $V_2$ time point were comparable between the two groups (**Table 3**).

## DISCUSSION

The present results revealed that both 0.5 mg/kg sugammadex for deep NMB and 0.25 mg/kg sugammadex for moderate NMB could be feasible for monitored thyroidectomy. Both groups were comparable in terms of surgical relaxation quality in terms of freedom from intraoperative limb movements, coughing, and swallowing. To the best of our knowledge, this is the first report evaluating the effects of sugammadex titrated

**TABLE 3 |** Time interval of procedures and quality of intraoperative neural monitoring comparison of neuromuscular blockade degree, neural monitoring recordings, and postoperative adverse events.

| | Group I (n = 76) | Group II (n = 40) | *P* value |
|---|---|---|---|
| **Time interval** | | | |
| Anesthesia to skin incision | 23.8 (7.2) | 22.2 (7.3) | 0.26 |
| Skin incision to sugammadex | 22.2 (6.2) | 21.2 (5.4) | 0.38 |
| Sugammadex to $V_1$ | 5.4 (2.1) | 5.1 (2.2) | 0.48 |
| Sugammadex to $V_2$ | 27.6 (12.7) | 31.4 (12.6) | 0.12 |
| **$V_1$ amplitude** | | | 0.23 |
| <500 μV | 1 (1.3%) | 2 (5%) | |
| >500 μV | 75 (98.7%) | 38 (95%) | |
| **$V_1$ stimulation** | | | |
| EMG amplitude (μV) | 1929 (806) | 1616 (939) | 0.06 |
| TOF ratio (%) | 36 (28) | 30 (32) | 0.29 |
| **$V_2$ stimulation** | | | |
| EMG amplitude (μV) | 2084 (972) | 1868 (1070) | 0.27 |
| TOF ratio (%) | 73 (24) | 76 (19) | 0.53 |

*$V_1$, initial vagal stimulation; $V_2$, final vagal stimulation; EMG, electromyography; TOF, train of four.*

according to the degree of NMB for IONM during thyroid surgery.

Two fundamental elements of successful neuromonitoring are a proper recording of electrode position and NMB recovery. With respect to electrode position, in this study, we used a pair of outer thyroid cartilage electrodes to ensure stable EMG signals (34–39) instead of electrodes of an EMG endotracheal tube, which was susceptible to rotational or depth changes (18, 38, 40). Regarding NMB management, several feasible regimens have been proposed to facilitate tracheal intubation and functional IONM (8). Sugammadex has gained increasing popularity in IONM during thyroid surgery. The reported dose of sugammadex that was effective for IONM ranged from 0.5 to 2.0 mg/kg (28, 29, 31, 32, 41, 42). There is a wide variation between patients in the spontaneous recovery time from rocuronium-induced NMB group. Hence, precise and timely titration of sugammadex dose according to different NMB doses could be more effective and practical during IONM.

Sugammadex at 0.5 mg/kg was reported to achieve a high EMG amplitude of 1,214 (± 623) μV at $V_1$ stimulation during thyroidectomy (31). Complete and early reversal of NMB was very effective for IONM, providing surgical relaxation. In clinical observations, vigorous movements might occur immediately after a dose of 1 or 2 mg/kg sugammadex. Chai et al. (32) also demonstrated that sugammadex at 2 mg/kg was associated with more bucking than 1 mg/kg (35% vs. 14%) during thyroid surgery with IONM. Since different sugammadex doses provided comparable high-quality EMG signals, this modified NMB protocol attempted to explore minimal sugammadex doses that could allow high-quality IONM signals. In a previous report, sugammadex at 0.5 mg/kg was effective for deep NMB, and sugammadex dose at 0.25 mg/kg provided moderate NMB or recovery. A reduction in sugammadex dose for a lower degree of NMB was found to be effective for high-quality IONM ($V_1$ amplitude >500 μV) in 98.7% (75/76) of patients. Although there was one patient with a $V_1$ signal of <500 μV (445 μV), typical EMG waveforms can be easily observed, and IONM was successfully performed without difficulty.

In addition to the dose of sugammadex, the timing of administration plays a key role in NMB management. Sugammadex has been developed to selectively bind to aminosteroidal NMBAs (i.e., rocuronium) selectively (43, 44). Sugammadex provides rapid and effective reversal of rocuronium-induced NMB not only for residual NMB after extubation but also for high-quality IONM signals during surgery. When considering the rapid time of onset, the interval between $V_1$ and sugammadex in this protocol was modified to be as short as possible. This study employed a team approach during IONM, wherein the anesthesiologist administered sugammadex per the surgeon's request after exposing the anterior surface of the thyroid gland and preparing for initial ($V_1$) vagal stimulation. The overall interval from sugammadex administration to $V_1$ stimulation was 5.32 (± 2.2) min.

There is a lack of consensus regarding sugammadex timing before vagal stimulation; several time points reported for administration were as follows: immediately after tracheal tube fixation, at skin incision, at 10 min after skin excision, and at exposure and identification of the vagus nerve. The interval from sugammadex to V1 stimulation was between 3 and 32 min (9, 12, 13, 22). In a selective protocol, sugammadex was used after $V_1$ stimulation when the EMG amplitude was absent or below 100 μV. However, a low initial $V_1$ amplitude limits the application of the IONM troubleshooting algorithm in case of signal loss (10). Sugammadex timing may affect the reversal of NMB. In this study, the mean TOF ratio was 30% at $V_1$ stimulation after sugammadex 0.5 mg/kg was administered before $V_1$ stimulation. In our previous report, the TOF ratio was 59% after sugammadex 0.5 mg/kg was administered 10 min after starting the operation (12). Both regimens were able to present comparable high-quality IONM signals during thyroid surgery.

There are several advantages to this surgeon-centered NMB degree titrated sugammadex protocol for monitored thyroidectomy. First, sugammadex titration based on NMB degree provided two effective rocuronium doses (0.6 mg/kg) to provide an excellent condition for tracheal intubation in most patients (9, 12). Second, sugammadex administration approximately 5 min before $V_1$ stimulation ensured an adequate onset time to reverse NMB. The protocol maximizes the sugammadex-free interval to avoid bucking or movement resulting from a lower degree of NMB (13). Finally, regarding IONM quality, a high EMG amplitude was noted in 97.4% (113/116) of patients. An initial high-quality $V_1$ signal is crucial to the signal loss algorithm because the initial EMG amplitude is a standard reference to be compared (1, 5, 45, 46) and to detect imminent nerve stress or injury (11, 12, 47–50).

In addition to the application of sugammadex, several alternative methods could be used for IONM during thyroid surgery. Since sugammadex is not available in all institutes because of its high cost, dose titration of neuromuscular blocking agents might also enable tracheal intubation and surgical relaxation. In a review of NMB management for IONM without using sugammadex, regimens including relaxant-free, succinylcholine, and low to standard dose of rocuronium (0.3~0.6 mg/kg) were all feasible with some clinical limitations (24, 27).

This study had several limitations. First, the study design lacked patient randomization and blinding regarding the administered sugammadex dose because of grouping based on the degree of NMB. Patients in both groups showed comparable demography, disease, and procedure profiles. Second, there might be a selection bias due to the high cost of sugammadex. This was a self-payment regimen; thus, patients who could afford sugammadex and had a high socioeconomic status were included. Third, this protocol was limited by the NMB monitoring equipment in addition to sugammadex. The NMB degree was measured by the TOF ratio generally *via* acceleromyography or kinemyography devices in Taiwan. However, both devices and sugammadex are not easily available for every institute. Finally, caution should be exercised when interpreting the outcomes in this trial. The outcomes were based on the close cooperation between the surgery and the anesthesia team with much clinical and laboratory experience in thyroid surgery with IONM. The IONM outcomes may be influenced by team members in various clinical backgrounds.

## CONCLUSIONS

Before vagal stimulation, this surgeon-centered sugammadex protocol according to NMB degree allowed high IONM quality and adequate surgical relaxation. Both sugammadex 0.5 mg/kg for deep NMB and 0.25 mg/kg for moderate NMB or less showed comparable high EMG amplitude at $V_1$ stimulation. Sugammadex titration for reversal of NMB prevented undetectable or markedly low EMG amplitudes whenever nerve stimulation was required during thyroidectomy. Moreover, the flexibility of sugammadex administration timing based on the surgical procedure was also feasible for IONM during thyroid surgery. These initial positive results warrant further randomized controlled trials.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the institutional review board of Kaohsiung Medical University Hospital, Kaohsiung Taiwan. Written informed consent for participation was not required for this study in accordance with the national legislation and institutional requirements.

## AUTHOR CONTRIBUTIONS

C-WW had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Y-WK and C-WW contributed equally to this work. Concept and design: I-CL and C-WW. Acquisition, analysis, or interpretation of data: I-CL, C-DH, P-YC, GD, YJC, C-WW. Drafting of the article: I-CL, F-YC, Y-WK, C-WW. Critical revision of the article and final approval: All authors. Statistical analysis: I-CL, F-YC, Y-CL, C-WW. Obtained funding: I-CL, T-YH, C-WW. Administrative, technical, or material support: S-HW, T-YH, Y-CL, H-YK, and F-YC. Supervision: Y-WK and C-WW.

## FUNDING

This study was supported by grants from the Kaohsiung Municipal Siaogang Hospital (H-109-001, Kmhk-110-08) and the Ministry of Science and Technology, Taiwan (MOST 109-2314-B-037-059).

## ACKNOWLEDGMENTS

The authors express gratitude to Hsiu-Ya Chen (nurse anesthetist, Department of Anesthesiology, KMUH, KMU), Hui-Chun Chen (clinical nurse specialist, Department of Nursing, KMUH, KMU), and Pao-Chu Hun (veterinarian, Laboratory Animal Center, KMU) for their excellent technical assistance.

## REFERENCES

1. Randolph GW, Dralle H, Abdullah H, Barczynski M, Bellantone R, Brauckhoff M, et al. Electrophysiologic Recurrent Laryngeal Nerve Monitoring During Thyroid and Parathyroid Surgery: International Standards Guideline Statement. *Laryngoscope* (2011) 121(Suppl 1):S1–16. doi: 10.1002/lary.21119
2. Sanabria A, Kowalski LP, Nixon I, Angelos P, Shaha A, Owen RP, et al. Methodological Quality of Systematic Reviews of Intraoperative Neuromonitoring in Thyroidectomy: A Systematic Review. *JAMA Otolaryngol Head Neck Surg* (2019) 145(6):563–73. doi: 10.1001/jamaoto.2019.0092
3. Feng AL, Puram SV, Singer MC, Modi R, Kamani D, Randolph GW. Increased Prevalence of Neural Monitoring During Thyroidectomy: Global Surgical Survey. *Laryngoscope* (2020) 130(4):1097–104. doi: 10.1002/lary.28210
4. Genther DJ, Kandil EH, Noureldine SI, Tufano RP. Correlation of Final Evoked Potential Amplitudes on Intraoperative Electromyography of the Recurrent Laryngeal Nerve With Immediate Postoperative Vocal Fold Function After Thyroid and Parathyroid Surgery. *JAMA Otolaryngol Head Neck Surg* (2014) 140(2):124–8. doi: 10.1001/jamaoto.2013.6139
5. Wu CW, Randolph GW, Barczyński M, Schneider R, Chiang FY, Huang TY, et al. Training Courses in Laryngeal Nerve Monitoring in Thyroid and Parathyroid Surgery- The INMSG Consensus Statement. *Front Endocrinol (Lausanne)* (2021) 12:705346:705346. doi: 10.3389/fendo.2021.705346
6. Fundakowski CE, Hales NW, Agrawal N, Barczyński M, Camacho PM, Hartl DM, et al. Surgical Management of the Recurrent Laryngeal Nerve in Thyroidectomy: American Head and Neck Society Consensus Statement. *Head Neck* (2018) 40(4):663–75. doi: 10.1002/hed.24928
7. Vasileiadis I, Karatzas T, Charitoudis G, Karakostas E, Tseleni-Balafouta S, Kouraklis G. Association of Intraoperative Neuromonitoring With Reduced Recurrent Laryngeal Nerve Injury in Patients Undergoing Total Thyroidectomy. *JAMA Otolaryngol Head Neck Surg* (2016) 142(10):994–1001. doi: 10.1001/jamaoto.2016.1954
8. Patel KN, Yip L, Lubitz CC, Grubbs EG, Miller BS, Shen W, et al. The American Association of Endocrine Surgeons Guidelines for the Definitive Surgical Management of Thyroid Disease in Adults. *Ann Surg* (2020) 271(3):e21–93. doi: 10.1097/sla.0000000000003580
9. Al-Qurayshi Z, Randolph GW, Alshehri M, Kandil E. Analysis of Variations in the Use of Intraoperative Nerve Monitoring in Thyroid Surgery. *JAMA Otolaryngol Head Neck Surg* (2016) 142(6):584–9. doi: 10.1001/jamaoto.2016.0412
10. Abdelhamid A, Aspinall S. Intraoperative Nerve Monitoring in Thyroid Surgery: Analysis of United Kingdom Registry of Endocrine and Thyroid Surgery Database. *Br J Surg* (2021) 108(2):182–7. doi: 10.1093/bjs/znaa081
11. Schneider R, Randolph GW, Dionigi G, Wu CW, Marcin Barczynski M, Chiang FU, et al. International Neural Monitoring Study Group Guideline 2018 Part I: Staging Bilateral Thyroid Surgery With Monitoring Loss of Signal. *Laryngoscope* (2018) 128(Suppl 3):S1–17. doi: 10.1002/lary.27359
12. Wu CW, Dionigi G, Barczynski M, Chiang FY, Dralle H, Schneider R, et al. International Neuromonitoring Study Group Guidelines 2018: Part II: Optimal Recurrent Laryngeal Nerve Management for Invasive Thyroid Cancer-Incorporation of Surgical, Laryngeal, and Neural Electrophysiologic Data. *Laryngoscope* (2018) 128(Suppl 3):S18–27. doi: 10.1002/lary.27360
13. Lu IC, Chu KS, Tsai CJ, Wu CW, Kuo WR, Chen HY, et al. Optimal Depth of NIM EMG Endotracheal Tube for Intraoperative Neuromonitoring of the Recurrent Laryngeal Nerve During Thyroidectomy. *World J Surg* (2008) 32(9):1935–9. doi: 10.1007/s00268-008-9549-1
14. Berkow L, Dackiw AP, Tufano RP. Use of the GlideScope for Placement of a Recurrent Laryngeal Nerve Monitoring Endotracheal Tube. *J Clin Anesth* (2011) 23(1):81–3. doi: 10.1016/j.jclinane.2009.12.013

15. Tsai CJ, Tseng KY, Wang FY, Lu IC, Wang HM, Wu CW, et al. Electromyographic Endotracheal Tube Placement During Thyroid Surgery in Neuromonitoring of Recurrent Laryngeal Nerve. *Kaohsiung J Med Sci* (2011) 27(3):96–101. doi: 10.1016/j.kjms.2010.08.002
16. Kanotra SP, Kuriloff DB, Lesser J, Rest-Flarer F. GlideScope-Assisted Nerve Integrity Monitoring Tube Placement for Intra-Operative Recurrent Laryngeal Nerve Monitoring. *J Laryngol Otol* (2012) 126(12):1271–3. doi: 10.1017/S0022215112002460
17. Cherng CH, Huang YH, Shih ML. Middle Fixation of Electromyographic Endotracheal Tube for Intraoperative Recurrent Laryngeal Nerve Monitoring. *J Clin Anesth* (2014) 26(3):252–3. doi: 10.1016/j.jclinane.2014.01.009
18. Barber SR, Liddy W, Kyriazidis N, Cinquepalmi M, Brian M Lin BM, Modi R, et al. Changes in Electromyographic Amplitudes But Not Latencies Occur With Endotracheal Tube Malpositioning During Intraoperative Monitoring for Thyroid Surgery: Implications for Guidelines. *Laryngoscope* (2017) 127 (9):2182–8. doi: 10.1002/lary.26392
19. Huang JM, Hsu CD, Wu SH, Kuo YW, Huang TY, Wu CW, et al. Optimization of Electromyographic Endotracheal Tube Electrode Position by UEScope for Monitored Thyroidectomy. *Laryngoscope Investig Otolaryngol* (2021) 6(5):1214–19. doi: 10.1002/lio2.635
20. Marusch F, Hussock J, Haring G, Hachenberg T, Gastinger I. Influence of Muscle Relaxation on Neuromonitoring of the Recurrent Laryngeal Nerve During Thyroid Surgery. *Br J Anaesth* (2005) 94(5):596–600. doi: 10.1093/bja/aei110
21. Shi Y, Hou V, Tucker A, Cohen J. Changes of Extremity and Laryngeal Muscle Electromyographic Amplitudes After Intravenous Administration of Vecuronium. *Laryngoscope* (2008) 118(12):2156–60. doi: 10.1097/MLG.0b013e318184574e
22. Chu KS, Wu SH, Lu IC, Tsai CJ, Wu CW, Kuo WR, et al. Feasibility of Intraoperative Neuromonitoring During Thyroid Surgery After Administration of Nondepolarizing Neuromuscular Blocking Agents. *World J Surg* (2009) 33(7):1408–13. doi: 10.1007/s00268-009-0049-8
23. Chu KS, Tsai CJ, Lu IC, Tseng KY, Chau SW, Wu CW, et al. Influence of Nondepolarizing Muscle Relaxants on Intraoperative Neuromonitoring During Thyroid Surgery. *J Otolaryngol Head Neck Surg* (2010) 39(4):397–402.
24. Lu IC, Tsai CJ, Wu CW, Cheng KI, Wang FY, Tseng KY, et al. A Comparative Study Between 1 and 2 Effective Doses of Rocuronium for Intraoperative Neuromonitoring During Thyroid Surgery. *Surgery* (2011) 149(4):543–8. doi: 10.1016/j.surg.2010.11.006
25. Brunaud L, Fuchs-Buder T. In Reference to Reversal of Rocuronium-Induced Neuromuscular Blockade by Sugammadex Allows for Optimization of Neural Monitoring of the Recurrent Laryngeal Nerve. *Laryngoscope* (2017) 127(1): E50. doi: 10.1002/lary.25990
26. Lu IC, Lin IH, Wu CW, Chen HY, Lin YC, Chiang FY, et al. Preoperative, Intraoperative and Postoperative Anesthetic Prospective for Thyroid Surgery: What's New. *Gland Surg* (2017) 6(5):469–75. doi: 10.21037/gs.2017.05.02
27. Lu IC, Wu SH, Wu CW. Neuromuscular Blockade Management for Intraoperative Neural Monitoring. *Kaohsiung J Med Sci* (2020) 36(4):230–5. doi: 10.1002/kjm2.12153
28. Lu IC, Wu CW, Chang PY, Chen HY, Tseng KY, Randolph GW, et al. Reversal of Rocuronium-Induced Neuromuscular Blockade by Sugammadex Allows for Optimization of Neural Monitoring of the Recurrent Laryngeal Nerve. *Laryngoscope* (2016) 126(4):1014–9. doi: 10.1002/lary.25577
29. Empis de Vendin O, Schmartz D, Brunaud L, Fuchs-Buder T. Recurrent Laryngeal Nerve Monitoring and Rocuronium: A Selective Sugammadex Reversal Protocol. *World J Surg* (2017) 41(9):2298–303. doi: 10.1007/s00268-017-4004-9
30. Wu CW, Huang TY, Chen HC, Chen HY, Tsai TY, Chang PY, et al. Intra-Operative Neural Monitoring of Thyroid Surgery in a Porcine Model. *J Vis Exp* (2019) 144:e57919. doi: 10.3791/57919
31. Lu IC, Wu SH, Chang PY, Ho PY, Huang TY, Lin YC, et al. Precision Neuromuscular Block Management for Neural Monitoring During Thyroid Surgery. *J Invest Surg* (2020) 34(12):1389–96. doi: 10.1080/08941939.2020.1805055
32. Chai YJ, Lee JM, Won D, Jiwon Lee J, Hwang JY, Kim TK, et al. Comparison of Sugammadex Dose for Intraoperative Neuromonitoring in Thyroid Surgery: A Randomized Controlled Trial. *Laryngoscope* (2021) 131 (9):2154–9. doi: 10.1002/lary.29515
33. Fuchs-Buder T, Meistelman C, Raft J. Sugammadex: Clinical Development and Practical Use. *Korean J Anesthesiol* (2013) 65(6):495–500. doi: 10.4097/kjae.2013.65.6.495
34. Chiang FY, Wu CW, Chang PY, Wu SH, Chen HY, Lin YC, et al. Trans-Thyroid Cartilage Recording for Neural Monitoring of the Recurrent Laryngeal Nerve in Thyroid Surgery. *Laryngoscope* (2020) 130(4):E280–3. doi: 10.1002/lary.28049
35. Türk Y, Kıvratma G, Özdemir M, İçöz G, Makay Ö. The Use of Thyroid Cartilage Needle Electrodes in Intraoperative Neuromonitoring During Thyroidectomy: A Case-Control Study. *Head Neck* (2021) 43(11):3287–93. doi: 10.1002/hed.26810
36. Jung SM, Tae K, Song CM, Lee SH, Jeong JH, Ji YB. Efficacy of Transcartilaginous Electrodes for Intraoperative Neural Monitoring During Thyroid Surgery. *Clin Exp Otorhinolaryngol* (2020) 13(4):422–8. doi: 10.21053/ceo.2019.01529
37. Liddy W, Lawson BR, Barber SR, Kamani D, Shama M, Soylu S, et al. Anterior Laryngeal Electrodes for Recurrent Laryngeal Nerve Monitoring During Thyroid and Parathyroid Surgery: New Expanded Options for Neural Monitoring. *Laryngoscope* (2018) 128(12):2910–5. doi: 10.1002/lary.27362
38. Chiang FY, Lu IC, Chang PY, Dionigi G, Randolph GW, Sun H, et al. Comparison of EMG Signals Recorded by Surface Electrodes on Endotracheal Tube and Thyroid Cartilage During Monitored Thyroidectomy. *Kaohsiung J Med Sci* (2017) 33(10):503–9. doi: 10.1016/j.kjms.2017.06.014
39. Huang TY, Kim HY, Dionigi G, Lu IC, Chang PY, Chiang FY, et al. Laryngeal Neural Monitoring During Pediatric Thyroid Cancer Surgery—Is Transcartilage Recording a Preferable Method? *Cancers* (2021) 13(16):4051. doi: 10.3390/cancers13164051
40. Kim HY, Tufano RP, Randolph G, Marcin Barczyński M, Wu CW, Chiang FY, et al. Impact of Positional Changes in Neural Monitoring Endotracheal Tube on Amplitude and Latency of Electromyographic Response in Monitored Thyroid Surgery: Results From the Porcine Experiment. *Head Neck* (2016) 38 (Suppl 1):E1004–8. doi: 10.1002/hed.24145
41. Donmez T, Erdem VM, Sunamak O, Ozcevik H. Thyroid Surgery, Ionm and Sugammadex Sodium Relationships: Benefits in Sugammadex Sodium Use for Ionm. *Acta Endocrinol (Buchar)* (2019) 15(4):454–9. doi: 10.4183/aeb.2019.454
42. Gunes ME, Dural AC, Akarsu C, Guzey D, Sahbaz NA, Tulubas EK, et al. Effect of Intraoperative Neuromonitoring on Efficacy and Safety Using Sugammadex in Thyroid Surgery: Randomized Clinical Trial. *Ann Surg Treat Res* (2019) 97(6):282–90. doi: 10.4174/astr.2019.97.6.282
43. Kovac AL. Sugammadex: The First Selective Binding Reversal Agent for Neuromuscular Block. *J Clin Anesth* (2009) 21(6):444–53. doi: 10.1016/j.jclinane.2009.05.002
44. Yang LP, Keam SJ. Sugammadex: A Review of its Use in Anaesthetic Practice. *Drugs* (2009) 69(7):919–42. doi: 10.2165/00003495-200969070-00008
45. Chiang FY, Lu IC, Kuo WR, Lee KW, Chang NC, Wu CW. The Mechanism of Recurrent Laryngeal Nerve Injury During Thyroid Surgery–the Application of Intraoperative Neuromonitoring. *Surgery* (2008) 143(6):743–9. doi: 10.1016/j.surg.2008.02.006
46. Chiang FY, Lee KW, Chen HC, Chen HY, Lu IC, Kuo WR, et al. Standardization of Intraoperative Neuromonitoring of Recurrent Laryngeal Nerve in Thyroid Operation. *World J Surg* (2010) 34(2):223–9. doi: 10.1007/s00268-009-0316-8
47. Wu CW, Wang MH, Chen CC, Chen HC, Chen HY, Yu JY, et al. Loss of Signal in Recurrent Nerve Neuromonitoring: Causes and Management. *Gland Surg* (2015) 4(1):19–26. doi: 10.3978/j.issn.2227-684X.2014.12.03
48. Wu CW, Hao M, Tian M, Dionigi G, Tufano RP, Kim HY, et al. Recurrent Laryngeal Nerve Injury With Incomplete Loss of Electromyography Signal During Monitored Thyroidectomy-Evaluation and Outcome. *Langenbecks Arch Surg* (2017) 402(4):691–9. doi: 10.1007/s00423-016-1381-8
49. Wu CW, Dionigi G, Sun H, Liu X, Kim HY, Hsiao PJ, et al. Intraoperative Neuromonitoring for the Early Detection and Prevention of RLN Traction Injury in Thyroid Surgery: A Porcine Model. *Surgery* (2014) 155(2):329–39. doi: 10.1016/j.surg.2013.08.015

50. Schneider R, Randolph GW, Sekulla C, Phelan E, Thanh PN, Bucher M, et al. Continuous Intraoperative Vagus Nerve Stimulation for Identification of Imminent Recurrent Laryngeal Nerve Injury. *Head Neck* (2013) 35 (11):1591–8. doi: 10.1002/hed.23187

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Publisher's Note:** All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Endocrinology

ORIGINAL RESEARCH
published: 17 February 2022
doi: 10.3389/fendo.2021.774228

# A Nomogram to Predict Regrowth After Ultrasound-Guided Radiofrequency Ablation for Benign Thyroid Nodules

Lin Yan, Mingbo Zhang, Xinyang Li, YingYing Li and Yukun Luo*

Department of Ultrasound, First Medical Center, Chinese PLA General Hospital, Beijing, China

OPEN ACCESS

**Edited by:**
Kyung Tae,
Hanyang University, South Korea

**Reviewed by:**
Tzu-Yen Huang,
Kaohsiung Medical University, Taiwan
Leong-Perng Chan,
Kaohsiung Medical University Hospital, Taiwan
Ming Xu,
The First Affiliated Hospital of Sun Yat-Sen University, China
Jia Joanna Wang,
Kaohsiung Medical University Hospital, Taiwan

***Correspondence:**
Yukun Luo
lyk301@163.com

**Specialty section:**
This article was submitted to Thyroid Endocrinology, a section of the journal Frontiers in Endocrinology

**Received:** 11 September 2021
**Accepted:** 27 December 2021
**Published:** 17 February 2022

**Citation:**
Yan L, Zhang M, Li X, Li Y and Luo Y (2022) A Nomogram to Predict Regrowth After Ultrasound-Guided Radiofrequency Ablation for Benign Thyroid Nodules. Front. Endocrinol. 12:774228. doi: 10.3389/fendo.2021.774228

**Objective:** To develop and validate a nomogram to predict regrowth for patients with benign thyroid nodules undergoing radiofrequency ablation (RFA).

**Methods:** A total of 200 patients with 220 benign thyroid nodules who underwent RFA were included in this respective study. After RFA, patients were followed up at 1, 3, 6, and 12 months, and every 12 months thereafter. Regrowth was defined as an increase in nodule volume 50% over the previously recorded smallest volume. A nomogram was developed based on the variables identified by multivariate logistic regression and the model performance was evaluated by discrimination(concordance index) and calibration curves.

**Results:** The incidence of regrowth was 13.64% (30/220) after a mean follow-up period of 27.43 ± 17.99 months. Multivariate logistic regression revealed initial volume (OR = 1.047, 95%CI 1.020–1.075), vascularity (OR = 2.037, 95%CI 1.218–3.404), and location close to critical structure (OR = 4.713, 95%CI 1.817–12.223) were independent factors associated with regrowth. The prognostic nomogram incorporating these three factors achieved good calibration and discriminatory abilities with a concordance index of 0.779 (95%CI 0.686–0.872).

**Conclusions:** A prognostic nomogram was successfully developed to predict nodule regrowth after RFA, which might guide physician in stratifying patients and provide precise guidance for individualized treatment protocols.

**Keywords: ablation techniques, radiofrequency ablation, ultrasonography, nomograms, thyroid nodule**

## INTRODUCTION

Thyroid nodules are a common finding, present in up to 65% of the general population (1). Most nodules are benign and asymptomatic; however, a minority may require treatment because of the compressive symptomatic or cosmetic problems. Surgery is the standard treatment, which can remove a nodule completely at the cost of potential risk of complications, scar formation, and damage to normal thyroid parenchyma (2, 3). Thus, there has been a growing interest in developing the minimally invasive treatment that is much safer and allows gland retention for the treatment of benign thyroid nodules.

Ultrasound (US)-guided thermal ablation techniques, namely, radiofrequency ablation (RFA), microwave ablation (MWA), and laser ablation (LA) have been recommended as alternatives to surgery for benign thyroid nodules (3–7). These thermal ablation techniques have been successfully applied in treating patients with benign thyroid nodules (8–16). A recent meta-analysis included 24 studies on ablation and found that the volume reduction rates (VRR) at 6, 12, 24, and 36 months during the follow-up period were 60, 66, 62, and 53%, respectively (17). Moreover, the major complications rate was only 1.3% without life-threatening adverse events (18). Although satisfactory results were achieved, several studies found that approximately 5.6–38% of the treated nodule occurred regrowth after 2 to 3 years after ablation (19–23). Regrowth was defined as ≥50% volume increase compared to the previously recorded smallest volume (24). It usually occurred from the untreated peripheral area and additional ablation might be beneficial (19, 20, 22, 25, 26). Therefore, early evaluation of the risk of regrowth after ablation for benign thyroid nodules was essential for the treatment planning and follow-up strategy. Previous studies found that when dividing the total volume of ablated nodule after ablation into the ablated volume (Va) and the incompletely vital volume (Vv), an increased Vv could be an early sign of nodule regrowth (20, 27). Several other predictors were also reported to be associated with regrowth, namely, the 12-month VRR (23), energy applied per volume (EPV) (21), and residual vital ratio (RVR) (27). Because they could be only obtained during the follow-up after ablation, none of them could be used as an early predictor for nodule regrowth. Negro et al. (28) recent developed a machine learning algorithm to discriminate nodules with a VRR >50% at 12 months after RFA to identify the best candidates for effective treatment in one single session. However, accurate prediction of nodule regrowth after ablation is still lacking. A nomogram has been considered to be evidence-based, individualized and accurate in risk estimation, which has been applied to various malignancies (29–32). It has also been used to predict the clinical outcomes of patients with hepatocellular carcinoma who underwent thermal ablation (33–36). However, to our best knowledge, a prognostic nomogram for benign thyroid nodules following RFA has not yet been reported.

Therefore, the purpose of this study was to construct a nomogram to predict regrowth for patients with benign thyroid nodules undergoing RFA.

## MATERIALS AND METHODS

Approval for this retrospective study was obtained from the Institutional Review Board of our institution (No. S2019-2111-01). Written information consent was obtained from all the patients prior to RFA procedure.

### Patients

The study inclusion criteria were as follows: (1) nodules confirmed as benign *via* two separated fine-needle aspiration or core-needle biopsy; (2) nodules without suspicious malignant features on US examination, namely, very hypoechoic, irregular margin, taller than wide, microcalcification, evidence of extrathyroidal extension, and suspicious cervical lymph node; (3) patients with solid(≤10% of fluid component) or predominantly solid nodules (11–50% of fluid component) (24); (4) patients who were complained about cosmetic, symptomatic problems or rapid growth; (5) serum thyroid hormone and thyrotropin levels within normal ranges; (6) patients who were refusal or ineligibility for surgical treatment; and (7) follow-up time was larger than 6 months. Exclusion criteria were: (1) malignancy findings or follicular neoplasm by biopsy; (2) nodules with benign result by biopsy had suspicious of malignancy on US examination; and (3) follow-up time was less than 6 months.

We retrospectively searched the database for patients who would be eligible for this study and selected the period from August 2014 to December 2018. After the exclusion of patients, 200 patients with 220 benign thyroid nodules with full medical records were included in this study.

### Pre-Ablation Assessment

US were performed using a Siemens Acuson Sequoia 512 Ultrasound System (Siemens, Mountain View, CA, USA) or a Philips iU22 Ultrasound System (Philips Healthcare, Bothell, WA) or a Mindray M9 Ultrasound System (Mindray, Shenzhen, China). Before RFA, patients underwent US, biopsy, clinical evaluation, and also the laboratory examination. The nodule volume was calculated by ellipsoid formula: $V = \pi abc / 6$ (V, nodule volume; a, the largest nodule diameter; b and c, the other two perpendicular diameters of the nodule). Nodule location was classified as normal location and close to critical structures (less than 2 mm), namely, trachea, cervical carotid artery, jugular vein, esophagus and recurrent laryngeal nerve. According to the component, the nodules were categorized as solid (≤10% of fluid component) and predominantly solid (11–50% of fluid component) (24). Nodule vascularity was classified using a 1–4 grade scale (4): grade 1, no vascularity; grade 2, peripheral vascularity; grade 3, intra-nodular vascularity<50%; and grade 4, intra-nodular vascularity ≥50%. The nodule-related symptom score was self-measured by the patient using a 10-cm visual analogue scale (grades 0–10) (4). The cosmetic score was evaluated by the physician as follows: 1, no palpable mass; 2, no cosmetic problem but palpable mass; 3, a cosmetic problem on swallowing only; and 4, a readily detected cosmetic problem) (4). The laboratory examination included a complete blood count, thyroid function tests, and also the blood coagulation tests.

### Ablation Procedure

One experienced US physician performed all RFA procedures using a bipolar RFA generator (CelonLabPOWER, Olympus Surgical Technologies Europe) and an 18-gauge bipolar RF electrodes with 0.9 cm active tip (CelonProSurge micro 100-T09, Olympus Surgical Technologies Europe).

Patients were in supine position with their necks extended. RFA was performed using the trans-isthmic approach and moving-shot technique after local anesthesia with 1%

lidocaine. If the distance between the nodule and surrounding critical structures was <5 mm, hydrodissection technique was performed with injection of normal saline to prevent thermal injury. The output RFA power was 3–9 W. Contrast-enhanced ultrasound (CEUS) was conducted immediately after the RFA procedure to evaluate the ablation area. CEUS was performed after bolus injection of SonoVue (2.4 ml, Bracco), followed by a 5 ml of normal saline flush. If any enhancement existed in the treated nodule, a supplementary ablation was performed. The patients were observed for 1-2 h to check for possible adverse events or side effects.

## Post-Ablation Evaluation

After ablation, patients were followed up at 1, 3, 6, and 12 months and every 12 months thereafter and the volume, VRR, cosmetic and symptom scores were evaluated. VRR was calculated as follows: VRR = [(initial volume − final volume) × 100%] / initial volume (24). A >50% volume reduction at 12 months after ablation was defined as technical efficacy (24). Regrowth was defined as an increase in total volume 50% over the previously recorded smallest volume (24). According to the detection of regrowth, the nodules were divided into non-regrowth group and regrowth group. To exclude neoplastic transformation, CNB was performed to all the regrowth nodules, which was performed by a disposable 1.5- or 2.2-cm excursion, 20-gauge double-action spring-loaded needle (BARD Magumn, Bard Peripheral Vascular, Inc.) to the vital area of the nodule.

## Statistical Analysis

Continuous variables were reported as mean ± SD and categorical variables were expressed as numbers with percentages. Mann–Whitney U test were used to compare volume, VRR, symptom and cosmetic scores between the two groups. Univariate and multivariate logistic regression analysis of independent factors influencing regrowth were assessed, and the odds ratios (OR) with 95% confidence intervals (CI) were reported. A nomogram incorporated these independent factors was constructed to predict the probability of regrowth after RFA. The model performance was evaluated by discrimination and calibration (29). The discrimination of the nomogram was evaluated by the concordance index (C-index), which was equivalent to the area under the receiver operating characteristic curve. The value of the C-index varied between 0.5 and 1.0, with 1.0 indicating the perfect ability to correctly discriminate outcomes, and 0.5 indicating a random chance. Model validation was performed using bootstrap validation method with 1,000 resamples to quantify the overfitting of modeling strategy and predict future performance of the model (29). Calibration was evaluated using a calibration curve, which was a graphic representation of the relationship between the observed outcome frequencies and the predicted probabilities, with 1,000 bootstrap resamples of the study group. In a well-calibrated model, the predictions should fall on a 45-degree diagonal line. Statistical analyses were performed by using SPSS statistical software(Version 25.0) and R software version 3.6.2 (R Foundation for Statistical Computing). A two-sided *P* <0.05 was considered as statistically significant.

# RESULTS

In this study, 200 patients (176 females, 24 males, mean age 46.02 ± 11.95 years) with 220 benign thyroid nodules were enrolled (**Table 1**). Among these 200 patients, 183 patients had 1 nodule, 14 patients had 2 nodules and 3 patients had 3 nodules. The initial volume was 10.30 ± 13.41 ml and the largest diameter was 3.00 ± 1.37 cm. During RFA, the mean power of was 6.83 ± 3.11 W. The mean energy was 2,639.32 ± 2,173.70 J and the mean EPV was 648.04 ± 678.55 J/ml.

The mean follow-up time was 27.43 ± 17.99 months. The mean VRR was 88.82 ± 11.98% and the technical efficacy was 96.82% (213/220). Symptom score significantly decreased from 2.72 ± 2.15 to 0.95 ± 1.18 (*P* <0.001). Cosmetic score significantly decreased from 2.45 ± 1.22 to 1.34 ± 0.58 (*P* <0.001).

Regrowth was observed in 30 out 220 nodules (13.64%), which all occurred in the untreated peripheral area. The mean timing of regrowth was at 22.40 ± 12.10 months after RFA. All the regrowth nodules underwent additional RFA. The changes of volume and VRR in the two groups are present in **Table 2**. In the first 12 months, VRR in the two groups were nonsignificant (all *P* >0.05). However, at 24 months after RFA, VRR in the non-regrowth group were significantly larger than that in the regrowth group (90.39 ± 11.23% vs 78.65 ± 12.24%, *P* = 0.002) (**Figure 1**). A total of 7 nodules had volume reduction less than 50% at 12 months. Five nodules were in the regrowth group and 2 in the non-regrowth group (16.67% vs 1.05%, *P* <0.001). Representative cases in the two groups are shown in **Figures 2**, **3**.

The comparison of the two groups is shown in **Table 3**. The initial volume (19.33 ± 19.79 ml vs 8.88 ± 11.54 ml, *P* <0.001) and vascularity (3.0 ± 0.8 vs 2.4 ± 0.9, *P* = 0.002) in the regrowth group were significantly larger than those in the non-regrowth group. In the regrowth group, 33.67% (11/30) nodules were located close to the critical structure, while in the non-regrowth group 17.37% (33/190) of the nodules were close to the critical structure (*P* = 0.017). The energy and EPV in the regrowth group and non-regrowth group were nonsignificant (3,369.66 ± 2,281.05 J vs 2,527.84 ± 2,141.21 J, *P* = 0.070; 440.49 ± 684.83 J/ml vs 679.72 ± 673.78 J/ml, *P* = 0.085).

**TABLE 1** | Clinical characteristics.

| Characteristics | Data |
|---|---|
| No. of patients/nodules | 200/220 |
| Age (years) | 46.02 ± 11.95 |
| Sex (F/M) | 176/24 (88.0/12.0) |
| Component | |
| Solid/ Predominately solid | 155/65 (70.5/20.5) |
| Location | |
| Right lobe/Left lobe/Isthmus | 114/104/2 (51.82/47.27/0.91) |
| Largest diameter (cm) | 3.00 ± 1.37 |
| Initial volume (ml) | 10.30 ± 13.41 |
| Vascularity | 2.5 ± 0.9 |

*Data are presented as mean ± SD or number of nodules (percentages).*

**TABLE 2 |** Changes of volume and VRR at each follow-up period after RFA.

| Time (months) | Volume (ml) | | | | VRR (%) | | | |
|---|---|---|---|---|---|---|---|---|
| | Total | Non-regrowth group | Regrowth group | *P*-value | Total | Non-regrowth group | Regrowth group | *P*-value |
| 1 | 4.89 ± 6.19 | 4.60 ± 6.22 | 6.86 ± 5.75 | 0.007 | 48.62 ± 19.63 | 48.26 ± 18.79 | 51.12 ± 25.03 | 0.350 |
| 3 | 2.72 ± 3.79 | 2.44 ± 3.54 | 4.54 ± 4.82 | 0.023 | 69.89 ± 16.61 | 69.59 ± 16.50 | 71.83 ± 17.60 | 0.394 |
| 6 | 2.60 ± 4.13 | 2.21 ± 3.44 | 4.65 ± 6.37 | 0.015 | 79.42 ± 13.44 | 79.22 ± 13.58 | 80.46 ± 12.95 | 0.595 |
| 12 | 2.06 ± 4.07 | 1.76 ± 3.36 | 4.42 ± 7.39 | 0.031 | 84.38 ± 14.07 | 84.92 ± 13.04 | 80.08 ± 20.47 | 0.489 |
| 24 | 1.90 ± 3.81 | 1.48 ± 3.13 | 4.60 ± 6.31 | 0.005 | 88.82 ± 11.98 | 90.39 ± 11.23 | 78.65 ± 12.24 | 0.002 |

*Data are presented as mean ± SD.*

Multivariate logistic regression revealed initial volume (OR = 1.047, 95%CI 1.020–1.075), vascularity (OR = 2.037, 95%CI 1.218–3.404) and location close to critical structure (OR = 4.713, 95%CI 1.817–12.223) were independent factors associated with regrowth (**Table 4**). A nomogram based on these three independent factors to predict nodule regrowth after RFA was constructed (**Figure 4**). Each factor was allocated a predicting score, and the sum of three scores was located on the total points axis, suggesting the prediction of regrowth probabilities. Higher total points were associated with a higher regrowth probability during the follow-up. The discriminative ability of the model for regrowth was assessed using the C-index, which was 0.779 (95%CI 0.686–0.872) (**Figure 5**). The accuracy of the model and potential model overfit were assessed by bootstrap validation with 1,000 re-samplings. The calibration curves graphically showed good agreement between the actual and nomogram-predicted regrowth (**Figure 6**).

No major complications occurred during or after RFA. Eighteen patients (9.00%) had local pain or discomfort and resolved spontaneously within 1 week.

## DISCUSSION

No prediction model for regrowth after thermal ablation for benign thyroid nodules has been reported to date. This study developed and validated a nomogram to predict regrowth after RFA for benign thyroid nodules. The C-index of this nomogram was 0.779 with a good calibration, which suggested that the nomogram could successfully stratified patients before treatment according to their risk of regrowth and yielded excellent performance. This model would be helpful to guide decision-making and provide individualized ablation management.

As alternatives to surgery for benign thyroid nodules by guidelines (4–6), the ablation efficacy has attracted much attention. The volume reduction after ablation was significant with a low rate of complications (17, 18, 21). However, the effective treatment of ablation should be sustainable for longer follow-up period. Some studies showed a tendency for the nodules to regrow during the follow-up and the reported incidence of regrowth after RFA, MWA and LA was 5.6–24.1% (19–21), 14.55% (22) and 37.8–38% (21, 23), respectively. Several predictors were reported to be associated with regrowth, but the optimal prediction of regrowth was still unclear. Sim et al. (20) found that the total volume of nodule after ablation could be divided into Va and Vv. The results found that Vv increase which was defined as a more than 50% increase compared to the previously reported smallest Vv, occurred earlier than regrowth and might be used as an early sign (20). However, Vv increase was observed at 27.5 ± 18.5 months after RFA, making its predictive value limited. Negro et al. (23) reported that a 12-month VRR <50% increased the risk of regrowth after LA with an OR of 11.7 (95%CI 4.2–32.2). However, compared with LA, the efficacy of RFA or MWA seemed to be much better with a higher volume reduction (17, 37–40) and a lower regrowth rate (19–23). The predictive value of 12-month VRR of these two ablation techniques still needed further investigation. Furthermore, whether EPV could affect ablation efficacy or regrowth remained controversial. A higher EPV was found to be associated with the efficacy of ablation (21, 41, 42). Wang et al. (22) found that EPV in the non-regrowth group was significantly larger than that in the regrowth group after MWA. However, contradictory results were also observed. Negro et al. (28) found that EPV was significantly larger in the nodules with 12-month VRR <50% than that in nodules with 12-month VRR ≥50%, indicating the former were not treated with an insufficient amount of energy. In this study, although EPV in the non-regrowth group were larger than that in the regrowth group, no significant differences were found. The reason of different results might be related to the diverse thermal ablation techniques, nodule structure and volume, which could lead to different production and distribution of thermal energy (21), making the predict value of EPV still uncertain.

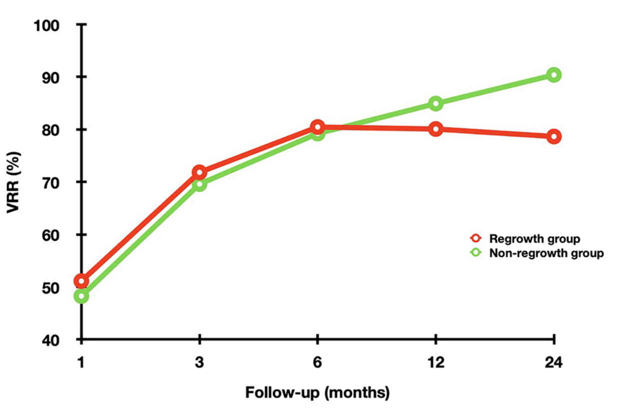



**FIGURE 1 |** The changes of VRR in the non-regrowth and regrowth groups at each follow-up point after RFA. In the first 12 months, VRR in the two groups were nonsignificant (all *P* >0.05). However, at 24 months after RFA, VRR in the non-regrowth group were significantly larger than that in the regrowth group (*P* = 0.002).

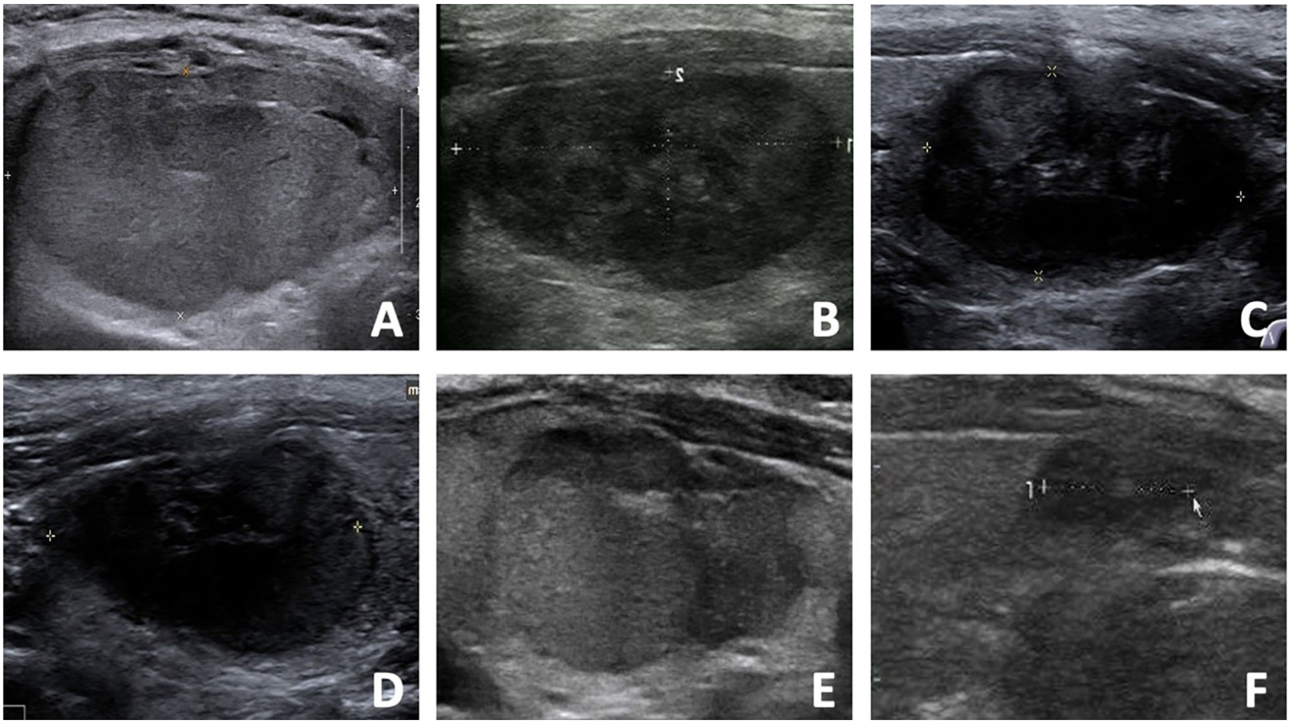



**FIGURE 2** | The US images of a 48- year-old male with a benign thyroid nodule in the regrowth group. **(A)** The initial volume of nodule was 22.27 ml before RFA. The nodule was located in the dangerous location, and the vascularity was grade 4. The risk of regrowth by the nomogram was 67%. **(B)** At 1 month after RFA, the volume was 5.28 ml and VRR was 76.29%. **(C)** At 3 months after RFA, the volume was 3.48 ml and VRR was 84.37%. **(D)** At 6 months after RFA, the volume was 2.89 ml and VRR was 87.02%. **(E)** At 12 months after RFA, the US showed nodule regrowth and the volume was 4.34 ml and VRR was 80.51%. Additional RFA was performed. **(F)** At 6 months after additional RFA, the volume was 1.65 ml and VRR was 92.59%.

CLT, also known as Hashimoto thyroiditis, is an autoimmune disease that destroys thyroid cells by cell and antibody-mediated immune process. The pathology of the disease involves the formation of antithyroid antibodies that attack the thyroid tissue, causing widespread lymphocyte infiltration, fibrosis, and parenchymal atrophy of the thyroid tissue. This study found that CLT was not an independent factor related to regrowth by multivariate analysis. It was consistent with previous study (43), which reported that the recovery after RFA in patients with PTMC + CLT was similar to that in patients with only PTMC. It suggested that although the thyroid parenchyma in the case of CLT was already infiltrated by diffuse chronic inflammatory cells, it did not influence the clinical outcomes of RFA for benign thyroid nodules.

In this study, a nomogram incorporated three easily identifiable variables was developed to predict nodule regrowth after RFA. The performance was well supported by the C-index of 0.779 and the calibration curves demonstrating the optimal agreements between prediction and actual observation, which guaranteed the repeatability and reliability of the established nomogram. To the best of our knowledge, it was the first nomogram to predict nodule regrowth after ablation, which could be helpful to improve the patient-physician communication, decision-making and individualized treatment management. Though this easy-to-use scoring system, physicians could perform an individualized prediction before ablation to identify patients at different risk of regrowth. Patients with a high score had an increased probability of nodule regrowth and were potential candidates for additional treatment. Therefore, these patients needed to be provided appropriate ablation strategy and intensive follow-up management or recommended surgery if they do not want multiple sessions.

So far, no consensus about the specific indication or optimal timing of additional ablation for benign thyroid nodules was achieved (43). In most studies, additional ablation was usually determined based on clinical evaluation findings, namely, incompletely symptom resolution, or unsatisfactory volume reduction, or regrowth (4). Sim et al. (20) suggested that additional ablation might be performed after the detection of Vv increase because it was important to identify regrowth. A recent study compared the efficacy of additional RFA after different indications. Additional RFA performed after Vv increased revealed superior efficacy, including a significant greater volume reduction improvement of cosmetic and symptom scores (44). It was because that the residual volume was markedly larger when Vv increase was observed. Additional ablation could be applied to a larger residual zone and achieve

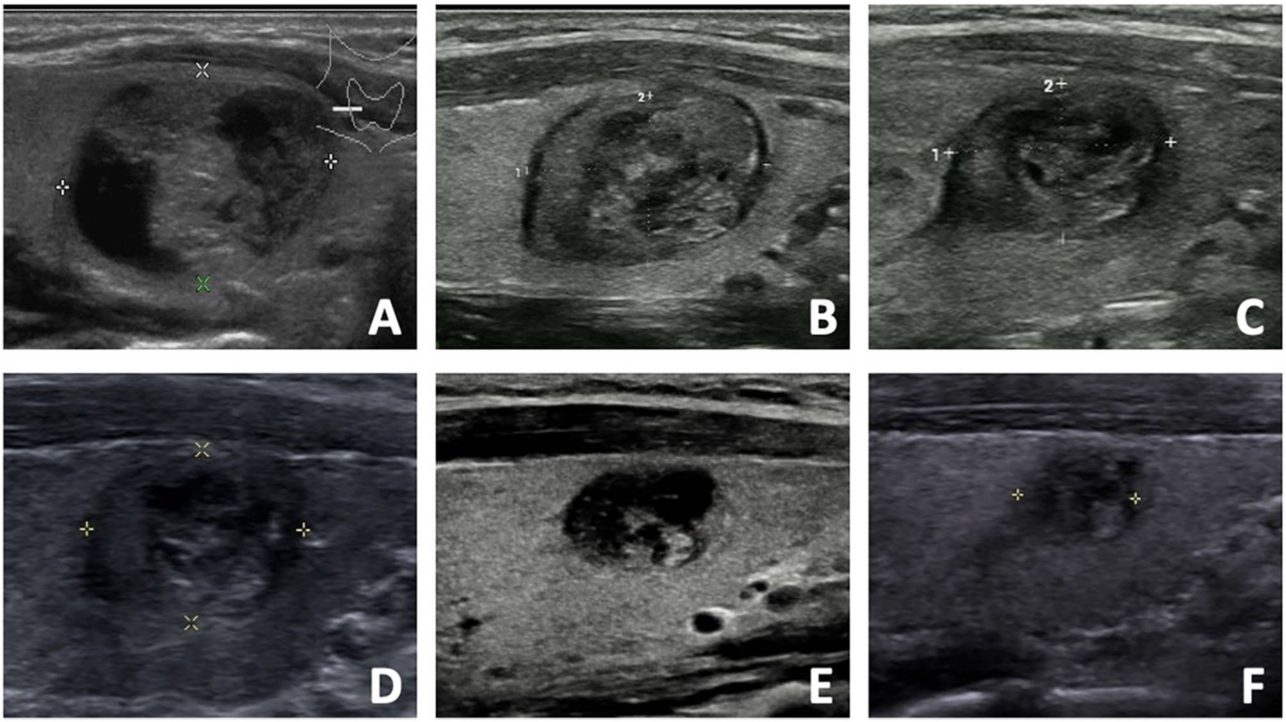



**FIGURE 3** | The US images of a 33- year-old female with a benign thyroid nodule in the non-regrowth group. **(A)** The initial volume of nodule was 5.32 ml before RFA. The nodule was located in the normal location, and the vascularity was grade 1. The risk of regrowth by the nomogram was 2.1%. **(B)** At 1 month after RFA, the volume was 1.58 ml and VRR was 70.30%. **(C)** At 3 months after RFA, the volume was 0.88 ml and VRR was 83.46%. **(D)** At 6 months after RFA, the volume was 0.76 ml and VRR was 85.71%. **(E)** At 12 months after RFA, the volume was 0.32 ml and VRR was 93.98%. **(F)** At 18 months after RFA, the volume was 0.18 ml and VRR was 96.62%.

substantial incremental volume reduction. Therefore, to maximize the efficacy of ablation, additional RFA could be considered after the detection of Vv increase.

This study found that initial volume, location close to critical structure and vascularity were independent factors related to regrowth. Initial volume has been recognized as an important factor for regrowth (19, 20, 43). It might be difficult to ablate all the nodule margin of a large nodule by a single session, leading to incomplete treatment and subsequent regrowth. Location was another factor associated with regrowth (22). The neck was relatively narrow, where contained many critical structures. As a result, complications might be inevitable when a nodule located close to the critical structures. For hyper-vascular nodules, the possibility of regrowth also existed (22). The vasculature in the thyroid nodules could cause heat-sink effect, which decreased the ablation efficacy and induced regrowth (45). To obtain complete ablation, several techniques have been recommended, namely, the moving shot technique, the hydrodissection

**TABLE 3 |** The comparison between the non-regrowth and regrowth groups.

| Characteristics | Non-regrowth group | Regrowth group | OR (95%CI) | *P*-value |
|---|---|---|---|---|
| Pre-treated variables | | | | |
| Age (years) | 46.84 ± 11.98 | 42.55 ± 11.35 | 0.970 (0.938–1.003) | 0.074 |
| Female | 163 (85.8) | 24 (80.0) | 0.663 (0.248–1.771) | 0.412 |
| Solid | 137 (72.11) | 18 (60.00) | 0.580 (0.262–1.287) | 0.180 |
| Initial volume (ml) | 8.88 ± 11.54 | 19.33 ± 19.79 | 1.043 (1.019–1.068) | <0.001 |
| Location close to critical structure | 33 (17.37) | 11 (33.67) | 2.754 (1.199–6.330) | 0.017 |
| Hashimoto's thyroiditis | 34 (17.89) | 3 (10) | 0.510 (0.146–1.778) | 0.290 |
| Vascularity | 2.4 ± 0.9 | 3.0 ± 0.8 | 2.161 (1.312–3.561) | 0.002 |
| Ablate-related variables | | | | |
| Power (W) | 6.88 ± 3.25 | 6.50 ± 2.01 | 0.957 (0.831–1.101) | 0.535 |
| Energy (J) | 2,527.84 ± 2,141.21 | 3,369.66 ± 2,281.05 | 1.148 (0.989–1.333) | 0.070 |
| EPV (J/ml) | 679.72 ± 673.78 | 440.49 ± 684.83 | 0.999 (0.998–1.000) | 0.085 |

*Data are presented as mean ± SD or number of tumors (percentages).*
*EPV, Energy per volume.*

**TABLE 4** | Multivariate logistic regression analysis of regrowth.

| Characteristics | OR | 95%CI | *P*-value |
|---|---|---|---|
| Initial volume (ml) | 1.047 | 1.020–1.075 | <0.001 |
| Location close to critical structure | 4.713 | 1.817–12.223 | 0.001 |
| Vascularity | 2.037 | 1.218–3.404 | 0.007 |

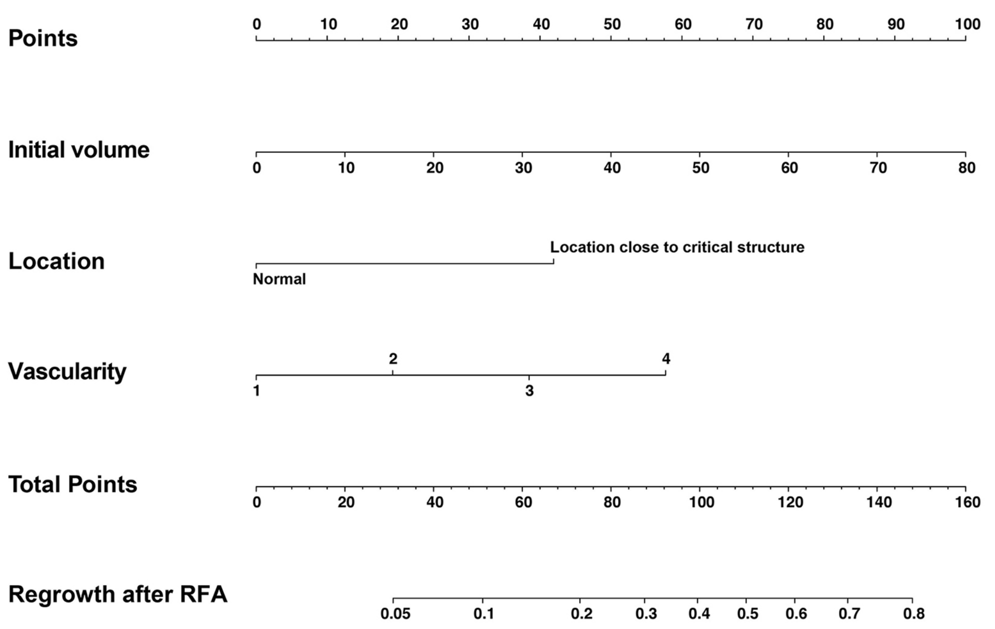



**FIGURE 4** | The nomogram for predicting regrowth after RFA for benign thyroid nodules. A nomogram based on initial volume, vascularity and location was constructed.

technique, and vascular ablation techniques (4). The moving shot technique has been suggested as a suitable method for the peripheral ablation. This technique could treat the nodule completely and safely by dividing it into multiple small ablation units (45). Moreover, the hydrodissection technique was effective to separate the nodule from the adjacent critical structures (45, 46). By injecting the fluid into the naturally existed gap between the cervical anatomical structures, a protective thermal barrier was formed to minimize the complications and improve the efficacy. Additionally, vascular ablation techniques have been introduced as an advanced technique for hyper-vascular nodules (45). The main feeding artery was ablated first followed by the draining vein along the nodule margin, which could not only damage the blood vessels and decrease the heat-sink effect, but also prevent incomplete ablation of the peripheral area.

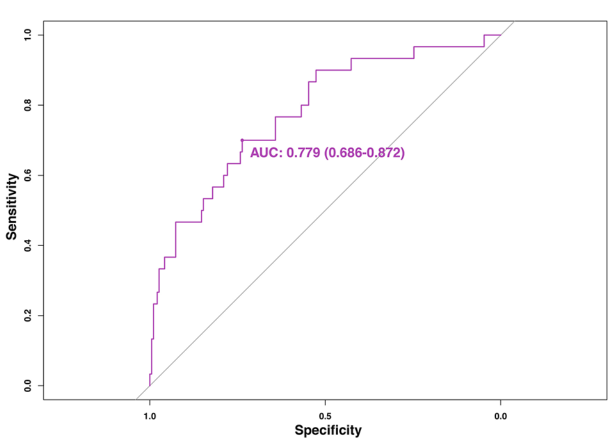



**FIGURE 5** | The ROC of the nomogram for predicting regrowth in patients with benign thyroid nodules after RFA. AUC for the nomogram to predict regrowth was 0.779 (95%CI 0.686–0.872).

This study had some limitations. First, because of the retrospective nature, sample bias was existed. Moreover, some potentially variables were not available in the data set and thus could not be included in this nomogram, such as the experience of US physician, different ablation techniques and inflammatory response caused by ablation. A large prospective study is needed to further confirm the reliability of the nomogram. Second, although this nomogram was internally validated using bootstrap validation, the clinical use must be externally validated and evaluated. Third, the follow-up was relatively short. There were two peaks of nodule regrowth (20). First

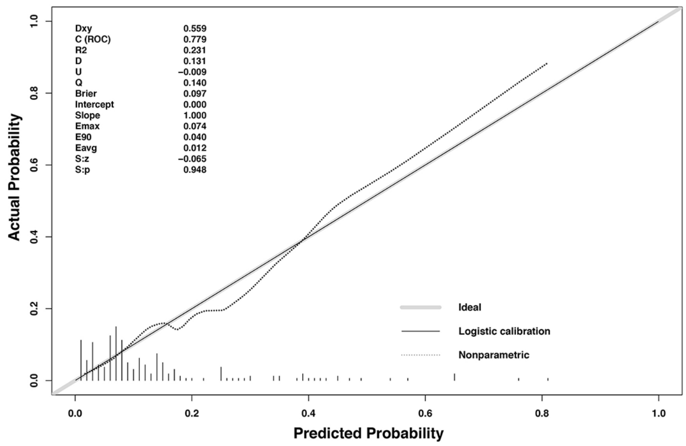



**FIGURE 6** | The calibration curves for predicting regrowth in patients with benign thyroid nodules after RFA. The x-axis represents the nomogram predicted probability and the y-axis represents the actual probability. The calibration curves were close to the 45° line. The diagonal dashed line indicates ideal prediction by a perfect model, and the solid line represents the predictive power of the nomogram. The closer the solid line is to the dotted line, the better is the predictive power of the model.

peak of regrowth ranged from 1 year to 2 or 3 years, and the second one appeared later than 5 years (20). The predictive value of this nomogram on the second peak of regrowth is still needed further investigation.

## CONCLUSION

This study constructed a nomogram to predict regrowth in patients with benign thyroid nodules after RFA with good discrimination and calibration capabilities. The use of this prognostic nomogram may guide physician in stratifying patients and provide precise guidance for individualized treatment protocols.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary files, further inquiries can be directed to the corresponding authors.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of Chinese PLA General Hospital. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

YL interpreted the patient data and drafted the manuscript. LYK performed RFA procedure, conceived of the study and coordination. MBZ, XYL, YYL collected and analyzed the patient data. All authors contributed to the article and approved the submitted version.

## FUNDING

This study is supported by the Popularization of Military Medical and Health Achievements (No. 21WKS09).

## REFERENCES

1. Durante C, Grani G, Lamartina L, Filetti S, SJ M, Cooper DS. The Diagnosis and Management of Thyroid Nodules: A Review. *JAMA* (2018) 319(9):914–24. doi: 10.1001/jama.2018.0898
2. Gharib H, Papini E, Paschke R, Duick DS, Valcavi R, Hegedus L, et al. American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association Medical Guidelines for Clinical Practice for the Diagnosis and Management of Thyroid Nodules. *J Endocrinol Invest* (2010) 33(5 Suppl):1–50. doi: 10.4158/10024.GL
3. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients With Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid* (2015) 26(1):1–133. doi: 10.1089/thy.2015.0020
4. Kim JH, Baek JH, Lim HK, Ahn HS, Baek SM, Choi YJ, et al. 2017 Thyroid Radiofrequency Ablation Guideline: Korean Society of Thyroid Radiology. *Korean J Radiol* (2018) 19(4):632–55. doi: 10.3348/kjr.2018.19.4.632
5. Papini E, Pacella CM, Solbiati LA, Achille G, Barbaro D, Bernardi S, et al. Minimally-Invasive Treatments for Benign Thyroid Nodules: A Delphi-Based Consensus Statement From the Italian Minimally-Invasive Treatments of the Thyroid (MITT) Group. *Int J Hyperthermia* (2019) 36(1):376–82. doi: 10.1080/02656736.2019.1575482
6. Dietrich CF, Müller T, Bojunga J, Dong Y, Mauri G, Radzina M, et al. Statement and Recommendations on Interventional Ultrasound as a Thyroid

Diagnostic and Treatment Procedure. *Ultrasound Med Biol* (2018) 44(1):14–36. doi: 10.1016/j.ultrasmedbio.2017.08.1889

7. Garberoglio R, Aliberti C, Appetecchia M, Attard M, Boccuzzi G, Boraso F, et al. Radiofrequency Ablation for Thyroid Nodules: Which Indications? The First Italian Opinion Statement. *J Ultrasound* (2015) 18(4):423–30. doi: 10.1007/s40477-015-0169-y
8. Deandrea M, Sung JY, Limone P, Mormile A, Garino F, Ragazzoni F, et al. Efficacy and Safety of Radiofrequency Ablation Versus Observation for Nonfunctioning Benign Thyroid Nodules: A Randomized Controlled International Collaborative Trial. *Thyroid* (2015) 25(8):890–6. doi: 10.1089/thy.2015.0133
9. Cesareo R, Pasqualini V, Simeoni C, Sacchi M, Saralli E, Campagna G, et al. Prospective Study of Effectiveness of Ultrasound-Guided Radiofrequency Ablation Versus Control Group in Patients Affected by Benign Thyroid Nodules. *J Clin Endocrinol Metab* (2015) 100(2):460–6. doi: 10.1210/jc.2014-2186
10. Hamidi O, Callstrom MR, Lee RA, Dean D, Castro MR, Morris JC, et al. Outcomes of Radiofrequency Ablation Therapy for Large Benign Thyroid Nodules: A Mayo Clinic Case Series. *Mayo Clin Proc* (2018) 93(8):1018–25. doi: 10.1016/j.mayocp.2017.12.011
11. Radzina M, Cantisani V, Rauda M, Nielsen MB, Ewertsen C, D'Ambrosio F, et al. Update on the Role of Ultrasound Guided Radiofrequency Ablation for Thyroid Nodule Treatment. *Int J Surg* (2017) 41:S82–93. doi: 10.1016/j.ijsu.2017.02.010
12. Rabuffi P, Spada A, Bosco D, Bruni A, Vagnarelli S, Ambrogi C, et al. Treatment of Thyroid Nodules With Radiofrequency: A 1-Year Follow-Up Experience. *J Ultrasound* (2019) 22(2):193–9. doi: 10.1007/s40477-019-00375-4
13. Kotewall N, Lang BHH. High-Intensity Focused Ultrasound Ablation as a Treatment for Benign Thyroid Diseases: The Present and Future. *Ultrasonography* (2019) 38(2):135–42. doi: 10.14366/usg.18040
14. Bernardi S, Dobrinja C, Carere A, Giudici F, Calabrò V, Zanconati F, et al. Patient Satisfaction After Thyroid RFA Versus Surgery for Benign Thyroid Nodules: A Telephone Survey. *Int J Hyperthermia* (2018) 35(1):150–8. doi: 10.1080/02656736.2018.1487590
15. Lang BHH, Woo YC, Chiu KW. Two-Year Efficacy of Single-Session High-Intensity Focused Ultrasound (HIFU) Ablation of Benign Thyroid Nodules. *Eur Radiol* (2019) 29(1):93–101. doi: 10.1007/s00330-018-5579-8
16. Lin WC, Kan NN, Chen HL, Luo SD, Tung YC, Chen WC, et al. Efficacy and Safety of Single-Session Radiofrequency Ablation for Benign Thyroid Nodules of Different Sizes: A Retrospective Study. *Int J Hyperthermia* (2020) 37(1):1082–9. doi: 10.1080/02656736.2020.1782485
17. Trimboli P, Castellana M, Sconfienza LM, Virili C, Pescatori LC, Cesareo R, et al. Efficacy of Thermal Ablation in Benign Non-Functioning Solid Thyroid Nodule: A Systematic Review and Meta-Analysis. *Endocrine* (2019) 67(1):35–43. doi: 10.1007/s12020-019-02019-3
18. Chung SR, Suh CH, Baek JH, Park HS, Choi YJ, Lee JH. Safety of Radiofrequency Ablation of Benign Thyroid Nodules and Recurrent Thyroid Cancers: A Systematic Review and Meta-Analysis. *Int J Hyperthermia* (2017) 33(8):920–30. doi: 10.1080/02656736.2017.1337936
19. Lim HK, Lee JH, Ha EJ, Sung JY, Kim JK, Baek JH. Radiofrequency Ablation of Benign Non-Functioning Thyroid Nodules: 4-Year Follow-Up Results for 111 Patients. *Eur Radiol* (2013) 23(4):1044–9. doi: 10.1007/s00330-012-2671-3
20. Sim JS, Baek JH, Lee J, Cho W, Jung SI. Radiofrequency Ablation of Benign Thyroid Nodules: Depicting Early Sign of Regrowth by Calculating Vital Volume. *Int J Hyperthermia* (2017) 33(8):905–10. doi: 10.1080/02656736.2017.1309083
21. Bernardi S, Giudici F, Cesareo R, Antonelli G, Cavallaro M, Deandrea M, et al. Five-Year Results of Radiofrequency and Laser Ablation of Benign Thyroid Nodules: A Multicenter Study From the Italian Minimally Invasive Treatments of the Thyroid Group. *Thyroid* (2020) 30(12):1759–70. doi: 10.1089/thy.2020.0202
22. Wang B, Han ZY, Yu J, Cheng Z, Liu F, Yu XL, et al. Factors Related to Recurrence of the Benign Non-Functioning Thyroid Nodules After Percutaneous Microwave Ablation. *Int J Hyperthermia* (2017) 33(4):459–64. doi: 10.1080/02656736.2016.1274058
23. Negro R, Greco G, Deandrea M, Rucco M, Trimboli P. Twelve-Month Volume Reduction Ratio Predicts Regrowth and Time to Regrowth in Thyroid Nodules Submitted to Laser Ablation: A 5-Year Follow-Up Retrospective Study. *Korean J Radiol* (2020) 21(6):764–72. doi: 10.3348/kjr.2019.0798
24. Mauri G, Pacella CM, Papini E, Solbiati L, Goldberg SN, Ahmed M, et al. Image-Guided Thyroid Ablation: Proposal for Standardization of Terminology and Reporting Criteria. *Thyroid* (2019) 29(5):611–8. doi: 10.1089/thy.2018.0604
25. Dossing H, Bennedbaek FN, Hegedus L. Long-Term Outcome Following Interstitial Laser Photocoagulation of Benign Cold Thyroid Nodules. *Eur J Endocrinol* (2011) 165(1):123–8. doi: 10.1530/eje-11-0220
26. Valcavi R, Riganti F, Bertani A, Formisano D, Pacella CM. Percutaneous Laser Ablation of Cold Benign Thyroid Nodules: A 3-Year Follow-Up Study in 122 Patients. *Thyroid* (2010) 20(11):1253–61. doi: 10.1089/thy.2010.0189
27. Yan L, Luo Y, Xie F, Zhang M, Xiao J. Residual Vital Ratio: Predicting Regrowth After Radiofrequency Ablation for Benign Thyroid Nodules. *Int J Hyperthermia* (2020) 37(1):1139–48. doi: 10.1080/02656736.2020.1825835
28. Negro R, Rucco M, Creanza A, Mormile A, Limone PP, Garberoglio R, et al. Machine Learning Prediction of Radiofrequency Thermal Ablation Efficacy: A New Option to Optimize Thyroid Nodule Selection. *Eur Thyroid J* (2020) 9(4):205–12. doi: 10.1159/000504882
29. Iasonos A, Schrag D, Raj GV, Panageas KS. How to Build and Interpret a Nomogram for Cancer Prognosis. *J Clin Oncol* (2008) 26(8):1364–70. doi: 10.1200/JCO.2007.12.9791
30. Hu H, Han H, Han XK, Wang WP, Ding H. Nomogram for Individualised Prediction of Liver Failure Risk After Hepatectomy in Patients With Resectable Hepatocellular Carcinoma: The Evidence From Ultrasound Data. *Eur Radiol* (2018) 28(2):877–85. doi: 10.1007/s00330-017-4900-2
31. Wang Y, Li J, Xia Y, Gong R, Wang K, Yan Z, et al. Prognostic Nomogram for Intrahepatic Cholangiocarcinoma After Partial Hepatectomy. *J Clin Oncol* (2013) 31(9):1188–95. doi: 10.1200/jco.2012.41.5984
32. Levy DA, Li H, Sterba KR, Hughes-Halbert C, Warren GW, Nussenbaum B, et al. Development and Validation of Nomograms for Predicting Delayed Postoperative Radiotherapy Initiation in Head and Neck Squamous Cell Carcinoma. *JAMA Otolaryngol Head Neck Surg* (2020) 146(5):455–64. doi: 10.1001/jamaoto.2020.0222
33. An C, Li X, Yu X, Cheng Z, Han Z, Liu F, et al. Nomogram Based on Albumin-Bilirubin Grade to Predict Outcome of the Patients With Hepatitis C Virus-Related Hepatocellular Carcinoma After Microwave Ablation. *Cancer Biol Med* (2019) 16(4):797–810. doi: 10.20892/j.issn.2095-3941.2018.0486
34. Ni JY, Fang ZT, Sun HL, An C, Huang ZM, Zhang TQ, et al. A Nomogram to Predict Survival of Patients With Intermediate-Stage Hepatocellular Carcinoma After Transarterial Chemoembolization Combined With Microwave Ablation. *Eur Radiol* (2020) 30(4):2377–90. doi: 10.1007/s00330-019-06438-8
35. Huang Z, Gu Y, Zhang T, Wu S, Wang X, An C, et al. Nomograms to Predict Survival Outcomes After Microwave Ablation in Elderly Patients (>65 Years Old) With Early-Stage Hepatocellular Carcinoma. *Int J Hyperthermia* (2020) 37(1):808–18. doi: 10.1080/02656736.2020.1785556
36. Kao WY, Su CW, Chiou YY, Chiu NC, Liu CA, Fang KC, et al. Hepatocellular Carcinoma: Nomograms Based on the Albumin-Bilirubin Grade to Assess the Outcomes of Radiofrequency Ablation. *Radiology* (2017) 285(2):670–80. doi: 10.1148/radiol.2017162382
37. Shi YF, Zhou P, Zhao YF, Liu WG, Tian SM, Liang YP. Microwave Ablation Compared With Laser Ablation for Treating Benign Thyroid Nodules in a Propensity-Score Matching Study. *Front Endocrinol (Lausanne)* (2019) 10: org/10.3389/fendo.2019.00874. doi: 10.3389/fendo.2019.00874
38. Ha EJ, Baek JH, Kim KW, Pyo J, Lee JH, Baek SH, et al. Comparative Efficacy of Radiofrequency and Laser Ablation for the Treatment of Benign Thyroid Nodules: Systematic Review Including Traditional Pooling and Bayesian Network Meta-Analysis. *J Clin Endocrinol Metab* (2015) 100(5):1903–11. doi: 10.1210/jc.2014-4077
39. Cesareo R, Manfrini S, Pasqualini V, Ambrogi C, Sanson G, Gallo A, et al. Laser Ablation Versus Radiofrequency Ablation for Thyroid Nodules: 12-Month Results of a Randomized Trial (LARA II Study). *J Clin Endocrinol Metab* (2021) 106(6):1692–701. doi: 10.1210/clinem/dgab102
40. Cesareo R, Pacella CM, Pasqualini V, Campagna G, Iozzino M, Gallo A, et al. Laser Ablation Versus Radiofrequency Ablation for Benign Non-Functioning Thyroid Nodules: Six-Month Results of a Randomized, Parallel, Open-Label, Trial (LARA Trial). *Thyroid* (2020) 30(6):847–56. doi: 10.1089/thy.2019.0660
41. Deandrea M, Trimboli P, Mormile A, Cont AT, Milan L, Buffet C, et al. Determining an Energy Threshold for Optimal Volume Reduction of Benign

Thyroid Nodules Treated by Radiofrequency Ablation. *Eur Radiol* (2021) 31 (7):5189–97. doi: 10.1007/s00330-020-07532-y

42. Trimboli P, Deandrea M. Treating Thyroid Nodules by Radiofrequency: Is the Delivered Energy Correlated With the Volume Reduction Rate? A Pilot Study. *Endocrine* (2020) 69(3):682–7. doi: 10.1007/s12020-020-02275-8
43. Zhang Y, Zhang MB, Luo YK, Li J, Zhang Y, Tang J. Effect of Chronic Lymphocytic Thyroiditis on the Efficacy and Safety of Ultrasound-Guided Radiofrequency Ablation for Papillary Thyroid Microcarcinoma. *Cancer Med* (2019) 8(12):5450–8. doi: 10.1002/cam4.2406
44. Sim JS, Baek JH. Long-Term Outcomes Following Thermal Ablation of Benign Thyroid Nodules as an Alternative to Surgery: The Importance of Controlling Regrowth. *Endocrinol Metab (Seoul)* (2019) 34(2):117–23. doi: 10.3803/EnM.2019.34.2.117
45. Yan L, Luo Y, Zhang M, Xiao J. Vital Volume Increase Versus Clinical Evaluation as the Indication of Additional Radiofrequency Ablation for Benign Thyroid Nodule: A Single Center Retrospective Study. *Int J Hyperthermia* (2020) 37(1):777–85. doi: 10.1080/02656736.2020.1778197
46. Park HS, Baek JH, Park AW, Chung SR, Choi YJ, Lee JH. Thyroid Radiofrequency Ablation: Updates on Innovative Devices and Techniques. *Korean J Radiol* (2017) 18(4):615–23. . doi: 10.3348/kjr.2017.18.4.615

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Publisher's Note:** All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Endocrinology

ORIGINAL RESEARCH
published: 10 March 2022
doi: 10.3389/fendo.2022.843573

# The Application Value of the Central Lymph Node Metastasis Risk Assessment Model in Papillary Thyroid Microcarcinoma of Stage cN0: A Study of 828 Patients

*Jinqiu Wang[1], Xianneng Sheng[1], Yongping Dai[1], Jiabo Zhang[1], Lihua Song[2] and Yu Guo[1]**

*[1] Department of Thyroid and Breast Surgery, Ningbo First Hospital, Ningbo, China, [2] School of Medicine, Ningbo University, Ningbo, China*

OPEN ACCESS

**Edited by:**
*Che-Wei Wu,*
*Kaohsiung Medical University, Taiwan*

**Reviewed by:**
*Hyoung Shin Lee,*
*Kosin University, South Korea*
*Yong Bae Ji,*
*Hanyang University, South Korea*
*Jia Joanna Wang,*
*Kaohsiung Medical University Hospital, Taiwan*

***Correspondence:**
*Yu Guo*
*guoyu308@163.com*

**Specialty section:**
*This article was submitted to Thyroid Endocrinology, a section of the journal Frontiers in Endocrinology*

**Received:** *26 December 2021*
**Accepted:** *08 February 2022*
**Published:** *10 March 2022*

**Citation:**
*Wang J, Sheng X, Dai Y, Zhang J, Song L and Guo Y (2022) The Application Value of the Central Lymph Node Metastasis Risk Assessment Model in Papillary Thyroid Microcarcinoma of Stage cN0: A Study of 828 Patients. Front. Endocrinol. 13:843573. doi: 10.3389/fendo.2022.843573*

**Background:** The aim of this study is to build a risk assessment system for central lymph node metastasis (CLNM) in papillary thyroid microcarcinoma (PTMC) of stage cN0 and to explore its application value in clinical practice.

**Methods:** A total of 500 patients with PTMC who underwent thyroid operation from 2013 to 2015 in Ningbo First Hospital were selected as the model group. Independent risk factors related to CLNM in PTMC were analyzed and determined, and a risk assessment system for CLNM was preliminarily established. Furthermore, the clinicopathological data from 328 PTMC patients with the same conditions as the model group from 2016 to 2017 were further collected as the validation group to verify the diagnostic value of the risk assessment system.

**Results:** The risk assessment system was based on the score rating (score ≤ 5 was classified as low risk, 6–8 was classified as medium risk, and ≥9 was classified as high-risk). The area under the receiver operating characteristic curve (ROC) was 0.687 (95% CI: 0.635–0.783). According to the risk assessment system, 328 PTMC patients in the validation group were scored. Among the low-risk group, the moderate-risk group, and the high-group, 96.8%, 58.1%, and 43.2% were the CLNM (-) patients, and 3.1%, 41.9%, and 65.8% were CLNM (+) patients, respectively. The area under ROC was 0.837 (95% CI: 0.778–0.869).

**Conclusions:** The risk assessment system in this study is of diagnostic value and can provide a theoretical foundation for intraoperative decision-making of prophylactic central neck dissection (pCND).

**Keywords: papillary thyroid microcarcinoma, central lymph node metastasis, central lymph node dissection, risk factors, surgery**

## INTRODUCTION

Thyroid carcinoma is the most common malignant endocrine tumor, of which papillary thyroid microcarcinoma (PTMC) is the most frequent pathological type. In recent years, due to the development of ultrasound (US) technology and the enhancement of people's health awareness, the detection rate of PTMC is gradually increasing (1, 2). Studies have found that latent central lymph node metastasis (CLNM) can occur in the early stage of PTMC, especially in the central region (3), and central lymph node dissection (CLND) may increase the risk of the recurrent laryngeal nerve (RLN) and parathyroid gland injury. The rate of RLN injury after thyroid surgery is 0.3%–18.9%, and the incidences of postoperative temporary and permanent parathyroidism are 14%–60% and 4%–11%, respectively (4, 5). These complications are often the main factors of medical disputes. What is worse, the discomfort has a huge impact on the follow-up life and psychology of patients. Accurate preoperative evaluation is important to determine to operate preventive central lymph node dissection (pCND) (6).

Domestically and overseas, there is no consensus on whether to operate pCND for patients with cN0 PTMC. American Thyroid Association (ATA) Guidelines (2015 edition) (7) do not recommend pCND for cN0 PTMC patients while the domestic guidelines emphasize that the dissection can be performed prophylactically with technical support. In this study, we retrospectively analyzed the clinicopathological data of 828 cN0 PTMC patients, who underwent operation in Ningbo First Hospital, summarized the risk factors for CLNM, established a risk assessment model, and validated it, to help make a reasonable surgical plan and achieve the best treatment effectiveness.

## METHODS

### Patients

The model group enrolled 500 patients who underwent thyroid operation in Ningbo First Hospital and were pathologically proved as PTMC between January 2013 and December 2015. The average age of this group was 46.8 years old. A total of 328 patients with PTMC who underwent surgery for the first time in Ningbo First Hospital from 2016 to 2017 were selected as the validation group.

Inclusion criteria: All patients were in good physical conditions before surgery, without other major diseases affecting thyroid surgery and prognosis. Preoperative US showed no suspicious signs of CLNM in patients with thyroid carcinoma. There were pathological reports after operation.

Exclusion criteria: The reports of preoperative US or fine-needle aspiration biopsy suggested CLNM. The patients had previous underlying diseases or other major diseases.

The scope of CLNM (8): upper boundary to thyroid cartilage, lower boundary to thymus, lateral boundary to the medial margin of carotid sheath, including anterior tracheal, paratracheal, and anterior laryngeal lymph nodes.

### Statistics Analysis

Software SPSS 18.0 was used for statistics analysis. *T* test was used for univariate analysis, and data were expressed as $\bar{x} + s$. The multivariate analysis was performed with logistic regression analysis. Statistical significance was considered when $p < 0.05$.

### Risk Assessment System

The odds ratio (OR) of each independent risk factor and its 95% confidence interval could be obtained through statistical analysis. Referring to relevant literatures (9), the OR value of each independent risk factor was selected, and then assigned according to the clinical conditions. The sum was used as the risk score for CLNM. According to the risk score, the receiver operating characteristic curve (ROC) of each patient in the model group was made. The maximum value of the Yoden index was calculated to select the optimal cutoff value of the ROC curve. Meanwhile, the risk scores were stratified by Logistic regression equation, and the risk assessment system was preliminarily established. Statistical significance was considered when $p < 0.05$.

### Verifying the Risk Assessment System

#### Model Group

Hosmer–Lemeshow goodness-of-fit test was used to assess the calibration capability of the risk assessment system. The diagnostic value of the model group was evaluated in accordance with the area under the ROC curve (AUC) of model group cases. The risk score and risk degree calculated by the risk assessment system were compared with the CLNM indicated by postoperative pathology to verify its prediction reliability.

#### Validation Group

The diagnostic value of the system was verified by calculation and comparison.

## RESULTS

### Univariate Analysis of CLNM in PTMC of Model Group

Of the 500 patients, 142 (28.4%) developed CLNM, while the remaining 358 (71.6%) did not. One-way ANOVA analysis showed that gender, tumor size, extra-glandular invasion, boundary, presence of calcification foci, accompanying blood flow, and aspect ratio >1 were independent risk factors for CLNM ($p < 0.05$). However, age, combined Hashimoto, TSH, and TPOAb had no significant relationship with CLNM (**Table 1**).

### Multivariate Analysis of CLNM in PTMC of the Model Group

Logistic regression was used to analyze the independent risk factors found in the above study. It was found that male (OR = 1.924, $p$ = 0.011), the maximum diameter of tumor ≥ 0.5 cm (OR = 2.844, $p$ = 0.037), extra-glandular invasion (OR = 3.721, $p$ = 0.004), US features as unclear tumor boundary (OR = 1.674, $p$ = 0.039), tumor with calcification (OR = 1.801, $p$ = 0.007), and tumor aspect

**TABLE 1** | Relationship between clinical features and CLNM.

| Observed Factors | Amount | CLNM (-) | CLNM (+) | *p*-value |
|---|---|---|---|---|
| **Gender** | | | | |
| Male | 93 | 57 (61.29%) | 36 (38.71%) | 0.002 |
| Female | 407 | 301 (73.71%) | 106 (26.29%) | |
| **Age** | 500 | 358 (71.60%) | 142 (28.40%) | |
| | (46.74 ± 10.86) | (47.32 ± 10.52) | (45.31 ± 11.59) | 0.066 |
| **Tumor Size (cm)** | | | | |
| <0.5 | 195 | 153 (78.46%) | 42 (21.54%) | 0.008 |
| ≥0.5 | 305 | 205 (67.21%) | 100 (32.79%) | |
| **Extra-glandular Invasion** | | | | |
| Yes | 24 | 10 (41.67%) | 14 (58.33%) | 0.002 |
| No | 476 | 348 (73.11%) | 28 (5.88%) | |
| **Boundary** | | | | |
| Clear | 175 | 142 (81.14%) | 33 (18.86%) | 0.001 |
| Unclear | 325 | 216 (66.46%) | 109 (33.54%) | |
| **Calcification** | | | | |
| Yes | 277 | 183 (66.06%) | 94 (33.94%) | 0.003 |
| No | 223 | 175 (75.11%) | 48 (21.52%) | |
| **Multifocal** | | | | |
| Yes | 105 | 69 (65.71%) | 36 (34.29%) | 0.003 |
| No | 395 | 289 (73.16&) | 106 (26.84%) | |
| **Aspect Ratio** | | | | |
| <1 | 287 | 225 (78.40%) | 62 (21.60%) | 0.000 |
| ≥1 | 213 | 133 (62.44%) | 80 (37.56%) | |
| **Blood Flow** | | | | |
| Yes | 275 | 182 (66.18%) | 93 (33.45%) | 0.004 |
| No | 225 | 176 (78.22%) | 49 (21.78%) | |
| **Combined Hashimoto** | | | | |
| Yes | 97 | 70 (72.16%) | 27 (27.84%) | 1.000 |
| No | 403 | 288 (71.46%) | 115 (28.54%) | |
| **TPOAb** | 500 | 358 (71.60%) | 142 (28.40%) | |
| | (50.1 ± 170.05) | (55.09 ± 181.86) | (37.60 ± 135.57) | 0.300 |
| **TSH** | 500 | 358 (71.60%) | 142 (28.40%) | |
| | (2.29 ± 2.21) | (2.31 ± 2.33) | (2.25 ± 1.89) | 0.060 |

ratio ≥ 1 (OR = 2.056, $p = 0.001$) were independent risk factors for CLNM (**Table 2**).

## Establish a Risk Assessment System for CLNM in PTMC

Six independent risk factors were assigned in combination with clinical conditions (10) (**Table 3**). The sum of the scores of each risk factor was used as the risk score of CLNM in patients with PTMC. This scoring method was used to calculate the risk score of 500 patients in the model group, and the ROC curve of the risk score was made. By calculating the maximum value of the Yoden index, the critical value of the risk score for predicting the occurrence of CLNM in PTMC was 5.5 (sensitivity = 73.2%, specificity = 59.5%); thus, risk score was classified.

To classify the risk score of CLNM in PTMC further, the logistic regression equation was established.

$$ln = \left(\frac{P}{1-P}\right) = 0.654X_1 + 1.045X_2 + 1.312X_3 + 0.515X_4 + 0.588X_5 + 0.721X_6 - 2.969$$

X1: gender, male X1 = 1, female X1 = 0;

**TABLE 2** | Independent risk factors for CLNM.

| | B | S.E. | Wald | *p*-value | OR value | 95% CI of OR value | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower Limit | Upper Limit |
| Gender | 0.654 | 0.256 | 6.545 | 0.011 | 1.924 | 1.156 | 3.177 |
| Maximum Diameter of Tumor | 1.045 | 0.501 | 4.357 | 0.037 | 2.844 | 1.066 | 7.590 |
| Extra-glandular Invasion | 1.312 | 0.458 | 8.190 | 0.004 | 3.721 | 1.512 | 9.116 |
| Boundary | 0.515 | 0.249 | 4.272 | 0.039 | 1.674 | 1.027 | 2.728 |
| Calcification | 0.588 | 0.218 | 7.292 | 0.007 | 1.801 | 1.175 | 2.760 |
| Focus | 0.152 | 0.252 | 0.364 | 0.546 | 1.164 | 0.711 | 1.906 |
| Aspect Ratio | 0.721 | 0.217 | 10.998 | 0.001 | 2.056 | 1.343 | 3.149 |
| Blood Flow | 0.342 | 0.227 | 2.274 | 0.132 | 1.407 | 0.903 | 2.195 |
| Constant | –2.969 | 0.383 | 60.019 | 0.000 | 0.051 | | |

**TABLE 3** | Assignment of independent risk factors.

| Independent risk factors | Score | |
|---|---|---|
| | Yes | No |
| Male | 2 | 0 |
| Maximum tumor diameter ≥ 0.5 cm | 3 | 0 |
| Extra-glandular invasion | 4 | 0 |
| US showed that the tumor boundary was unclear | 2 | 0 |
| US showed tumor with calcification | 2 | 0 |
| US showed that the aspect ratio of tumor was ≥ 1 | 2 | 0 |

X2: maximum diameter of tumor, ≥0.5 cm X2 = 1, <0.5 cm X2 = 0;
X3: extra-glandular invasion, yes X3 = 1, no X3 = 0;
X4: boundary, unclear or not clear enough X4 = 1, clear or barely clear X4 = 0;
X5: calcification, with X5 = 1, without X5 = 0;
X6: aspect ratio, ≥1 X6 = 1, <1 X6 = 0.

According to the regression equation, the incidence (P) of CLNM in PTMC of 500 cases in the model group could be calculated by substituting the specific properties into the equation. When $p = 0.5$, it was considered that the incidence of CLNM in PTMC is the same as that without CLNM. When $p > 0.5$, it was considered that the incidence of CLNM in PTMC is higher than that without CLNM. To prove the correlation between the risk scores calculated by assignment and the incidence of CLNM in PTMC calculated by regression equation, a scatter plot was made (**Figure 1**). It is found that there was a linear correlation between the incidence of CLNM in PTMC and the risk scores; the incidence of CLNM rose gradually with the increase of CLNM risk scores. As shown in the scatter plot, when the risk score is 9, $p = 0.5$.

Therefore, a risk assessment system for predicting CLNM in PTMC was preliminarily established: ≤5 was classified as low risk, 6–8 was classified as medium risk, and ≥9 was classified as high risk.

## Risk Assessment System Verification

### Verification of the Model Group

#### *Hosmer–Lemeshow Goodness-of Fit Test*

Hosmer–Lemeshow goodness-of-fit test was used for multivariate analysis of the model group with logistic regression. The evaluation result was $\chi^2 = 3.641$, $p = 0.888$, suggesting that the predicted value and the actual value had no statistical significance, indicating that the fitting degree was high, and the calibration ability was good.

#### *The Evaluation of the Value of System by ROC Curve*

The risk of the model group was scored with the risk assessment system. The AUC was 0.687 (95% CI: 0.635–0.783) and the cutoff was 5.5 ($p < 0.01$) (**Figure 2**). It showed that the risk assessment system had good diagnostic value.

#### *Comparison and Verification With Postoperative Pathological Results*

Among the 500 patients in the model group, the proportions of low-risk, medium-risk, and high-risk CLNM (+) patients were 15.1%, 35.8%, and 50.5%, respectively, while the proportions of low-risk, medium-risk, and high-risk CLNM (-) patients were 84.9%, 64.2%, and 49.5% respectively (**Figure 3**). According to the risk scores, there was significant difference in the distribution of low risk, medium risk, and high risk between the CLNM (+) and CLNM (-) group ($\chi^2 = 137.669$, $p < 0.001$) (**Table 4**).

### Verification of the Validation Group

#### *Establishment of Validation Group Database*

From 2016 to 2017, 328 patients with PTMC were selected as the validation group, among which 106 cases were CLNM (+), accounting for 32.3%, while 222 cases were CLNM (-), accounting for 67.7%.

#### *The Evaluation of the Value of System by ROC Curve*

Risks of 328 patients were assessed with PTMC. The results of ROC showed that the cutoff value of the system was 5.5 (Sensitivity = 0.962, Specificity = 0.559, AUC = 0.837, $p < 0.001$) and the 95% CI was 0.778–0.869 (**Figure 4**), which proved that the risk assessment system had good diagnostic value.

#### *Comparison and Verification With Postoperative Pathological Results*

Comparing the patient scores with their actual pathological results, it was found that in the low-risk group, CLNM (+)

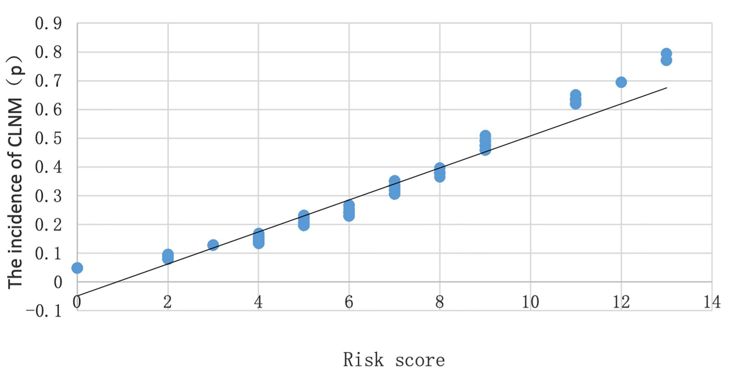



**FIGURE 1** | Scatter plot of the relationship between the probability of occurrence (P) and risk score of CLNM.

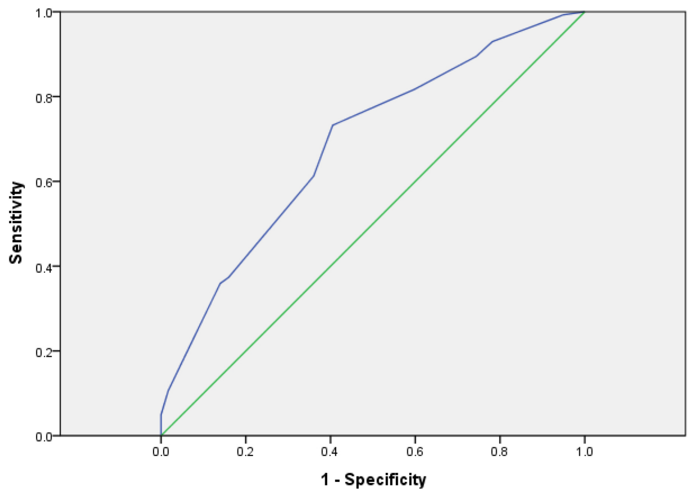



**FIGURE 2** | ROC curve of risk factor scores in model group.

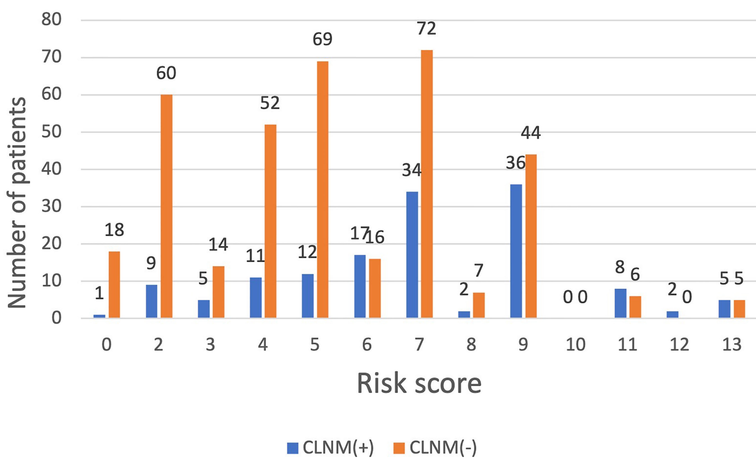



**FIGURE 3** | The distribution of CLNM-negative and positive patients with different risk scores inthe model group.

**TABLE 4** | Model group scoring.

| CLNM | Risk Score | | | *p*-value |
|---|---|---|---|---|
| | Low risk | Medium risk | High risk | <0.001 |
| | (≤5) | (5–8) | (≥9) | |
| (-) | 213 | 95 | 50 | |
| (+) | 38 | 53 | 51 | |

patients accounted for 3.1% and CLNM (-) patients accounted for 96.8%; in the high-risk group, CLNM (+) patients accounted for 65.8%, and CLNM (-) patients accounted for 34.2%; the proportions of CLNM (+) patients and CLNM (-) patients were 41.9% and 58.1%, respectively (**Figure 5**). That is to say, the distribution of low risk, medium risk, and high risk between CLNM (+) group and CLNM (-) had significant difference ($\chi^2$ = 47.021, $p$ < 0.001) (**Table 5**).

## DISCUSSION

Thyroid cancer is a common malignant tumor with a 10-year survival rate of more than 90% (11). It was found that CLNM may occur to 40%–90% of PTMC patients (12–14). CLNM will increase the risk of postoperative recurrence and affect the prognosis of patients (15–17). Although thyroid surgery is one of the most common and safest procedures in endocrine surgery, the risk of complications is still unavoidable on account of the unique anatomy of the thyroid gland (18, 19). Numbness of

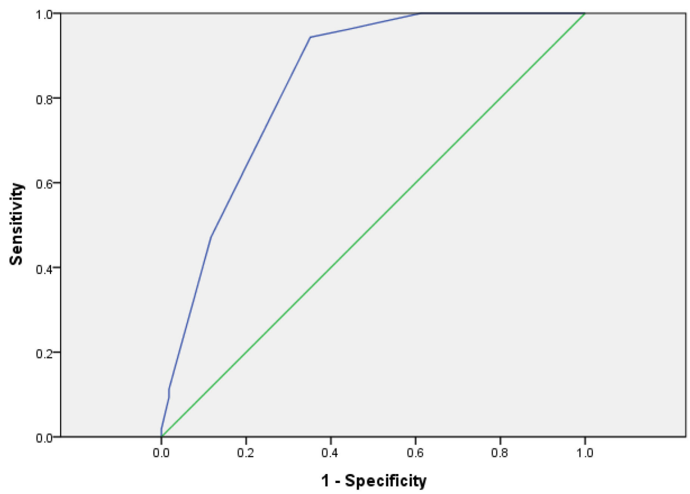



**FIGURE 4** | Validation group risk score ROC curve.

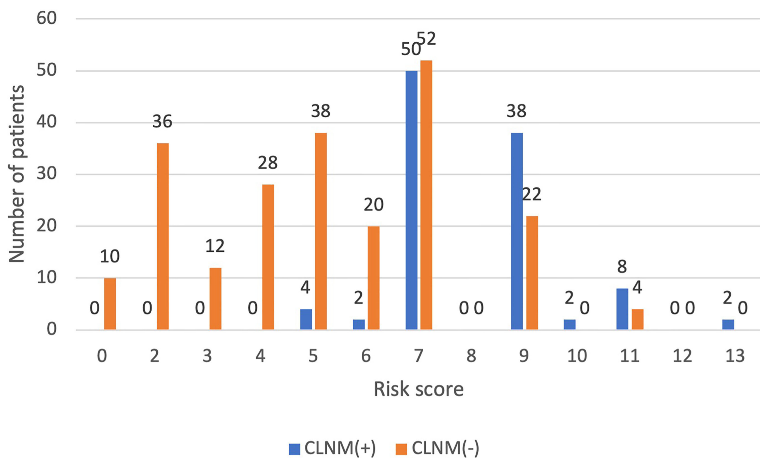



**FIGURE 5** | The distribution of CLNM-negative and positive patients with different risk scores inthe validation group.

**TABLE 5** | Validation group scoring.

| CLNM | Risk Score | | | *p*-value |
|---|---|---|---|---|
| | Low risk | Medium risk | High risk | <0.001 |
| | (≤5) | (5–8) | (≥9) | |
| (-) | 124 | 72 | 26 | |
| (+) | 4 | 52 | 50 | |

hands and feet, difficulty in articulation, and even inability to breathe are still the major problems perplexing surgeons. These issues need to be addressed, especially in an era when changes in quality of life are incorporated into surgical outcomes (20, 21).

pCND is more prone to RLN injury because the path of the RLN is included in the surgical field of CLND.

There are many possible causes of injury to the RLN, such as traction, ligation, heat injury, and so on. Traction is the main cause of injury to the RLN (22, 23). So, how to effectively reduce traction will play an important role in the protection of RLN.

Due to the connective tissue, the RLN should be dissected from the lymph node capsule prior to CND, which could reduce the probability of injury to the RLN (22).

This was also a test of the operator's ability. The invention of energy-based devices (EBDs) is a great progress in thyroid surgery. EBDs can decrease operative time, incision length, blood loss, pain, wound drainage, neck hematoma, and hypocalcemia (24–27). However, the heat from the EBDs can cause iatrogenic thermal injury to the RLN. A study of 11,355 patients who underwent thyroidectomy found a higher rate of hoarseness with EBDs compared to the non-EBD group (24, 28). A 10-year meta-analysis also found that the use of EBDs could cause a higher rate of paralysis (29). IONM allows real-time monitoring of RLN function through continuous intraoperative neural monitoring, significantly improving postoperative quality of life (30, 31). However, IONM is not widely used in clinical practice due to its high cost and the consumable medical supplies. At the same time, the false-positive rate of IONM, the lack of experience with IONM, and the failures of IONM instrument are often the reasons that hinder the application of IONM in clinic (32, 33).

For recurrent PTMC patients, reoperation may not only significantly increase surgical complications, but also decrease the life quality of patients. Therefore, how to deal with the cervical lymph nodes during the initial operation is particularly important.

Domestic experts have different opinions on whether to perform pCND. Some experts think pCND can fundamentally eliminate the occult metastasis lymph node in central region and reduce tumor recurrence or lymph node metastasis. More importantly, it can avoid surgical complications that may be caused by the second operation, and also reduce the financial and mental burden of patients (34, 35). However, some experts disagree to perform pCND. When lymph node metastasis occurs, treatment has no significant impact on the postoperative survival rate of patients. What is more, avoiding pCND can reduce the incidence of postoperative complications caused by surgery (36, 37).

For PTMC patients with unclear tumor boundary, tumor with calcification, and tumor aspect ratio ≥ 1, the incidence of CLNM is higher. However, it should be noted that our result depends on the operator's diagnostic experience to a large extent, as well as the US instrument's resolution, which may lead to an impact to research results.

Through retrospective analysis and logistic regression equation, this study pioneered a complete risk assessment system for CLNM in PTMC and determined that the score ≤ 5 is low risk, 6–8 is medium risk, and ≥9 is high risk. The area under the ROC curve of the risk score in the model group and that in the validation group were >0.5, which proved that the assessment system had high diagnostic value. Substituting pathological information of the model group and the validation group were into the risk assessment system. We found that CLNM (-) accounted for the majority of patients with low-risk scores (model group: 84.9%; validation group: 96.8%). That is, the risk of CLNM in PTMC of low-risk patients was low. Among the high-risk patients, the proportion of CLNM (+) patients was higher than that of CLNM (-) patients (model group: 50.5% vs. 49.5%; validation group: 65.8% vs. 34.2%); in other words, the risk of CLNM in PTMC in high-risk patients was relatively high. The proportion of CLNM (+) patients in medium-risk patients is slightly higher (model group: 35.8% vs. 64.2%; validation group: 41.9% vs. 58.1%). However, compared with low-risk patients, the incidence of CLNM was significantly increased. Therefore, these patients should be cautious in choosing whether to perform pCND.

There are several previous studies regarding prediction models for CLNM. Wang et al. (38) analyzed the factors of Level VI metastasis in PTMC with stage cN0. However, the sample size of this study was small and lacks further verification. Although Jiang et al. (39) analyzed 4,884 PTMC patients from 2 hospitals, they only explored related risk factors. Our model not only screened related risk factors, but also established relevant formulas through statistical analysis to furthermore conveniently assess the risk of central region lymph node metastasis in PTMC patients.

Through AUC calculation, Hosmer–Lemeshow goodness-of-fit test as well as comparison between assessment results analyses and actual pathological conditions, it is suggested that the risk assessment system had certain diagnostic value. All risk factors mentioned above can be easily obtained before CLND. Such a risk assessment system is simple and convenient for clinical application, and conducive to assisting physicians in intraoperative decision-making. The analysis shows that CLND is not recommended for low-risk patients, but for high-risk patients. As for medium-risk patients, whether to perform pCND should be considerably decided in combination with the operator's surgical ability and the patient's comprehensive situation. So as to realize the precise treatment to PTMC patients, which not only reduces the risk of local recurrence and distant metastasis, but also avoids the injury of recurrent laryngeal nerve and parathyroid gland caused by pCND.

At present, the current findings about the treatment of PTMC lymph nodes are not consistent at home and abroad. In this study, we retrospectively analyzed the clinicopathological data of 828 patients with cN0 PTMC, and established and verified a prediction model. For patients with PTMC in stage cN0, we recommend to perform pCND, especially for medium-risk and high-risk patients. However, we refer to this model for some patients who have underlying diseases, or who are strongly worried about postoperative thyroid complications, or who resist surgery strongly, or whose rapid frozen sections during operation suggest a suspected malignant tumor. For those low-risk patients screened by the model, we can choose not to pCND or recommend them to follow-up closely. Meanwhile, in future clinical practice, PTMC patients with stage cN0 who undergo pCND can be classified according to the model. We can verify this model by comparing the prognosis of the three risk levels.

In the next phase, we plan to carry out long-term follow-up of patients to master their postoperative survival, whether they have postoperative local recurrence, distant metastasis, or even death. In the meantime, we will improve the risk assessment system further *via* multi-center and large-sample prospective clinical research, to achieve its better clinical guidance.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Ningbo First Hospital.

Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

JW, XS, and YG contributed to the concept design, planning of the study, revision, and final approval of the present article. JW, YD, JZ, and LS were responsible for gathering the data, writing, analysis, revision, and final approval of the present article. All authors contributed to the article and approved the submitted version.

## FUNDING

This study was funded by the Medical Science and Technology project of Zhejiang Province (grant no. 2022KY1110) and Key Disciplines of Ningbo First Hospital.

## REFERENCES

1. Davies L, Welch HG. Increasing Incidence of Thyroid Cancer in the United States, 1973-2002. *Jama* (2006) 295(18):2164–7. doi: 10.1001/jama.295.18.2164
2. Lee YS, Lim H, Chang HS, Park CS. Papillary Thyroid Microcarcinomas are Different From Latent Papillary Thyroid Carcinomas at Autopsy. *J Korean Med Sci* (2014) 29(5):677–9. doi: 10.3346/jkms.2014.29.5.676
3. Zhang B, Jiang YX, Liu JB, Yang M, Dai Q, Zhu QL, et al. Utility of Contrast-Enhanced Ultrasound for Evaluation of Thyroid Nodules. *Thyroid Off J Am Thyroid Assoc* (2010) 20(1):51. doi: 10.1089/thy.2009.0045
4. Cheah WK, Arici C, Ituarte P, Siperstein AE, Duh QY, Clark OH. Complications of Neck Dissection for Thyroid Cancer. *World J Surg* (2002) 26(8):1013–6. doi: 10.1007/s00268-002-6670-4
5. Giordano D, Val Ca Vi R, Thompson GB, Pedroni C, Renna L, Gradoni P, et al. Complications of Central Neck Dissection in Patients With Papillary Thyroid Carcinoma: Results of a Study on 1087 Patients and Review of the Literature. *Thyroid Off J Am Thyroid Assoc* (2016) 22(9):911. doi: 10.1089/thy.2012.0011
6. Liu Y, Lv HJ, Zhang SQ, Shi BY, Sun YS. The Impact of Coexistent Hashimoto's Thyroiditis on Central Compartment Lymph Node Metastasis in Papillary Thyroid Carcinoma. *Front Endocrinol* (2021) 12:772071:772071. doi: 10.3389/fendo.2021.772071
7. Haugen BR, D M. 2015 American Thyroid Association Management Guidelines for Adult Patients With Thyroid Nodules and Differentiated Thyroid Cancer: What is New and What has Changed? *Cancer* (2017) 123 (3):372–81. doi: 10.1089/thy.2015.0020
8. Pisello F, Geraci G, Nigro CL, Volsi FL, Sciumè C. Neck Node Dissection in Thyroid Cancer. A Review. *IL Giornale Di Chirurgia* (2010) 31(3):112–8.
9. Cai ZQ, Liao QG, Guo XW, Weng ZJ, Ou XM, Lu SR. Analysis of Risk Factors for Acute Kidney Injury in Patients With non-ST-Segment Elevation Myocardial Infarction. *Chin J Emerg Med* (2016) 025(003):343–8. doi: 10.3760/cma.j.issn.1671-0282.2016.03.018
10. Laurence L, Pascale G, Laurence CC, Committee TC. Increased Incidence of Thyroid Carcinoma in France: A True Epidemic or Thyroid Nodule Management Effects? report from the french thyroid cancer committee. *Thyroid: Off J Am Thyroid Association,2004* (2005) 14:1056–60. doi: 10.1089/thy.2004.14.1056
11. Lundgren CI, Hall P, Dickman PW, Zedenius J. Clinically Significant Prognostic Factors for Differentiated Thyroid Carcinoma: A Population-Based, Nested Case-Control Study. *Cancer* (2010) 106(3):524–31. doi: 10.1002/cncr.21653
12. Malterling RR, Andersson RE, Falkmer S, Falkmer U, Niléhn E, J?Rhult J. Differentiated Thyroid Cancer in a Swedish County–Long-Term Results and Quality of Life. *Acta Oncol* (2010) 49(4):454–9. doi: 10.3109/02841860903544600
13. Jiang LH, Chen C, Tan Z, Lu XX, Hu SS, Wang QL, et al. Clinical Characteristics Related to Central Lymph Node Metastasis in Cn0 Papillary Thyroid Carcinoma: A Retrospective Study of 916 Patients. *Int J Endocrinol* (2014) 2014:385787. doi: 10.1155/2014/385787
14. Lee YM, Sung TY, Kim WB, Chung KW, Yoon JH, Hong SJ. Risk Factors for Recurrence in Patients With Papillary Thyroid Carcinoma Undergoing Modified Radical Neck Dissection. *Br J Surg* (2016) 103(8):1020–5. doi: 10.1002/bjs.10144
15. Qiao N, Bai X, Wang G, Sun B, Linfeng WU. Controversy and Progress on Prophylactic Central Neck Dissection in Cn_0 Papillary Thyroid Carcinoma. *Chin J Gen Surgery* (2016) 25(5):729–34. doi: 10.3978/j.issn.1005-6947.2016.05.018
16. Hay ID, Grant CS, H Ee Rden J, Goellner JR, Bergstralh EJ. Papillary Thyroid Microcarcinoma: A Study of 900 Cases Observed in a 60-Year Period. *Surgery* (1992) 144(6):980–8. doi: 10.1016/j.surg.2008.08.035
17. Pisanu A, Reccia I, Nardello O, Uccheddu A. Risk Factors for Nodal Metastasis and Recurrence Among Patients With Papillary Thyroid Microcarcinoma: Differences in Clinical Relevance Between Nonincidental and Incidental Tumors. *World J Surg* (2012) 33(3):460–8. doi: 10.1007/s00268-008-9870-8
18. Jin S, Sugitani I. Narrative Review of Management of Thyroid Surgery Complications. *Gland Surg* (2021) 10(3):1135–46. doi: 10.21037/gs-20-859
19. Liu CH, Huang TY, Wu CW, Wang JJ, Wang LF, Chan LP, et al. New Developments in Anterior Laryngeal Recording Technique During Neuromonitored Thyroid and Parathyroid Surgery. *Front Endocrinol* (2021) 12:763170:763170. doi: 10.3389/fendo.2021.763170
20. Dralle H, Lorenz K, Machens A. Verdicts on Malpractice Claims After Thyroid Surgery: Emerging Trends and Future Directions. *Head Neck* (2012) 34(aop):1591–6. doi: 10.1002/hed.21970
21. Gualniera P, Scurria S, Mondello C, Asmundo A, Gianlorenzo D. Narrative Review of Proving the Causal Link of Recurrent Laryngeal Nerve Injury and Thyroidectomy: A Medico Legal Appraisal. *Gland Surg* (2020) 9(5):1564–72. doi: 10.21037/gs-20-203
22. Liu X, Zhang D, Zhang G, Zhao L, Zhou L, Fu Y, et al. Laryngeal Nerve Morbidity in 1.273 Central Node Dissections for Thyroid Cancer. *Surg Oncol* (2018) 27(2):A21–5. doi: 10.1016/j.suronc.2018.01.003
23. Chiang FY, Lu IC, Kuo WR, Lee KW, Wu CW. The Mechanism of Recurrent Laryngeal Nerve Injury During Thyroid Surgery - the Application of Intraoperative Neuromonitoring. *Surgery* (2008) 143(6):743–9. doi: 10.1016/j.surg.2008.02.006
24. Moran K, Grigorian A, Elfenbein D, Schubl S, Nahmias J. Energy Vessel Sealant Devices are Associated With Decreased Risk of Neck Hematoma After Thyroid Surgery. *Updates Surg* (2020) 72(4):1135–41. doi: 10.1007/s13304-020-00776-9
25. Canu GL, Medas F, Podda F, Tatti A, PG Calò. Thyroidectomy With Energy-Based Devices: Surgical Outcomes and Complications—Comparison Between Harmonic Focus, Ligasure Small Jaw and Thunderbeat Open Fine Jaw. *Gland Surgery* (2020) 9(3):721. doi: 10.21037/gs.2020.03.31
26. Konturek A, Szpyra B, Stopa-Barczynska M, Barczynski M. Energy-Based Devices for Hemostasis in Thyroid Surgery. *Gland Surg* (2020) 9(S2):S153–8. doi: 10.21037/gs.2019.10.17
27. Liu CH, Wang CC, Wu CW, Lin YC, Chiang FY. Comparison of Surgical Complications Rates Between Ligasure Small Jaw and Clamp-and-Tie Hemostatic Technique in 1,000 Neuro-Monitored Thyroidectomies. *Front Endocrinol* (2021) 12:638608. doi: 10.3389/fendo.2021.638608
28. Christakis I, Klang P, Talat N, Galata G, Schulte KM. Long-Term Quality of Voice is Usually Acceptable After Initial Hoarseness Caused by a Thyroidectomy or a Parathyroidectomy. *Gland Surg* (2019) 8(3):226–36. doi: 10.21037/gs.2018.09.02
29. Garas G, Okabayashi K, Ashrafian H, Shetty K, Palazzo F, Tolley N, et al. Which. Hemostatic Device in Thyroid Surgery? A Network Meta-Analysis of Surgical Technologies. *Thyroid* (2013) 23(9):1138–50. doi: 10.1089/thy.2012.0588

30. Schneider R, Randolph GW, Barczynski M, Dionigi G, Wu C-W, Chiang F- Y, et al. Continuous Intraoperative Neural Monitoring of the Recurrent Nerves in Thyroid Surgery: A Quantum Leap in Technology. *Gland Surg* (2016) 5 (6):607–16. doi: 10.21037/gs.2016.11.10
31. Mangano A, Kim HY, Wu CW, Rausei S, Hui S, Xiaoli L, et al. Continuous Intraoperative Neuromonitoring in Thyroid Surgery: Safety Analysis of 400 Consecutive Electrode Probe Placements With Standardized Procedures. *Head Neck* (2016) 38(S1):E1568–74. doi: 10.1002/hed.24280
32. Randolph GW, Dralle H, Abdullah H, Barczynski M, Bellantone R, Brauckhoff M, et al. Electrophysiologic Recurrent Laryngeal Nerve Monitoring During Thyroid and Parathyroid Surgery: International Standards Guideline Statement. *Laryngoscope* (2011) 121(Suppl 1):S1–16. doi: 10.1002/lary.21119
33. Dionigi G, Bacuzzi A, Boni L, Rausei S, Rovera F, Dionigi R. Visualization Versus Neuromonitoring of Recurrent Laryngeal Nerves During Thyroidectomy: What About the Costs? *World J Surg* (2012) 36(4):748–54. doi: 10.1007/s00268-012-1452-0
34. Xiang Y, Lin K, Dong S, Qiao L, He Q, Zhang X. Prediction of Central Lymph Node Metastasis in 392patients With Cervical Lymph Node-Negative Papillary Thyroid Carcinoma in Eastern China. *Oncol Lett* (2015) 10 (4):2559–64. doi: 10.3892/ol.2015.3544
35. Xue S, Wang P, Liu J, Li R, Zhang L, Chen G. Prophylactic Central Lymph Node Dissection in Cn0 Patients With Papillary Thyroid Carcinoma: A Retrospective Study in China. *Asian J Surg* (2016) 39(3):131–6. doi: 10.1016/j.asjsur.2015.03.015
36. Kim SK, Woo JW, Lee JH, Park I, Choe JH, Kim JH, et al. Prophylactic Central Neck Dissection Might Not Be Necessary in Papillary Thyroid Carcinoma: Analysis of 11,569 Cases From a Single Institution. *J Am Coll Surg* (2016) 222 (5):853–64. doi: 10.1016/j.jamcollsurg.2016.02.001
37. Liu L, Xu Z, Li Z, Zhang Z, Tang P, Liu S. Long-Term Outcomes of Observation for Clinically Negative Central Compartment Lymph Nodes in Papillary Thyroid Carcinoma. *Eur Arch Oto Rhino Laryngology* (2015) 272 (12):3801–4. doi: 10.1007/s00405-014-3453-0
38. Wang Y, Ji QH, Huang CP, Zhu YX, Ling Z. Predictive Factors for Level Vi Lymph Node Metastasis in Papillary Thyroid Microcarcinoma. *Zhonghua Wai Ke Za Zhi* (2008) 46(24):1899–901. doi: 10.3321/j.issn:0529-5815.2008.24.020
39. Jiang LH, Yin KX, Wen QL, Chen C, Tan Z. Predictive Risk-Scoring Model for Central Lymph Node Metastasis and Predictors of Recurrence in Papillary Thyroid Carcinoma. *Sci Rep* (2020) 10(1):710. doi: 10.1038/s41598-019-55991-1

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Publisher's Note:** All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Surgery

SYSTEMATIC REVIEW
published: 06 April 2022
doi: 10.3389/fsurg.2022.876228

# Management of Unilateral Vocal Fold Paralysis after Thyroid Surgery with Injection Laryngoplasty: State of Art Review

*Li-Jen Liao*[1,2] *and Chi-Te Wang*[1,2,3]*

[1]Department of Otolaryngology Head and Neck Surgery, Far Eastern Memorial Hospital, Taipei, Taiwan, [2]Department of Electrical Engineering, Yuan Ze University, Taoyuan, Taiwan, [3]Department of Special Education, University Of Taipei, Taipei, Taiwan

**Background:** Unilateral vocal fold paralysis (UVFP) after thyroid surgery often leads to significant morbidity including dysphonia, dysphagia, and aspiration. Injection laryngoplasty (IL) is an effective treatment of UVFP with numerous readily available materials. However, few studies focus on IL for UVFP following thyroidectomy.

**Objectives:** This review aims to critically review current literature to determine the timing, materials, methods and outcomes of IL for UVFP after thyroid surgery.

**Type of Review:** Literature review.

**Methods:** A literature review was performed using the Pubmed, Medline and EMBASE databases. All relevant articles published in English addressing the effect of IL in post thyroid surgery related UVFP were analyzed. Studies using IL for UVFP of multiple etiologies were excluded. Meta-analysis was conducted using fixed and random effect model.

**Results:** Five original studies were identified, including 214 patients received IL for UVFP following thyroid surgery. Two studies injected autologous fat via direct suspension laryngoscope under general anesthesia, while the other 3 studies injected polyacrylamide, hyaluronic acid, and polymethyl methacrylate from cricothyroid membrane under local anesthesia. All 5 studies reported improved voice outcomes of IL for post-thyroidectomy UVFP. Meta-analysis showed MPT increased for 3.18 s (95% CI: 2.40–3.96, fix effect model) after IL. Another common acoustic parameter, jitter (%) also improved for 1.46 (95% CI: 0.73–2.19, random effects model) after IL for post-thyroidectomy UVFP.

**Conclusions:** This review supported that IL can improve the voice outcome for post-thyroidectomy UVFP. Autologous fat remains a good augmentation material with a potential longer lasting effect. More research and long-term surveys are needed to document the safety and longevity of other synthetic materials.

**Keywords: vocal cord paralysis, injection laryngoplasty, dysphonia, larynx, review**



***Edited by:***
*Che-Wei Wu,*
*Kaohsiung Medical University, Kaohsiung, Taiwan*

***Reviewed by:***
*Tzu-Yen Huang,*
*Kaohsiung Medical University, Kaohsiung, Taiwan;*
*Hsin-Yi Tseng,*
*Kaohsiung Medical University, Kaohsiung, Taiwan*

****Correspondence:***
*Chi-Te Wang*
*drwangct@gmail.com*

***Speciality section:***
*This article was submitted to Otorhinolaryngology - Head and Neck Surgery, a section of the journal Frontiers in Surgery*

***Received:*** *15 February 2022*
***Accepted:*** *21 March 2022*
***Published:*** *06 April 2022*

***Citation:***
*Liao L-J and Wang C-T (2022) Management of Unilateral Vocal Fold Paralysis after Thyroid Surgery with Injection Laryngoplasty: State of Art Review. Front. Surg. 9:876228. doi: 10.3389/fsurg.2022.876228*

## BACKGROUND

The synonymous term of unilateral vocal fold paralysis (UVFP) includes vocal cord palsy, vagal paralysis and recurrent laryngeal neuropathy. Iatrogenic injury is now the prevailing etiologies for UVFP (1) and thyroid surgery related recurrent laryngeal nerve injury is one of the most common cause for iatrogenic UVFP. The an average incidence of transient and permanent UVFP following thyroid surgeries were 9.8 and 2.3%, respectively (2). UVFP often leads to significant morbidity that may include dysphonia, dysphagia, aspiration, or even pneumonia after thyroid surgery, especially in elder patients (3). Several modalities had been introduced for post-thyroidectomy UVFP, e.g., voice therapy, medialization thyroplasty, and injection laryngoplasty (IL).

The first IL was reported by Dr. Bruening in 1911 using liquid paraffin (4). Unfortunately, this material is not tissue compatible and resulted in chronic granuloma formation and material extrusion (5). Later on, IL using Teflon paste was re-introduced in 1960's (6). Although short-term effectiveness was satisfactory, Teflon paste was gradually noted to cause serious long-term sequel, i.e., Teflon granuloma, owing to profound foreign body reaction (7). After the frustrating experience with paraffin and Teflon (8), subsequent study shifted to more histologically compatible materials, i.e. homologous and autologous collagen (9–11), and bovine / porcine collagen (12, 13). Since 2000s, other synthetic compatible materials had been introduced to clinical use during IL (14), e.g. carboxymethylcellulose (15), hyaluronic acid (13, 16), and calcium hydroxylappatite (17).

Compared with other treatment modalities for post-thyroidectomy UVFP, IL has several advantages. IL can be performed in the office under local anesthesia. Real-time feedback of voice improvement can also be conducted. Most-importantly, patient did not need another open-surgery (e.g. thyroplasty) to correct UVFP resulting from prior thyroid surgeries. From our clinical experience, IL is well tolerated in the office and most patients exhibit stable hemodynamics throughout the procedure (18). Although IL is effective for UVFP, most of the existing studies included a mixture of different etiologies of UVFP (e.g., iatrogenic, neoplastic, idiopathic). Only a few studies focused on IL in the management of post-thyroidectomy related UVFP. Accordingly, we conducted this literature review to summarize the state of art practice and evidence in this specific clinical scenario.

## MATERIAL AND METHOD

A literature review was performed using the Pubmed, Medline and EMBASE database. The following keywords and MeSH Terms were applied: vocal fold palsy OR vocal cord palsy AND injection therapy. All relevant articles published in English addressing the effect of injection laryngoplasty in UVFP were reviewed. We limit the literatures into IL for UVFP after thyroidectomy. Studies including multiple etiologies of UVFP were excluded. We evaluated the risk of bias in recruited studies using Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) (19).

Retrieved information include the number of patients, injected material, injection approach, and treatment outcomes before and after injection laryngoplasty. Owing to different reporting timeline across each studies, outcomes of the longest follow-up period was selected for subsequent meta-analysis (R software, version 4.1.2, with packages for meta-analysis (20). We adapted results from either fixed or random effect model for statistical inference based on the significance of potential heterogeneity among the recruited research.

## RESULTS

The flow chart of the study selection process is shown in **Figure 1**. We identified 5 original articles summarized in **Table 1**. Totally 214 patients received IL after thyroid surgery related UVFP were reported. Fang et al. (21) reported acoustic outcomes of 27 patients with autologous fat injection and follow-up the residual fat volume with 3-dimensional imaging. The mean residual fat volume remained consistent after 26-month follow-up. The maximal phonation time (MPT), s/z ratio, jitter, and noise-to-harmonic ratio (NHR) were significantly improved during follow-up.

Lee et al. (22) reported 34 patients received polyacrylamide hydrogel (PAAG (Aquamid®) for permanent UVFP and Hyaluronic acid (Rofilan®) for temporary UVFP after thyroidectomy. Acoustic and perceptual parameters (GRBAS),

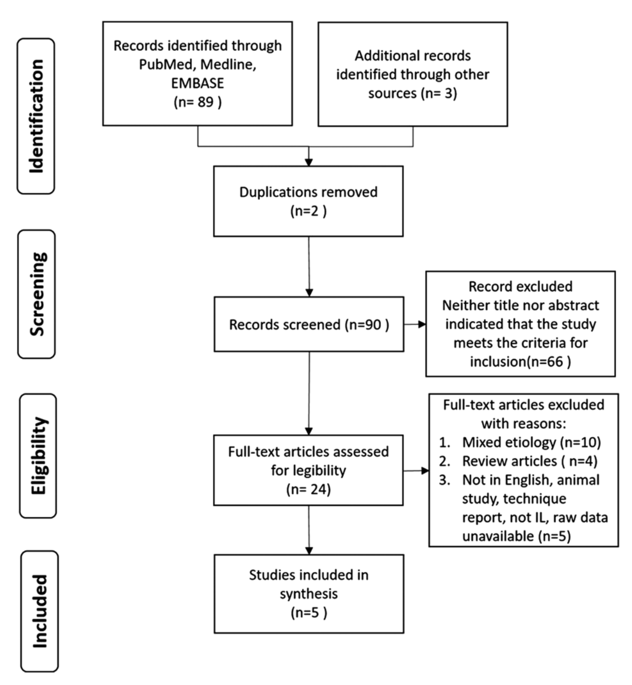



**FIGURE 1** | PRISMA flow diagram depicts the process of literature searching.

**TABLE 1 |** Summary for the literatures focus on the management of UVFP after thyroid surgery with IL.

| | Authors | Main findings |
|---|---|---|
| 1 | Fang et al. (21) | 27 patients with autologous **fat injection**<br>MPT, s/z ratio, jitter, and harmonic-to-noise ratio were significantly improved.<br>Mean residual fat volume remained consistent after 26-month follow-up. |
| 2 | Lee et al. (22) | 34 patients with **PAAG (PAAG (Aquamid®) and Hyaluronic acid (Rofilan®) injection**<br>Acoustic and perceptual parameters (overall GBRAS), MPT, jitter, and shimmer, voice handicap index, and grades of mucosal waves and glottic closure were significantly improved and remained stable over 6 months |
| 3 | Jang et al. (23) | 55 patients (24 early, 31 late injection) with **PMMA (polymethyl methacrylate, ArteSense™)** and early voice rehabilitation<br>All tested voice parameters were significantly improved in both the early and late groups. The amount of voice improvement was significantly larger in the early injection group, especially jitter % ($P = 0.02$) and shimmer % ($P = 0.03$). |
| 4 | Chun et al. (24) | 25 patients received IL using **hyaluronic acid**, comparing with 23 patients received voice therapy<br>Greater improvement in UVFP patients who underwent IL then voice therapy |
| 5. | Lin et al. (25) | 73 patients underwent **autologous fat injection**<br>Gender and age may stand as significant categories on analysis voice indicators |

*GBRAS, grade of hoarseness, roughness, breathiness, asthenia, and strain.*
S/Z ratio, the maximal length when pronouncing "S", divided by the maximal length when pronouncing "Z".

MPT, jitter, and shimmer, voice handicap index, and grades of mucosal waves and glottic closure were all significantly improved after the injection and remained stable over 6 months.

Jang et al. (23) reported 55 patients injected with PMMA (polymethyl methacrylate, ArteSense™, a relatively long-lasting injectable substance for soft-tissue augmentation) for UVFP after thyroidectomy. The authors further divided these patients into 24 early injection (within 3 months between IL and thyroid surgery) and 31 late injection (IL at longer than 3 months after thyroidectomy). All of the measured objective and subjective voice parameters were significantly improved in both the early and late groups. The degree of voice improvement was significantly larger in the early injection group, especially jitter % ($P = 0.02$) and shimmer % ($P = 0.03$) improvement.

Chun et al. (24) reported 25 patients of post-thyroidectomy with aspiration symptoms receiving injection laryngoplasty using hyaluronic acid (Rofilan), and another 23 patients without aspiration receiving only voice therapy. They found greater improvement in thyroidectomy-related voice questionnaire, GRBAS scale, jitter, shimmer and NHR in patients who underwent injection laryngoplasty comparing to voice therapy alone.

Lin et al. (25) reported 73 patients underwent autologous fat injection for UVFP after thyroid surgery. They reported a significant improvement of multi-dimensional voice parameters 1 year after lipoinjection. This study also found that patients under 60 years old presented better improvement of MPT then the other patient older than 60 years. BMI did not alter post-operative voice parameters, whereas sex may present differently upon acoustic analysis.

The numerical outcomes were summarized in **Table 2**. We also evaluated the risk of bias in the recruited studies using ROBINS-I tool as shown in **Table 3**. Most of recruited studies reveal low risk of bias, 2 studies have moderate concern of missing data bias due to short follow-up time; one study has moderate concern of bias in selection of the main reported result (lack of MPT outcomes); and the other one study had moderate bias in participant selection (vague description of inclusion criteria).

**TABLE 2 |** Compare the effects of ILs for post thyroid surgery UVFP with different injection material.

| | Pre-treatment | 3–6 month | 12-month | Post-treatment |
|---|---|---|---|---|
| **MPT (seconds)** | | | | |
| Fat (Fang et al. (21)) | **4.9 ± 2.9** | 9.3 ± 3.1 | 9.9 ± 2.5 | **10 ± 3.2** |
| PAAG &HA (Lee et al. (22)) | **4.7 ± 2.9** | | 8.8 ± 4.5 | **7.8 ± 5.4** |
| TVFP | 7.8 ± 4.9 | 12.1 ± 4.4 | | |
| PVFP | 4.3 ± 1.9 | 8.2 ± 3.6 | | |
| PMMA (Jang et al. (23)) | | | | |
| Early IL | **5.60 ± 3.19** | **7.93 ± 3.29** | | |
| Late IL | **5.41 ± 3.68** | **7.61 ± 3.77** | | |
| Fat (Lin et al. (25)) | **5.95 ± 4.15** | | 8.77 ± 4.92 | |
| **Jitter (%)** | | | | |
| Fat (Fang et al. (21)) | **3.1 ± 1.7** | 1.2 ± 0.6 | 1.2 ± 0.7 | **1.0 ± 0.4** |
| PAAG &HA (Lee et al. (22)) | **2.9 ± 1.1** | | 3.0 ± 2.7 | **2.2 ± 0.6** |
| TVFP | 3.8 ± 1.0 | 1.3 ± 0.3 | | |
| PVFP | 3.6 ± 2.6 | 2.7 ± 0.8 | | |
| PMMA (Jang et al. (23)) | | | | |
| Early IL | **5.12 ± 4.81** | **2.22 ± 1.80** | | |
| Late IL | **3.89 ± 2.34** | **3.10 ± 4.18** | | |
| HA (Chun et al. (24)) | **3.36 ± 2.05** | 2.12 ± 1.38 | **1.85 ± 1.23** | |

*MPT, Maximal phonation time; PAAG, PAAG (Aquamid®); HA, Hyaluronic acid (Rofilan®); TVFP, transient vocal fold paralysis; PVFP, permanent vocal fold paralysis; IL, injection laryngoplasty.*
*The bold values are used in meta-analysis.*

We combined the result of these studies for subsequent meta-analysis. The first outcome parameter iS MPT, reported among 4 studies. Because the heterogeneity test showed non-significance (I square = 46%, $p = 0.11$), we adapted the results of fixed effect model (**Figure 2**). Meta-analysis showed an increased MPT of 3.18s (95% CI: 2.40–3.96) after IL. The second outcome parameter was jitter (%), which was also reported in 4 studies. Considering significant heterogeneity among the recruited research (I square = 75%, $p < 0.01$), we adapted results of random effect model which showed an improvement of 1.46 (95% CI: 0.73–2.19).

**TABLE 3** | Evaluating the risk of bias in recruited studies using ROBINS-I (19).

| Publications | D1 | D2 | D3 | D4 | D5 | D6 | D7 |
|---|---|---|---|---|---|---|---|
| Fang et al. (21) | L | L | L | L | L | L | L |
| Lee et al. (22) | L | L | L | L | L | L | L |
| Jang et al. (23) | L | L | L | L | M | L | L |
| Chun et al. (24) | L | L | L | L | L | L | M |
| Lin et al. (25) | L | M | L | L | M | L | L |

*Domains included in ROBINS-I.*
*D1: Bias due to confounding.*
*D2: Bias in selection of participants into the study.*
*D3: Bias in classification of interventions.*
*D4: Bias due to deviations from intended interventions.*
*D5: Bias due to missing data.*
*D6: Bias in measurement of outcomes.*
*D7: Bias in selection of the reported result.*
*Judgement: Low risk of bias: **L**; Moderate risk of bias: **M**; Serious risk of bias: **S**; Critical risk of bias: C; No information: NA.*

## DISCUSSION

UVFP often leads to significant morbidity that may include dysphonia, swallowing problems and aspiration after thyroid surgery. Conservative treatment via voice therapy may ameliorate part of the symptoms of UVFP (26, 27). For patients not responding to voice therapy, surgical correction include injection laryngoplasty, medialization thyroplasty, arytenoid adduction and reinnervation of recurrent laryngeal nerve (28). Chen et al. (29) conduct a meta-analysis for management of UVFP, they recommend absorbable material injection laryngoplasty during the first year and reinnervation after 12 months. According to another systematic review for UVFP management, earlier IL is suggested to decrease the necessary of subsequent medialization thyroplasty (30). Considering IL for UVFP after thyroid surgery, Jang et al. (23) reported that the amount of voice improvement was significantly larger in the early injection group, especially in jitter (%) ($P = 0.02$) and shimmer (%) ($P = 0.03$). Therefore, earlier IL is suggested for post thyroid surgery related UVFP.

Despite continual reports show that IL is effective and are available for treatment of UVFP (16, 28–31), most of the

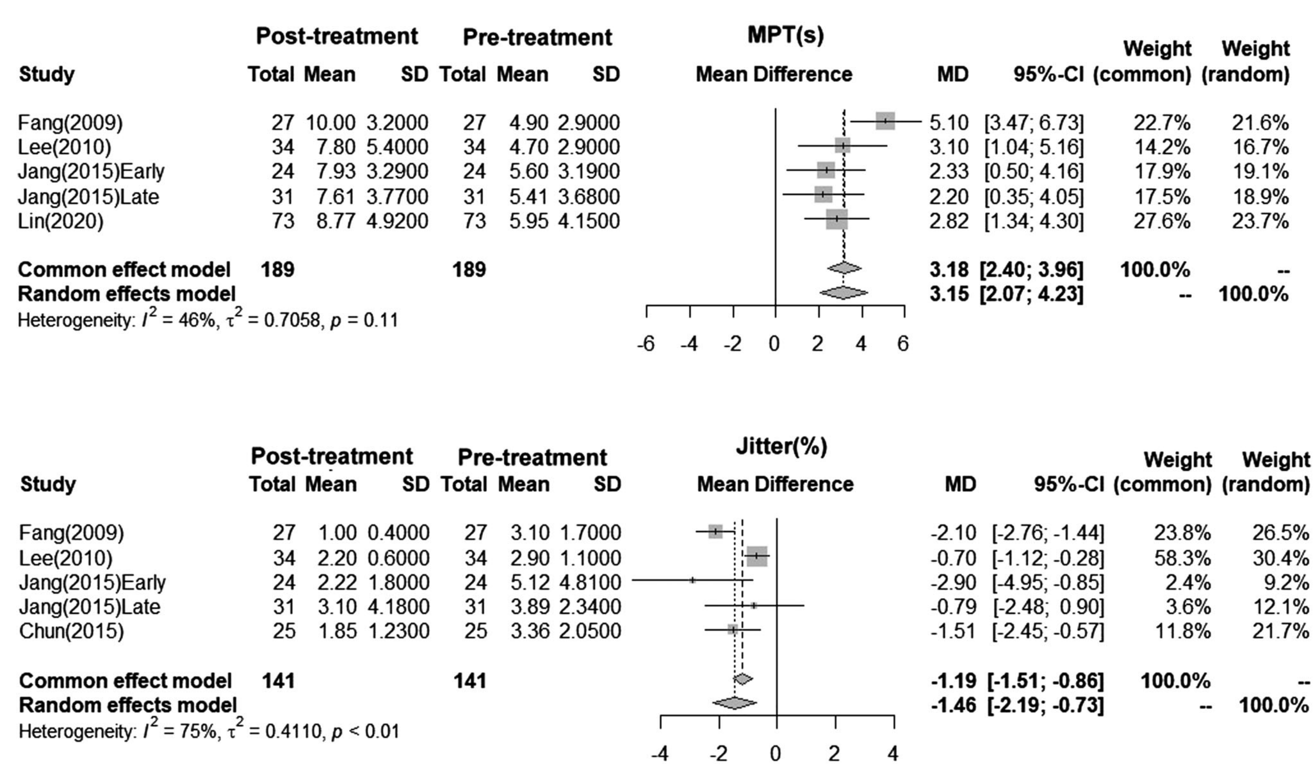



**FIGURE 2** | Forest plots show the results of meta-analysis from the included research. Fixed effect (i.e., common effect) model was selected for statistical inference when heterogeneity between research was non-significant, whereas random effects model was applied in presence of significant heterogeneity.

published literature mixed with different etiologies of UVFP. Considering the prevalence of thyroid neoplasm and the high incidence of thyroidectomy-related UVFP (2), this review specifically retain only original papers reporting IL for UVFP after thyroid surgeries. Considering the potential heterogeneity when pooling the effectiveness of IL, we adapted the results from either fixed effect or random effect model. Our literatures review supported that IL is an effective management for post-thyroidectomy related UVFP. Further meta-analysis showed IL could increase MPT for 3.18 (2.40–3.96) seconds and decrease Jitter (%) for 1.46 (0.73–2.19), both results were statistically significant (**Figure 2**).

Different injection material for IL were noticed in this literature review and may be further divided into temporary versus permanent intentions. Temporary material as hyaluronic acid and permanent material as autologous fat are the most common injection materials for IL. In the report by Fang et al, CT scan showed that injected autologous fat remained in situ with a mean interval of 26 ± 13 months after initial IL. The parameters from acoustic analyses also revealed stable results after 12 months, indicating that autologous fat may be a potential long-term filler. Similar results had also been reported by Umeno et al. (32), which showed that only a minimum patients (<5%) needs secondary IL following autologous fat injection. Nevertheless, controversial findings from other studies showed higher failure rates ranged from 30% to 41%, and patients may need further revision fat injection after 12 to 24 months (33, 34). Possible explanations for such a great diversity include different donor site of adipose tissues, harvesting techniques (e.g., liposuction vs. mincing), additive insulin, centrifugation, size of the injection needle, and pressurized instrument (35–38).

Another advantage of IL is that it could be performed under local anesthesia with multiple injection routes (39). In this review, 3 article performed transcutaneous injection route from cricothyoid membrane (**Figure 3**) (22–24). Other methods include ultrasound guided (40) or EMG guided (41, 42) injection. Otherwise, IL may also be performed under routine general anesthesia with direct laryngoscope suspension, similar to the 2 studies using autologous fat for IL in this review (21, 25). With regarding to the voice outcome, in our opinion, no technique is superior to other approaches. The choice of guiding and injection technique depends on the patient's preference and the operator's experience.

The long-term effect of IL remains undetermined. The recruited studies did not report the percentage of patients who need repeated IL or laryngeal framework surgery. Limited by varying reported parameters (2 studies using VHI-30 (22, 23) while another study use VHI-10 (25), we cannot perform a meta-analysis using patient-reported outcomes in this study. In addition, some of these studies were conducted retrospectively via chart review (23, 25) and may present some degree of bias. Further prospective study is still necessary to confirm the longer effect of IL for post-thyroidectomy related UVFP.

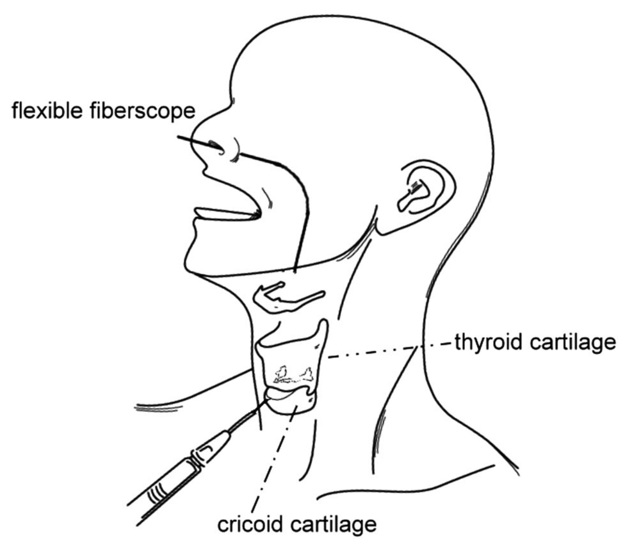



**FIGURE 3** | IL performed under local anesthesia with flexible fiberscope guidance via cricothyroid membrane.

## CONCLUSION

This review supported that IL could improve the voice outcome for post-thyroidectomy UVFP. Autologous fat remains a good augmentation material with a potential longer lasting effect. More research and long-term survey might be needed to document the safety and longevity of other synthetic materials.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author's.

## AUTHOR CONTRIBUTIONS

L-JL: Study conceptualization, Data extracting, Statistical Analysis, Manuscript drafting. C-TW: Manuscript drafting, Article proof-reading. All authors contributed to the article and approved the submitted version.

## FUNDING

This work was supported by grants from the Far Eastern Memorial Hospital (FEMH-2021-C-011).

## ACKNOWLEDGEMENTS

We thank CH Lee for drawing the pictures illustrating injection method.

## REFERENCES

1. Merati AL, Shemirani N, Smith TL, Toohill RJ. Changing trends in the nature of vocal fold motion impairment. *Am J Otolaryngol*. (2006) 27:106–8. doi: 10.1016/j.amjoto.2005.07.020
2. Tolley NS, Chaidas K, Bergenfelz A. Rates of RLN and SLN injury: Data from national quality registries and the literature. In: GW Randolph, editor. *The recurrent and superior laryngeal nerves*. Switzerland: Springer (2016). p. 1–16.
3. Tsai M-S, Yang Y-H, Liu C-Y, Lin M-H, Chang G-H, Tsai Y-T, et al. Unilateral vocal fold paralysis and risk of pneumonia: a nationwide population-based cohort study. *Otolaryngol Head Neck Surg*. (2018) 158:896–903. doi: 10.1177/0194599818756285
4. Cantarella G, Viglione S, Forti S, Pignataro L. Voice therapy for laryngeal hemiplegia: the role of timing of initiation of therapy. *J Rehabil Med*. (2010) 42:442–6. doi: 10.2340/16501977-0540
5. O'Leary MA, Grillone GA. Injection laryngoplasty. *Otolaryngol Clin North Am*. (2006) 39:43–54. doi: 10.1016/j.otc.2005.10.008
6. Arnold GE. Vocal rehabilitation of paralytic dysphonia: IX. Technique of intracordal injection. *Arch Otolaryngol*. (1962) 76:358–68. doi: 10.1001/archotol.1962.00740050368013
7. Varvares MA, Montgomery WW, Hillman RE. Teflon granuloma of the larynx: etiology, pathophysiology, and management. *Annals of Otology, Rhinol Laryngol*. (1995) 104:511–5. doi: 10.1177/000348949510400702
8. Kwon TK, Buckmire R. Injection laryngoplasty for management of unilateral vocal fold paralysis. *Curr Opin Otolaryngol Head Neck Surg*. (2004) 12:538–42. doi: 10.1097/01.moo.0000144393.40874.98
9. Remacle M, Lawson G, Keghian J, Jamart J. Use of injectable autologous collagen for correcting glottic gaps: initial results. *J Voice*. (1999) 13:280–8. doi: 10.1016/S0892-1997(99)80033-2
10. Courey MS. Homologous collagen substances for vocal fold augmentation. *Laryngoscope*. (2001) 111:747–58. doi: 10.1097/00005537-200105000-00001
11. Ford CN, Staskowski PA, Bless DM. Autologous collagen vocal fold injection: a preliminary clinical study. *Laryngoscope*. (1995) 105:944–8. doi: 10.1288/00005537-199509000-00014
12. Ford CN, Martin DW, Warner TF. Injectable collagen in laryngeal rehabilitation. *Laryngoscope*. (1984) 94:513–8. doi: 10.1288/00005537-198404000-00016
13. Wen MH, Cheng PW, Liao LJ, Chou HW, Wang CT. Treatment outcomes of injection laryngoplasty using cross-linked porcine collagen and hyaluronic acid. *Otolaryngol Head Neck Surg*. (2013) 149:900–6. doi: 10.1177/0194599813508082
14. Carroll TL. Ideal Material Selection for Vocal Fold Augmentation. In: BJ Lee, TK Kown, CA Rosen, editors. *Vocal fold injection*. Singapore: Springer (2021). p. 73–8.
15. Kwon T-K, Rosen CA, Gartner-Schmidt J. Preliminary results of a new temporary vocal fold injection material. *J Voice*. (2005) 19:668–73. doi: 10.1016/j.jvoice.2005.01.009
16. Wang C-C, Wu S-H, Tu Y-K, Lin W-J, Liu S-A. Hyaluronic acid injection laryngoplasty for unilateral vocal fold paralysis—a systematic review and meta-analysis. *Cells*. (2020) 9:2417. doi: 10.3390/cells9112417
17. Carroll TL, Rosen CA. Long-term results of calcium hydroxylapatite for vocal fold augmentation. *Laryngoscope*. (2011) 121:313–9. doi: 10.1002/lary.21258
18. Wang CT, Liao LJ, Lo WC, Huang TW, Cheng PW. Effects of comorbidity and medication use on the haemodynamic status during office-based laryngeal procedures: a prospective cohort study. *Clin Otolaryngol*. (2018) 43:124–30. doi: 10.1111/coa.12909
19. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. (2016) 355:i4919. doi: 10.1136/bmj.i4919
20. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Evid Based Ment Health*. (2019) 22:153–60. doi: 10.1136/ebmental-2019-300117
21. Fang TJ, Lee LA, Wang CJ, Li HY, Chiang HC. Intracordal fat assessment by 3-dimensional imaging after autologous fat injection in patients with thyroidectomy-induced unilateral vocal cord paralysis. *Surgery*. (2009) 146:82–7. doi: 10.1016/j.surg.2009.02.005
22. Lee SW, Kim JW, Chung CH, Mok JO, Shim SS, Koh YW, et al. Utility of injection laryngoplasty in the management of post-thyroidectomy vocal cord paralysis. *Thyroid*. (2010) 20:513–7. doi: 10.1089/thy.2009.0397
23. Jang JY, Lee G, Ahn J, Son YI. Early voice rehabilitation with injection laryngoplasty in patients with unilateral vocal cord palsy after thyroidectomy. *Eur Arch Otorhinolaryngol*. (2015) 272:3745–50. doi: 10.1007/s00405-015-3720-8
24. Chun BJ, Bae JS, Chae BJ, Park JO, Nam IC, Kim CS, et al. The therapeutic decision making of the unilateral vocal cord palsy after thyroidectomy using thyroidectomy-related voice questionnaire (TVQ). *Eur Arch Otorhinolaryngol*. (2015) 272:727–36. doi: 10.1177/0194599814541629a139
25. Lin WY, Chang WD, Ko LW, Tsou YA, Chen SH. Impact of patient-related factors on successful autologous fat injection laryngoplasty in thyroid surgical treated related unilateral vocal fold paralysis- observational study. *Medicine (Baltimore)*. (2020) 99:e18579. doi: 10.1097/MD.0000000000019406
26. Schindler A, Bottero A, Capaccio P, Ginocchio D, Adorni F, Ottaviani F. Vocal improvement after voice therapy in unilateral vocal fold paralysis. *J Voice*. (2008) 22:113–8. doi: 10.1016/j.jvoice.2006.08.004
27. D'Alatri L, Galla S, Rigante M, Antonelli O, Buldrini S, Marchese MR. Role of early voice therapy in patients affected by unilateral vocal fold paralysis. *J Laryngol Otol*. (2008) 122:936–41. doi: 10.1017/S0022215107000679
28. Siu J, Tam S, Fung K. A comparison of outcomes in interventions for unilateral vocal fold paralysis: a systematic review. *Laryngoscope*. (2016) 126:1616–24. doi: 10.1002/lary.25739
29. Chen X, Wan P, Yu Y, Li M, Xu Y, Huang P, et al. Types and timing of therapy for vocal fold paresis/paralysis after thyroidectomy: a systematic review and meta-analysis. *J Voice*. (2014) 28:799–808. doi: 10.1016/j.jvoice.2014.02.003
30. Vila PM, Bhatt NK, Paniello RC. Early-injection laryngoplasty may lower risk of thyroplasty: a systematic review and meta-analysis. *Laryngoscope*. (2018) 128:935–40. doi: 10.1002/lary.26894
31. Chang W-D, Chen S-H, Tsai M-H, Tsou Y-A. Autologous fat injection laryngoplasty for unilateral vocal fold paralysis. *J Clin Med*. (2021) 10:5034. doi: 10.3390/jcm10215034
32. Umeno H, Shirouzu H, Chitose S-I, Nakashima T. Analysis of voice function following autologous fat injection for vocal fold paralysis. *Otolaryngol Head Neck Surg*. (2005) 132:103–7. doi: 10.1016/j.otohns.2004.09.016
33. Laccourreye O, Papon JF, Kania R, Crevier-Buchman L, Brasnu D, Hans S. Intracordal injection of autologous fat in patients with unilateral laryngeal nerve paralysis: long-term results from the patient's perspective. *Laryngoscope*. (2003) 113:541–5. doi: 10.1097/00005537-200303000-00027
34. McCulloch TM, Andrews BT, Hoffman HT, Graham SM, Karnell MP, Minnick C. Long-term follow-up of fat injection laryngoplasty for unilateral vocal cord paralysis. *Laryngoscope*. (2002) 112:1235–8. doi: 10.1097/00005537-200207000-00017
35. Erdim M, Tezel E, Numanoglu A, Sav A. The effects of the size of liposuction cannula on adipocyte survival and the optimum temperature for fat graft storage: an experimental study. *J Plast Reconstr Aesthet Surg*. (2009) 62:1210–14. doi: 10.1016/j.bjps.2008.03.016
36. de Souza Kruschewsky L, de Mello-Filho FV, dos Santos AC, Rosen CA. Autologous fat graft absorption in unilateral paralyzed canine vocal folds. *Laryngoscope*. (2007) 117:96–100. doi: 10.1097/01.mlg.0000245013.98844.30
37. Shiffman MA, Mirrafati S. Fat transfer techniques: the effect of harvest and transfer methods on adipocyte viability and review of the literature. *Dermatol Surg*. (2001) 27:819–26. doi: 10.1046/j.1524-4725.2001.01062.x
38. Butterwick KJ, Nootheti PK, Hsu JW, Goldman MP. Autologous fat transfer: an in-depth look at varying concepts and techniques. *Facial Plast Surg Clin*. (2007) 15:99–111. doi: 10.1016/j.fsc.2006.10.003
39. Lee BJ, Kwon T-K, Rosen CA. *Vocal fold injection*. Singapore: Springer (2021).
40. Carrillo A, Garcia-Del-Salto L, Vaca M. Injection laryngoplasty under ultrasonographic control. *Eur Arch Otorhinolaryngol*. (2021) 278:2143–6. doi: 10.1007/s00405-021-06666-z
41. Wang CC, Chang MH, Jiang RS, Lai HC, De Virgilio A, Wang CP, et al. Laryngeal electromyography-guided hyaluronic acid vocal fold injection for unilateral vocal fold paralysis: a prospective long-term follow-up outcome report. *JAMA Otolaryngol Head Neck Surg*. (2015) 141:264–71. doi: 10.1001/jamaoto.2014.3466
42. Gotxi-Erezuma I, Ortega-Galan M, Laso-Elguezabal A, Prieto Puga G, Bullido-Alonso C, Garcia-Gutierrez S, et al. Electromyography-guided

hyaluronic acid injection laryngoplasty in early stage of unilateral vocal fold paralysis. *Acta Otorrinolaringol Esp (Engl Ed)*. (2017) 68:274–83. doi: 10.1016/j.otoeng.2017.08.008

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Publisher's Note:** All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Surgery

ORIGINAL RESEARCH
published: 28 April 2022
doi: 10.3389/fsurg.2022.867948

# Clinical and Anatomical Factors Affecting Recurrent Laryngeal Nerve Paralysis During Thyroidectomy *via* Intraoperative Nerve Monitorization

***Nurcihan Aygun*** [1]***, *Mehmet Kostek*** [1]**, *Mehmet Taner Unlu*** [1]**, *Adnan Isgor*** [2] ***and Mehmet Uludag*** [1]

*[1] Department of General Surgery, Sisli Hamidiye Etfal Training and Research Hospital, Istanbul, Turkey, [2] Department of General Surgery, Sisli Memorial Hospital, Istanbul, Turkey*

OPEN ACCESS

***Edited by:***
*Gianlorenzo Dionigi,*
*University of Milan, Italy*

***Reviewed by:***
*Alvaro Sanabria,*
*University of Antioquia, Colombia*
*Kyung Tae,*
*Hanyang University, South Korea*

****Correspondence:***
*Nurcihan Aygun*
*nurcihanaygun@hotmail.com*

***Specialty section:***
*This article was submitted to Otorhinolaryngology - Head and Neck Surgery, a section of the journal Frontiers in Surgery*

***Received:*** *01 February 2022*
***Accepted:*** *25 March 2022*
***Published:*** *28 April 2022*

***Citation:***
*Aygun N, Kostek M, Unlu MT, Isgor A and Uludag M (2022) Clinical and Anatomical Factors Affecting Recurrent Laryngeal Nerve Paralysis During Thyroidectomy via Intraoperative Nerve Monitorization. Front. Surg. 9:867948. doi: 10.3389/fsurg.2022.867948*

**Background:** Despite all the technical developments in thyroidectomy and the use of intraoperative nerve monitorization (IONM), recurrent laryngeal nerve (RLN) paralysis may still occur. We aimed to evaluate the effects of anatomical variations, clinical features, and intervention type on RLN paralysis.

**Method:** The RLNs identified till the laryngeal entry point, between January 2016 and September 2021 were included in the study. The effects of RLN anatomical features considering the International RLN Anatomical Classification System, intervention and monitoring types on RLN paralysis were evaluated.

**Results:** A total of 1,412 neck sides of 871 patients (672 F, 199 M) with a mean age of 49.17 + 13.42 years (range, 18–99) were evaluated. Eighty-three nerves (5.9%) including 78 nerves with transient (5.5%) and 5 (0.4%) with permanent vocal cord paralysis (VCP) were detected. The factors that may increase the risk of VCP were evaluated with binary logistic regression analysis. While the secondary thyroidectomy (OR: 2.809, 95%CI: 1.302–6.061, $p = 0.008$) and Berry entrapment of RLN (OR: 2.347, 95%CI: 1.425–3.876, $p = 0.001$) were detected as the independent risk factors for total VCP, the use of intermittent-IONM (OR: 2.217, 95% CI: 1.299–3.788, 0.004), secondary thyroidectomy (OR: 3.257, 95%CI: 1.340–7.937, $p = 0.009$), and nerve branching (OR: 1.739, 95%CI: 1.049–2.882, $p = 0.032$) were detected as independent risk factors for transient VCP.

**Conclusion:** Preference of continuous-IONM particularly in secondary thyroidectomies would reduce the risk of VCP. Anatomical variations of the RLN cannot be predicted preoperatively. Revealing anatomical features with careful dissection may contribute to risk reduction by minimizing actions causing traction trauma or compression on the nerve.

**Keywords: thyroidectomy, RLN injury, intraoperative neuromonitoring (IONM), RLN branching, inferior thyroid artery (ITA)**

# INTRODUCTION

Recurrent laryngeal nerve (RLN) is one of the most important anatomical structures at risk during thyroidectomy. In literature, it has been reported that factors such as thyroid cancer, neck dissection, Graves' disease, thyroiditis, large goiter, retrosternal goiter, recurrent benign, and malignant diseases, complete resection of the thyroid lobe, uncertain identification of RLN, reoperation for postoperative bleeding, previous neck radiotherapy, anatomic variations, low and medium hospital volume, low surgeon volume, extralaryngeal branching nerve, non-recurrent laryngeal nerve were related with an increased risk of post-thyroidectomy RLN paralysis (1–8).

Routine dissection and visual identification of the RLN were defined by Lahey in 1938 and are still the gold standard method (9).

It could be difficult to visually identify the RLN intraoperatively due to the factors such as anatomical variations of the RLN, recurrent goiter, large substernal goiter, and locally advanced thyroid cancer, which may be related to the increased risk of RLN paralysis (8).

Although many clinical factors associated with an increased risk of RLN paralysis can be predicted preoperatively, especially anatomical variations of the RLN cannot be predicted preoperatively (6).

With the improving data regarding the anatomy and function of the RLN, the use of intraoperative nerve monitoring (IONM), one of the technical and technological developments allowing functional evaluation of the nerve in addition to visual identification has been increasing recently (10, 11).

The visual identification rate of the nerve is increased by IONM, allowing the early localization and identification of RLN (8). Whether IONM reduces the risk of RLN paralysis is still controversial, and there are still studies reporting that it has no significant effect on RLN paralysis (12).

It has been demonstrated that the use of IONM reduces the risk of RLN injury (13), and continuous IONM (CIONM) is superior to intermittent IONM (IIONM) in preventing RLN injury (11, 14).

In many studies anatomical variations of RLN and its relationship with various landmarks such as Zuckerkandl tubercle, inferior thyroid artery (ITA), and Berry ligament have been investigated (15–20).

The International RLN anatomical classification system was published in 2016, including the trajectory of the main trunk of the RLN and its potential clinically important features such as extralaryngeal branching, neural entrapment, invasion, diameter of the nerve, dynamic components of surgery related to postoperative glottic function such as signal loss and extensive neural dissection. The estimated rates for the prevalence of anatomical features and RLN trajectory includes a literature review and expert opinions of the International Neural Monitoring Study Group (INMSG) (21).

A prospective international multicentric study evaluating 1,000 nerves considering this classification system and its associated RLN paralysis was recently published (22).

The study group continues to collect data and is preparing to publish the second part of the study which includes 5,000 nerves. The number of studies evaluating anatomical factors affecting RLN injury is limited. In this study, we aimed to evaluate the risk factors for RLN paralysis, including the anatomical data according to the International RLN Anatomic Classification System.

# MATERIALS AND METHODS

## Study Population

The data of patients who underwent thyroidectomy (± parathyroidectomy) with IONM between January 2016 and August 2021 were evaluated retrospectively.

Demographic, clinical, anatomical, IONM, and operative data of all patients have been recorded in the clinical standard database in detail and informed consents have been obtained from the patients for data collection.

Approval was obtained from the local ethics committee and patients' data were analyzed according to the guidelines in the Helsinki Declaration.

In the analysis of the data, each nerve at risk on each operated neck side was considered as a separate entity. Patients with preoperative vocal cord paralysis (VCP), intentional resection of the RLN due to tumor invasion, neck side where only parathyroidectomy or subtotal thyroidectomy was performed, neck sides without fully explored RLNs, neck side with missing data of RLN's anatomical features, and patients without postoperative vocal cord examinations, patients younger than 18 years of age were excluded from the study (**Figure 1**).

Patient's gender, age, body mass index, type of surgery performed (primary or secondary intervention), the extent of surgery (thyroidectomy with or without central neck dissection), type of neuromonitoring, presence of preoperative hyperthyroidism, postoperative diagnosis, pre- and postoperative vocal cord examinations, side of the nerve on the neck, anatomical trajectory of the RLN in the neck according to International RLN anatomical classification and anatomically important neural features, the relationship of RLN and inferior thyroid artery, the Zuckerkandl tubercle (ZT) grade, and weight of the removed thyroid lobe were evaluated.

It was defined as extralaryngeal branching in case of RLN branching at least >5 mm before its laryngeal entry point and all its branches entering the larynx (23). Zuckerkandl tubercle (ZT) size was classified into 4 degrees by Pelizzo et al. If it is not seen it is graded as 0 degree, only thickening on the lateral edge of the thyroid lobe is graded as 1st degree, <1 cm is graded as 2nd degree, >1 cm is graded as 3rd degree. ZT 0 and 1st degrees were accepted as a category, 2nd and 3rd degrees were accepted as another category (24).

According to the international RLN anatomical classification system, the anatomical trajectory of the RLN in the neck is evaluated as normal course, acquired, or embryologic variation. Left normal trace (L1); RLN running parallel to the tracheoesophageal groove or at an angle of less than 30 degrees, right normal trace (R1); RLN running at an angle of 15–45 degrees relative to the tracheoesophageal groove, acquired

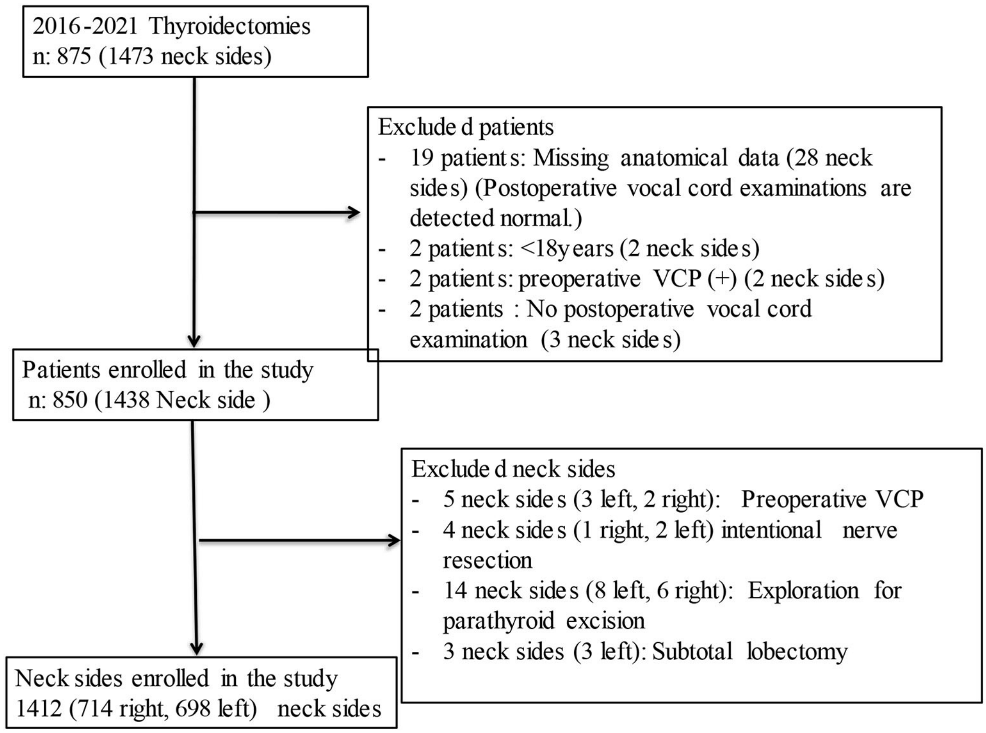



**FIGURE 1 |** Flow diagram of the patients enrolled in the study.

variations; lateral displacement of the nerve on the left (L2a), medial displacement (R2a) on the right, ventral displacement on the right and left (R2b, L2b, respectively), embryological variation was defined as non-recurrent nerve (R3 on the right, L3 on the left).

Clinically important features were evaluated whether fixed/splayed/entrapped (F), presence of nerve invasion (I), and RLN entrapped by Berry ligament posterior fibers or vascular structures (L) (21). All of the invaded nerves were excluded from the study because they had preoperative vocal cord paralysis or were resected intentionally.

## IONM and Thyroidectomy

All surgeries were performed under general anesthesia. All patients were intubated with a surface electrode-based endotracheal tube and a low-dose neuromuscular agent (recuronium 0.3 mg/kg) for induction. Muscle relaxants were not administered after induction. NIM 3.0 Nerve Monitoring system (Medtronic xomed, Jacksonville) with endotracheal tube was used. IONM was applied intermittently or continuously. Factors such as the choice of the surgeon depending on the case and the availability of the Automatic Periodic Stimulation (APS) probe (Medtronic Xomed Inc. Jacksonville, FL, USA) for the patient were effective in the selection of the IONM method. IONM installment, anesthesia induction and maintenance, tube position verification tests, IONM application (4-step procedure: V1, R1, R2, V2), and data evaluation were assessed according to the International nerve monitoring study group guidelines (25).

For intermittent IONM (IIONM), a monopolar stimulator probe (Medtronic Xomed) was used. The stimulations were applied with a current intensity of 1 mA, the stimulation duration of 100 ms, the threshold value of 100 mV, and the current frequency of 4 Hz.

Medtronic APS probe was used for continuous IONM (CIONM). At the level of the thyroid mid pole, the carotid sheath was opened, the vagus was dissected 360 degrees, and the APS probe was applied to the vagus and the electrode was connected to the monitor system. Baseline latency and amplitude responses were calibrated by giving 20 automatic periodic stimulations to the vagus nerve from the monitoring system. The system is set to stimulate with a current of 1 mA every second. Although the expected initial baseline value for CIONM was 500 $\mu$V, CIONM was applied at values above 300 $\mu$V. The device was set to give an audible and visual warning when the amplitude value is 50% below the baseline and/or the latency value increases by more than 10% of the baseline value.

The signal loss was defined as a decrease in amplitude below 100 $\mu$V or failure to receive it with supramaximal stimulation (25).

## Operational Technique

The approach to the thyroid gland was through the midline with an anterior approach between the strap muscles on both sides in primary thyroidectomies and/or in patients undergoing central neck dissection.

In secondary thyroidectomies and/or central dissection, the approach to the thyroid gland was through between the strap muscles and the sternocleidomastoid muscle with a backdoor lateral approach.

The sternohyoid and sternothyroid (or just the sternothyroid muscle) were divided 1/3 cranially to increase exposure and perform safer dissection in patients with large goiters and/or substernal goiters and patients with short necks.

In secondary central dissections, the sternothyroid muscle was routinely divided. After reaching the thyroid gland, the vagus nerve was found in the carotid sheath firstly and stimulated by the probe and the V1 response was recorded.

In general, dissection of the thyroid lobe was initiated from the upper pole. IONM was used for the identification, verification, and mapping of the external branch of the superior laryngeal nerve (EBSLN) during the dissection of the superior thyroid vessels.

In primary surgery, RLN was usually identified at the level of the inferior thyroid artery (ITA). The thyroid gland was carefully dissected from the anteromedial aspect of the RLN up to its entrance to the larynx. If the nerve was branched at the proximal of ITA, it was dissected to the point where it branched proximally.

In secondary interventions, to avoid scar tissue, the RLN was identified with an inferior approach, and it was mapped till its laryngeal entry point.

In severely large goiters or goiters with a large substernal component, the RLN was identified at the laryngeal entry point with a superior approach and dissected proximally. Rarely, in substernal or retropharyngeal enlarged goiters, the RLN was identified in the region of Berry's ligament with a medial approach. In cases with the persistent signal reduction due to the thyroid lobe traction in the lateral or superior approach, the medial approach was also preferred (26).

At the end of the operation, surgical data, vagus anatomical features, RLN anatomical trajectory and clinically important features, relationship with ITA, extralaryngeal branching features, the presence of Zuckerkandl tubercle, and its relationship with RLN, EBSLN anatomical features, IONM data were entered into the clinical database in detail.

In patients who were planned for bilateral intervention, the side where the malignancy was localized, the side with the dominant lobe or nodule was operated first. Staged thyroidectomy was performed in patients who developed signal loss on the first side, except for patients with a diagnosis of high and intermediate risk malignancy.

Completion of thyroidectomy to the contralateral lobe in patients who has a diagnosis of malignancy in the final pathology result after lobectomy or surgical intervention to the second side in staged thyroidectomy was accepted as the primary intervention.

The mechanisms of RLN injury were examined under 5 main headings; traction trauma due to medial traction and elevation of the thyroid lobe (A), blunt trauma with a surgical instrument during dissection of the nerve, contusion, accidental clamping of the nerve, pressure, compression, or suction with a surgical instrument (B), clipping or ligating during or after dissection of the nerve during the separation of small vessels or connective tissue, touching the nerve directly with electrocautery or energy-based device, or thermal injury by lateral heat spread (D), dividing the nerve due to visual misidentification (E) (22, 27).

Preoperative and postoperative vocal cord examinations were performed by an independent otolaryngologist. Postoperative periodic vocal cord examinations were applied to patients with postoperative VCP. If VCP improved in 12 months, it was defined as a transient, if it still persisted at 12 months, it was defined as permanent VCP (27).

## Statistical Analysis

Data were evaluated in the IBM SPSS Statistics version 25.0 program (IBM, Armonk, NY, USA). Data are presented as mean ± SD. The normal distribution of the data was tested and appropriate parametric or non-parametric tests were selected. Pearson Chi Square and Fisher exact tests were used to compare categorically independent groups, and the odd ratio was calculated for significant differences in 2 × 2 tables. To evaluate the independent factors affecting VCP, the formula formed from the features that were significant in pairwise comparisons was evaluated by binary logistic regression analysis. $p < 0.05$ values were considered statistically significant.

# RESULTS

Twenty-five patients (35 neck sides) of 875 patients who were operated on during the study period were excluded from the study. Completion thyroidectomy was performed in 21 of 850 patients, and a total of 871 operations were performed. The bilateral intervention was performed in 566 of 850 patients and unilateral intervention in 306 patients, and a totally 1,438 neck side interventions were performed in 850 patients. According to the exclusion criteria, 26 neck sides were excluded. A total of 1,412 neck sides were included in the study, 1,089 (77.1%) neck sides in 657 female patients and 323 (22.9%) neck sides in 193 male patients. In total, 714 (50.1%) of the nerves at risk were on the right side and 698 (49.9%) were on the left side.

IIONM was applied in 692 (49%) RLNs and CIONM was applied in 720 (51%) RLNs. Primary intervention was performed on 1,329 (94.1%) neck sides, and secondary intervention was performed on 83 (5.9%) neck sides. Central neck dissection was performed on 147 (10.4%) neck sides. The relationship between RLN and ITA was evaluated on the 1,396 neck sides. In total, 675 (48.4%) of the RLNs were crossing anterior to ITA, 596 (42.7%) of the RLNs were crossing posterior to ITA, and 125 (8.9%) of RLNs were crossing between the ITA branches. In total, 482 (34.1%) of RLNs had extralaryngeal branches, 449 (32.8%) had 2 branches, and 33 (2.3%) had 3 and more than 3 branches. Zuckerkandl's tubercle was evaluated in 1,291 lobes, of which 788 (61%) were 0 or 1st degree, and 503 (39%) were 2nd or 3rd degree.

RLNs (88.2%) were R1/L1, 7.8% of RLNs were R2a/L2a, 3.1% of RLNs were R2b/L2b, and 0.6% of RLNs were R3 according to the International RLN anatomical classification. R3 (non-recurrent nerves) were all on the right side, the ratio was 1.1% on the right side. RLN course was evaluated in 1,124 nerves, and 950 (84.5%) nerves had no features, 43 (3.8%) nerves were fixed, 59 (5.3%) nerves were splayed, 72 (6.4%) nerves were entrapped.

**TABLE 1 |** Evaluation of clinical and anatomical factors for total VCP by univariant analysis.

| Feature | | *n* | VCP *n* (%) | OR (95% CI min–max) | *p* |
|---|---|---|---|---|---|
| Age | | | | | |
| | No VCP | 1,329 (94.1%) | | 49.1 ± 13.5 (18–89) | 0.673 |
| | VCP | 83 (5.9%) | | 49.5 ± 11.7 (23–79) | |
| Gender | | 1,412 | | | |
| | Female | 1,089 (77.1%) | 65 (6%) | 0.928 (0.542–1.588) | 0.785 |
| | Male | 323 (22.9%) | 18 (5.6%) | | |
| BMI | | 1,230 | | | 0.883 |
| | No VCP | 1,170 | | 28.8 ± 6 (16.3–63) | |
| | VCP | 60 | | 28.7 ± 5.6 (18.4–44.4) | |
| Neck side of the nerve | | | | | |
| | Right | 714 (50.1%) | 46 (6.4%) | 0.813 (0.520–1.270) | 0.362 |
| | Left | 698 (49.9%) | 37 (5.3%) | | |
| Type of nerve monitoring | | | | | |
| | IIONM | 692 (49%) | 49 (7.1%) | 1.538 (0.980–2.413) | 0.061 |
| | CIONM | 720 (51%) | 34 (4.7%) | | |
| Type of intervention | | | | | |
| | Primary | 1,329 (94.1%) | 72 (5.4%) | 0.375 (0.190–0.738) | 0.005* |
| | Secondary | 83 (5.9%) | 11 (13.3%) | | |
| Central neck dissection | | | | | |
| | Applied | 147 (10.4%) | 10 (6.8%) | | 0.615 |
| | Not applied | 1,265 (89.6%) | 73 (5.8%) | 0.839 (0.423–1.663) | |
| RLN-ITA relationship | | 1,396 | | | 0.000* |
| | Anterior to ITA | 675 (48.4%) | 57 (8.4%) | 2.790 (0.994–7.833) | 0.051 |
| | Posterior to ITA | 596 (42.7%) | 19 (3.2%) | 0.996 (0.333–2.980) | 0.994 |
| | Between branches of ITA | 125 (8.9%) | 4 (3.2%) | | |
| Nerve branching | | 1,412 | | | 0.011* |
| | Non-branching | 930 (65.9%) | 44 (4.7%) | 1.773 (1.135–2.769) | |
| | Branching | 482 (34.1%) | 39 (8.1%) | | |
| Entrapment of RLN by Berry ligament | | 1,305 | | | |
| | Yes | 307 (23.5%) | 30 (9.8%) | 2.241 (1.388–3.619) | 0.001* |
| | No | 998 (76.5%) | 46 (4.6%) | | |
| Zuckerkandl tubercle | | 1,291 | | | |
| | 0 ve 1. grade | 788 (61%) | 48 (6.1%) | | 0.243 |
| | 2 ve 3. grade | 503 (39%) | 23 (4.6%) | | |
| RLN anatomy | | 1,232 | | | 0.208 |
| | R1/L1 | 1,091 (88.5%) | 56 (5.1%) | | |
| | R2a/L2a | 96 (7.8%) | 8 (8.3%) | | |
| | R2b/L2b | 38 (3.1%) | 4 (10.5%) | | |
| | R3/L3 | 7 (0.6%) | 1 (14.3%) | | |
| RLN trajectory | | 1,124 | | | 0.553 |
| | No feature | 950 (84.5%) | 56 (5.9%) | | |
| | Fixed | 43 (3.8%) | 1 (2.3%) | | |
| | Splayed | 59 (5.3%) | 5 (8.5%) | | |
| | Entrapped | 72 (6.4%) | 3 (4.2%) | | |
| Weight of thyroid gland lobe (gram) | | 1,059 | | | 0.127 |
| | No VCP | 1,008 | | 29.6 ± 32.7 (2–274) | |
| | VCP | 51 | | 32.4 ± 33 (5–204) | |
| Hyperthyroidism | | 1,412 | | | |
| | Yes | 1,091 (77.3%) | 62 (5.7%) | | 0.565 |

*(Continued)*

**TABLE 1** | Continued

| Feature | | n | VCP n (%) | OR (95% CI min–max) | p |
|---|---|---|---|---|---|
| | No | 321 (32.7%) | 21 (6.5%) | | |
| Final diagnosis | | 1,412 | | | |
| | Benign | 828 (58.6%) | 44 (5.3%) | | 0.148 |
| | Graves disease | 149 (10.6%) | 14 (9.4%) | | |
| | Malignant | 435 (30.8%) | 25 (5.7%) | | |

*VCP, vocal cord paralysis; IIONM, intermittent intraoperative nerve monitorization; CIONM, continuous intraoperative nerve monitorization; RLN, recurrent laryngeal nerve; ITA, inferior thyroid artery. *means statistically significant p value.*

Three hundred and seven (23.5%) of 1,305 nerves were entrapped in the Berry region by Berry fibers and/or vascular structures.

## VCP

VCP was detected in 83 (5.9%) of the total 1,412 RLNs, of which 78 (5.5%) were transient and 5 (0.4%) were permanent.

In paired comparison, total VCP rates in the secondary intervention compared to primary intervention (13.3 vs. 5.4%, $p = 0.005$, respectively), RLNs crossing anterior to ITA, compared to those crossing posterior to ITA and between the branches of ITA (8.4 vs. 3.2 vs. 3.2%, $p = 0.000$, respectively), extralaryngeal branching nerves compared to those without branching (8.1 vs. 4.7%, $p = 0.011$, respectively), RLNs with entrapment by Berry fibers and/or vascular structures compared with those without entrapment (9.8 vs. 4.6%, $p = 0.001$, respectively) were higher. No significant difference was found in terms of other factors (**Table 1**).

Temporary VCP rates in operations with the use of IIONM compared with those with the use of CIONM (6.9 vs. 4.2%, $p = 0.024$, respectively), secondary interventions compared to primary interventions (10.8 vs. 5.2%, $p = 0.033$, respectively), RLNs crossing ITA anteriorly, compared to those crossing posteriorly and between the branches (7.9 vs. 3 vs. 3.2%, $p = 0.000$, respectively), extralaryngeal branching nerves compared to the non-branching nerves(7.9 vs. 4.3%, $p = 0.005$, respectively), RLNs entrapped by Berry fibers and/or vascular structure compared to those without entrapment (9.8 vs. 4.1%, $p = 0.001$, respectively) were higher. No significant difference was detected in terms of other factors (**Table 2**).

Permanent VCP rates in secondary interventions compared to primary interventions (2.4 vs. 0.2%, $p = 0.009$, respectively), and patients with RLNs fixed, splayed, entrapped compared to those having normal RLN courses (2.3 vs. 1.7 vs. 1.4 vs. 0.2%, $p = 0.043$, respectively) were higher. No significant difference was detected in terms of other factors (**Table 3**).

In the logistic regression analysis, the type of monitoring, type of intervention, entrapment of the nerve in the Berry region, and RLN relationship with inferior thyroid artery were determined as independent risk factors for total VCP (**Table 4**). The risk of VCP was 2 times higher in those who underwent IIONM compared to those who underwent CIONM, 3.8 times higher in those who underwent secondary intervention compared to those who underwent primary intervention, 2.5 times higher in the entrapment of RLNs in the Berry region compared to those which has no entrapment 2.6 times in patients RLNs crossing ITA anteriorly compared to those crossing posteriorly or between the branches (**Table 4**).

## Mechanisms of RLN Injury

The mechanisms of RLN injury were traction trauma in 57 (68.8%) nerves, thermal injury in 17 (20.5%), unintentional nerve transection in 5 (6%), and mechanical trauma in 3 (3.7%). Rates of mechanisms of RLN injury were significantly different between IIONM and CIONM according to IONM type ($p = 0.042$). Traction trauma was more frequent in IIONM compared to CIONM (80 vs. 53%, respectively), however, mechanical trauma (2 vs. 8.8%, respectively), thermal injury (16 vs. 26.4%, respectively), unintentional transection (2 vs. 11.8%, respectively) were less frequent (**Table 5**).

# DISCUSSION

As far as we know, this study is the most extended study in terms of the number of nerves classified according to the International RLN anatomical classification system.

Despite the positive contribution of IONM to the reduction of RLN paralysis in thyroidectomy, VCP is still among the main post-thyroidectomy complications. In this study, IONM was used in all patients and post-thyroidectomy total VCP rate according to the number of nerves was 5.9%, temporary VCP rate was 5.5%, and permanent VCP was 0.4%. In our results, logistic regression analysis with the formula obtained from the factors that were significant in paired comparison; IIONM, secondary interventions, entrapment of the RLN in the Berry region, RLNs crossing the ITA from the anterior, nerve branching revealed as independent factors increasing the risk of VCP. In our study, the risk of VCP with IIONM was 2 times higher ($p = 0.008$) than with CIONM. The risk of VCP is approximately 3.8 times ($p = 0.001$) higher in secondary interventions compared to primary interventions, and 2.5 times ($p = 0.000$) higher in entrapment of RLN in the Berry region, 2.6 times ($p = 0.001$) higher with the RLNs crossing anterior to ITA compared with those crossing between the branches and posterior to ITA. Although the rate of VCP was 1.6 times higher in branched

**TABLE 2 |** Evaluation of clinical and anatomical factors for temporary VCP by univariant analysis.

| Feature | | *n* | VCP n (%) | OR (95% CI min–max) | *p* |
|---|---|---|---|---|---|
| Age | | | | | |
| | No VCP | 1,329 | | 49.2 ± 13.5 (18–89) | 0.979 |
| | VCP | 78 | | 48.9 ± 11.8 (23–79) | |
| Gender | | | | | |
| | Female | 1,089 | 61 (5.6%) | 0.934 (0.538–1.624) | 0.810 |
| | Male | 323 | 17 (5.3%) | | |
| BMI | | 1,225 | | | 0.638 |
| | No VCP | 1,170 | | 28.8 ± 6 (16.3–63) | |
| | VCP | 55 | | 28.4 ± 5.4 (18.4–44.4) | |
| Neck side of the nerve | | | | | |
| | Right | 714 | 43 (6%) | 0.824 (0.521–1.304) | 0.407 |
| | Left | 698 | 35 (5%) | | |
| Type of nerve monitoring | | | | | |
| | IIONM | 692 | 48 (6.9%) | 1.714 (1.073–2.739) | 0.024* |
| | CIONM | 720 | 30 (4.2%) | | |
| Type of intervention | | | | | |
| | Primary | 1,329 | 69 (5.2%) | 0.450 (0.216–0.937) | 0.033* |
| | Secondary | 83 | 9 (10.8%) | | |
| Central neck dissection | | | | | |
| | Applied | 147 | 8 (5.4%) | 1.018 (0.480–2.160) | 0.963 |
| | Not applied | 1,265 | 70 (5.5%) | | |
| RLN-ITA relationship | | | | | 0.000* |
| | Anterior to ITA | 675 | 53 (7.9%) | 2.578 (0.916–7.255) | 0.073 |
| | Posterior to ITA | 596 | 18 (3%) | 0.942 (0.313–2.833) | 0.915 |
| | Between branches of ITA | 125 | 4 (3.2%) | | |
| Nerve branching | | 1,412 | | | 0.005* |
| | Non-branching | 930 | 40 (4.3%) | 1.904 (1.204–3.012) | |
| | Branching | 482 | 38 (7.9%) | | |
| Entrapment of RLN by Berry ligament | | | | | |
| | Yes | 307 | 30 (9.8%) | 2.528 (1.549–4.124) | 0.001* |
| | No | 998 | 41 (4.1%) | | |
| Zuckerkandl tubercle | | 1,291 | | | |
| | 0 ve 1. grade | 788 | 43 (5.5%) | | 0.482 |
| | 2 ve 3. grade | 503 | 23 (4.6%) | | |
| RLN anatomy | | 1,232 | | | 0.280 |
| | R1/L1 | 1,091 | 53 (4.9%) | | |
| | R2a/L2a | 96 | 6 (6.3%) | | |
| | R2b/L2b | 38 | 4 (10.5%) | | |
| | R3/L3 | 7 | 1 (14.3%) | | |
| RLN trajectory | | 1,124 | | | 0.281 |
| | No feature | 950 | 54 (5.7%) | | |
| | Fixed | 43 | 0 | | |
| | Splayed | 59 | 4 (6.8%) | | |
| | Entrapped | 72 | 2 (2.8%) | | |
| Weight of thyroid lobe (gram) | | 1,059 | | | 0.052 |
| | No VCP | 1,008 | | 29.6 ± 32.8 (2–274) | |
| | VCP | 51 | | 32.8 ± 32.6 (5–204) | |
| Hyperthyroidism | | | | | |
| | Yes | 1,091 | 57 (5.2%) | | 0.364 |
| | No | 321 | 21 (6.5%) | | |

*(Continued)*

**TABLE 2** | Continued

| Feature | | *n* | VCP n (%) | OR (95% CI min–max) | *p* |
|---|---|---|---|---|---|
| Final diagnosis | | | | | |
| | Benign | 828 | 41 (5%) | | 0.089 |
| | Graves' disease | 149 | 14 (9.4%) | | |
| | Malignant | 435 | 23 (5.3%) | | |

*VCP, vocal cord paralysis; IIONM, intermittent intraoperative nerve monitorization; CIONM, continuous intraoperative nerve monitorization; RLN, recurrent laryngeal nerve; ITA, inferior thyroid artery. *means statistically significant p value.*

nerves than in non-branching nerves, the difference was not significant ($p = 0.055$).

Although the temporary VCP rate was lower in CIONM, the permanent VCP rate was higher in CIONM, although the statistical analysis was not significant (0.6 vs. 0.1%, $p = 0.375$).

The prevalence of IONM usage has increased significantly in the last 10 years by both general surgeons and otolaryngologists (10).

The effect of IONM on VCP is still controversial. In some studies, it has been reported that the use of IONM does not have a significant effect on VCP (4, 12). In some meta-analyses regarding this subject, it has been reported that IONM had no significant benefit over visualization in preventing RLN injury, and it should not be considered as standard care and replace visualization (28, 29).

On the other hand, Barczynski et al. demonstrated in their randomized clinical trial that IONM decreased the rate of transient RLN paralysis (30).

Vasileiadai et al. demonstrated in their study that the use of IONM decreased both transient and permanent RLN injuries significantly (31).

Bai and Chen detected that IONM decreased the rates of both temporary and permanent RLN paralyzes in a meta-analysis including 59,380 nerves, and they recommended routine use of IONM, especially in bilateral operations and malignant operations (13).

In our study, the most common cause of VCP was traction trauma (68.8%), similar to other studies (27).

Even though the rate of traction trauma was lower in the CIONM group than IIONM group (53 vs. 80%, respectively), the rates of thermal trauma (16 vs. 26.4%, respectively) and unintentional transection (2 vs. 11.8%, respectively) were higher in the CIONM group. CIONM supports the early detection of signs of traction trauma, contributing to the reduction of VCP associated with traction trauma by changing the action. On the other hand, all of the permanent VCPs in the study emerged after the unintentional transection.

Although CIONM is an effective method for preventing VCPs due to traction trauma, it is unlikely to prevent sudden actions such as transection, cauterization, and clamping (32).

In a study, in which 1,526 patients who were operated on for benign thyroid disease were evaluated, also IIONM and CIONM were compared, the rates of temporary VCP were comparable (2.3 vs. 2.6%, $p = 0.844$, respectively), and it was found that the rate of permanent VCP decreased with CIONM (0.4 vs. 0% $p = 0.019$) (33).

CIONM was also found to be more suitable for evaluating nerve electrophysiology in children (34).

In a comparative study involving 6,029 patients, CIONM was found to be an independent risk reducing factor for both temporary and permanent VCP, and it was found to reduce early VCP by 1.8 times (OR: 0.56) and permanent VCP by 29.4 times (OR: 0.0034) compared to IIONM. Permanent VCP develops in one out of every 4.2 early VCPs with IIONM and in one out of 75 early VCPs with CIONM, the probability of developing permanent VCP after early VCP is 17.9 times lower in CIONM, and it has been demonstrated to be a superior method in preventing VCP (14).

However, the rate of use of CIONM is still very low compared to IIONM (10).

Reoperations for thyroid disease are associated with an increased risk of RLN paralysis (4, 5, 35).

In the retrospective cohort study by Barczynski et al. IIONM significantly reduces the incidence of transient VCP in secondary surgeries compared to only visual identification of nerve (2.6 vs. 6.3%, respectively, $p = 0.003$). Although the difference is not significant, it also decreased the incidence of permanent VCP rate (1.4 vs. 2.4%, respectively, $p = 0.202$) (36).

In this study, secondary intervention is a risk factor for VCP in operations with IONM.

In secondary interventions, the trajectory of RLN changes by 80% and approximately 60% of RLN crosses within the scar tissue. These are important anatomical factors that increase the risk of RLN injury due to difficulties visualizing and identifying the nerve, and our results support this information (36, 37).

Anatomical variations of the RLN are common and these variations may increase the risk of RLN injury due to visual misidentification of the nerve (38).

In the literature, many studies have evaluated the relationship of RLN with other anatomical landmarks (15–20).

A prospective international multicentric study by Liddy et al. was the first study evaluating 1,000 nerves at risk according to the International RLN anatomical classification system.

In the study, nerve trajectory was found to be 77% L1/R1 (normal trajectory), 19.4% L2a/R2a, 3% R2b/L2b, 0.7% R3. In total, 30% of nerves at risk were fixed/splayed/entrapped at the level of the thyroid capsule. The rate of entrapment of the nerve by the ligament of Berry and/or vascular structure in the Berry

**TABLE 3 |** Evaluation of clinical and anatomical factors for permanent VCP by univariant analysis.

| Feature | | *n* | VCP n (%) | OR (95% CI min–max) | *p* |
|---|---|---|---|---|---|
| Age | | 1,412 | | | |
| | No VCP | 1,407 | | 49.2 ± 13.4 (18–89) | 0.074 |
| | VCP | 5 | | 58.2 ± 6.2 (49–66) | |
| Gender | | 1,412 | | | |
| | Female | 1,089 | 4 (0.4%) | 0.841 (0.094–7.549) | 1 |
| | Male | 323 | 1 (0.3%) | | |
| BMI | | 1,230 | | | 0.417 |
| | No VCP | 1,175 | | 28.8 ± 5.9 (16.3–63) | |
| | VCP | 5 | | 31.5 ± 7.6 (22.9–43.8) | |
| Neck side of the nerve | | 1,412 | | | |
| | Right | 714 | 3 (0.4%) | 0.681 (0.113–4.088) | 1 |
| | Left | 698 | 2 (0.3%) | | |
| Type of nerve monitoring | | 1,412 | | | |
| | IIONM | 692 | 1 (0.1%) | 1.714 (1.073–2.739) | 0.375 |
| | CIONM | 720 | 4(0.6%) | | |
| Type of intervention | | 1412 | | | |
| | Primary | 1,329 | 3 (0.2%) | 0.092 (0.015–0.556) | 0.009* |
| | Secondary | 83 | 2 (2.4%) | | |
| Central neck dissection | | 1,412 | | | |
| | Applied | 147 | 2 (1.4%) | | 0.055 |
| | Not applied | 1,265 | 3 (0.2%) | 0.172 (0.029–1.040) | |
| RLN-ITA relationship | | 1,396 | | | 0.351 |
| | Anterior to ITA | 675 | 4 (0.6%) | | |
| | Posterior to ITA | 596 | 1 (0.2%) | | |
| | Between Branches of ITA | 125 | 0 | | |
| Nerve branching | | 1,412 | | | 0.504 |
| | Non-branching | 930 | 4 (0.4%) | 0.481 (0.054–4.318) | |
| | Branching | 482 | 1 (0.2%) | | |
| Entrapment of RLN by Berry ligament | | 1,305 | | | |
| | Yes | 307 | 0 | 0.995 (0.991–0.999) | 0.597 |
| | No | 998 | 5(0.5%) | | |
| Zuckerkandl tubercle | | 1,291 | | | |
| | 0 ve 1. grade | 788 | 5 (0.6%) | | 0.163 |
| | 2 ve 3. grade | 503 | 0 | | |
| RLN anatomy | | 1,236 | | | 0.062 |
| | R1/L1 | 1,091 | 3 (0.3%) | | |
| | R2a/L2a | 96 | 2 (2.1%) | | |
| | R2b/L2b | 38 | 0 | | |
| | R3/L3 | 7 | 0 | | |
| RLN trajectory | | 1,124 | | | 0.043* |
| | No feature | 950 | 2(0.2%) | | |
| | Fixed | 43 | 1 (2.3%) | | |
| | Splayed | 59 | 1 (1.7%) | | |
| | Entrapped | 72 | 1 (1.4%) | | |
| Weight of thyroid gland lobe (gram) | | 1,059 | | | 0.127 |
| | No VCP | 1,008 | | 29.6 ± 32.8 (2–274) | |
| | VCP | 51 | | 32.8 ± 32.6 (5–204) | |

*(Continued)*

**TABLE 3 |** Continued

| Feature | | n | VCP n (%) | OR (95% CI min–max) | p |
|---|---|---|---|---|---|
| **Hyperthyroidism** | | | | | |
| | Yes | 1,091 | 5 (0.5%) | | 0.594 |
| | No | 321 | 0 | | |
| **Final diagnosis** | | | | | |
| | Benign | 828 | 3 (0.4%) | | 0.716 |
| | Graves disease | 149 | 0 | | |
| | Malignant | 435 | 2 (0.5%) | | |

*VCP, vocal cord paralysis; IIONM, intermittent intraoperative nerve monitorization; CIONM, continuous intraoperative nerve monitorization; RLN, recurrent laryngeal nerve; ITA, inferior thyroid artery. *means statistically significant p value.*

**TABLE 4 |** Multivariate analysis of risk factors for total VCP with binary logistic regression.

| | Vocal cord paralysis (VCP) | |
|---|---|---|
| | Odds ratio (95%CI Lower–Upper) | p |
| **Type of neuromonitoring** | | 0.008 |
| I-IONM | 2.000 (1.195–3.345) | |
| C-IONM | 1 (reference) | |
| **Type of intervention** | | 0.001 |
| Primary | 0.262 (0.117–0.588) | |
| Secondary | 1 (reference) | |
| **Berry entrapment** | | 0.000 |
| Absent | 0.406 (0.245–0.6719) | |
| Present | 1 (reference) | |
| **RLN—ITA relationship** | | 0.001 |
| Anterior to ITA | 2.603 (0.909–7.450) | 0.075 |
| Posterior to ITA | 0.973 (0.317–2.985) | 0.962 |
| Between the branches of ITA | 1.00 (reference) | |
| **Nerve branching** | | 0.055 |
| Non-branching | 0.618 (0.379–1.010) | |
| Branching | 1.00 (reference) | |

*Logistic regression OR < 1 decreases risk (e.g., VCP risk decreases in RLN posterior to ITA compared to the RLN anterior to ITA), OR > 1 increases risk (e.g., VCP risk increases in branching RLN compared to non-branching RLN).*

**TABLE 5 |** Types of mechanisms leading to RLN injury.

| | Vocal cord paralysis (VCP) | | |
|---|---|---|---|
| | IIONM VCP | CIONM VCP | P = 0.042 |
| **Traction** | 39 (80%) | 18 (53%) | |
| Mechanical trauma | 1 (2%) | 3 (8.8%) | |
| Clip or suture | 0 | 0 | |
| **Thermal** | 8 (16%) | 9 (26.4%) | |
| Transection | 1 (2%) | 4 (11.8%) | |
| Total | 49 | 34 | 83 |

*VCP, vocal cord paralysis; IIONM, intermittent intraoperative nerve monitorization; CIONM, continuous intraoperative nerve monitorization; RLN, recurrent laryngeal nerve.*

ligament region was 41%, rate of nerve thinner than 1 mm was found in 16%, and extralaryngeal branching was detected in 28% (22).

In this study, RLN trajectories were evaluated in 1,232 nerves, and it was found to be 88.5% L1/R1 (normal trajectory), 7.8% (L2a/R2a), 3.1% (L2b/R2b), and 0.0% R3. Fixed/splayed/entrapment nerve at the level of thyroid capsule was detected in 179 (15.5%) of 1,124 nerves. Berry entrapment was detected in 307 (23.5%) of 1305 nerves, and nerve branching was detected in 482 (34.1%) of 1,412 nerves.

According to the study of Liddy et al. the rate of normal trajectory was higher, while the rate of lateral or medial acquired abnormal trajectory was lower. In addition, the fixed/splayed/entrapment ratio at the level of the thyroid capsule and the entrapment of the RLN in the Berry ligament region were lower. In the study of Liddy et al. there are 17 centers from 7 geographical regions and 12 countries, and there are centers from our country, too also including our center. However, this difference may be related to differences in postoperative diagnoses and geographical anatomical differences in studies. Anatomical risk factors for RLN injury were evaluated among these anatomical features (22).

For loss of signal (LOS), presence of abnormal RLN trajectory (OR: 2.12, $p = 0.017$), entrapment of RLN in Berry's ligament (OR: 3.25, $p = 0.007$), lateral lymph node dissection (OR: 4.43, $p = 0.025$) for the right side, higher BMI (OR:0.98, $p = 0.032$) were determined as independent risk factors for the left side. However, for both right and left sides, invaded nerve (OR: 18.30, 15.50; $p = 0.002$, $p = 0.021$, respectively), fixed nerve in the thyroid capsule (OR: 16.63, 3.45; $p = 0.000$, $p = 0.044$, respectively), extended nerve dissection (OR: 11.56, 6.42; $p = 0.000$, $p = 0.008$, respectively) were determined as independent risk factors for LOS. For VCP, the fixed nerve in the thyroid capsule (OR: 2.57; $p = 0.006$), an increase in the length of the RLN exposure (OR > 999.99; $p = 0.006$) for the right side, the invaded nerve on both the right (OR: 21.07; $p < 0.001$) and the left side (OR: 43.75; $p < 0.001$) were determined as independent risk factors.

The researchers have recommended that the anatomical and intraoperative characteristics of the RLN, which may affect the risk of nerve injury, may be significantly variable, and the use of IONM should be routine since these cannot be predicted preoperatively (22).

In this study, no significant difference was found in terms of total and transient RLN paralysis, whether there were an abnormal nerve trajectory, clinically important features (fixed/splayed/entrapment) or not. Clinically important features (fixed/splayed/entrapment) were significantly higher in patients with permanent VCP ($p = 0.043$). We believe this is one of the important features that complicate the identification of the nerve. Total (9.8 vs. 4.6%, $p = 0.001$, respectively) and transient (9.8 vs. 4.6%, $p = 0.001$, respectively) VCP were significantly higher in patients with nerve entrapment in the Berry region than in those without. This is an important indicator that the risk of RLN injury is most likely and that traction trauma is the most common in the Berry region and these features are important risk factors.

In this study, extralaryngeal nerve branching (34.1%) was a frequent variation, and the probability of total (8.1 vs. 4.7%, $p = 0.011$, respectively) and transient (7.9 vs. 4.3%, $p = 0.005$, respectively). VCP was significantly higher than for non-branching nerves. In previous studies, it has been revealed that extralaryngeal branching is a risk factor for VCP (39–41).

Similar to our results, the transient VCP rate was found higher in branched nerves than in non-branched ones in a study by Barczynski et al. Increased risk of paralysis has been calculated as 2.98 times more in branched nerves (95 %CI 1.79–4.95; $p = 0.001$). In addition to that, there was no difference in branched and non-branched nerves in terms of permanent VCP rates (1.1 vs. 0.2%, respectively) (41).

In another study by Sancho et al. the VCP rate in branched nerves was higher than in non-branched nerves significantly (15.8 vs. 8.1%, respectively $p = 0.022$), moreover, the probability for VCP was determined 2.2 times higher in branched nerves (95% CI: 1.1–4.5) (40).

Estimated risks for unilateral RLN paralysis were 7.36 times higher for transient paralysis (95% CI: 1.84–29.4; $p = 0.0061$) and 13.25 times higher in permanent paralysis (95% CI: 1.42–123.73; $p = 0.0204$) in branched nerves, compared to non-branching nerves in a study by Casella et al. (39).

In this study, nerve–artery relationship was another anatomical feature evaluated for risk of VCP. In RLNs crossing ITA anteriorly compared to crossing posteriorly or crossing between branches, total VCP (8.4 vs. 3.2 vs. 3.2%, $p = 0.000$, respectively) and transient VCP (7.9 vs. 3 vs. 3.2%, $p = 0.000$, respectively) were significantly higher so that relationship was an independent risk factor for both. There was no significant difference in terms of permanent VCP. We think that a greater traction force is reflected to the nerve in the course of RLN anterior to the ITA by being exposed to more elevation and artificial angulation during the anteromedial traction of the thyroid lobe.

When the nerve is retracted, the maximum tension is reflected in the angulation area and the last 2 cm (42).

RLN-ITA relationship is a potential anatomical feature in terms of RLN paralysis, and we believe it can be evaluated for inclusion in the international RLN anatomy classification.

On the other hand, Sancho et al. had evaluated the anatomical relation of RLN to ITA, they found VCP rates as 15% if the RLN crossed the ITA anteriorly, 14.7% if crossed posteriorly, and 9.1% if crossed between the branches, and they did not determine a significant difference in VCP according to the position of the RLN ($p = 0.529$) (40).

The main limitation of our study is being retrospective. Although our center has standard technical equipment for IIONM, the vagus probe (APS probe) cannot be supplied to every patient. The use of CIONM was preferred in preoperatively predicted high-risk patients and when the vagus probe was accessible. It can be thought that this situation may affect the results related to the effect of IONM.

Although many factors have been evaluated, the presence of thin nerve and wide dissection, which are defined in the international RLN anatomic classification system, were not evaluated, also LOS and dynamic data were not evaluated in the study but only postoperative VCP was evaluated. Since the primary aim of the study was to evaluate RLNs anatomical factors on VCP development, not all dynamic factors were evaluated. However, many of the anatomical variations of the RLN in the international RLN classification system and the RLN–ITA relationship have been evaluated.

In conclusion, anatomic variations of the RLN are common in thyroidectomy. Among the anatomical factors, the RLN–ITA relationship, extralaryngeal branches, and entrapment of the RLN at Berry ligament are important factors affecting the development of postoperative VCP, which may make thyroidectomy high-risk and cannot be predicted preoperatively. Considering the potential anatomical variations of the RLN, IONM can be used in every thyroidectomy, CIONM has more advantages than IIONM, and VCP risk can be reduced with CIONM.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Sisli Hamidiye Etfal Training and Research Hospital. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

The conception, design, and supervision were contributed by MU and AI. The parts of materials, data collection and/or processing, and literature review were contributed by MK, MTU, and NA in the study. Writing and critical review were done by AI, MU, NA, MK, and MTU. All authors contributed to the article and approved the submitted version.

## REFERENCES

1. Godballe C, Madsen AR, Sørensen CH, Schytte S, Trolle W, Helweg-Larsen J, et al. Risk factors for recurrent nerve palsy after thyroid surgery: a national study of patients treated at Danish departments of ENT head and neck surgery. *Eur Arch Otorhinolaryngol.* (2014) 271:2267–76. doi: 10.1007/s00405-013-2767-7
2. Enomoto K, Uchino S, Watanabe S, Enomoto Y, Noguchi S. Recurrent laryngeal nerve palsy during surgery for benign thyroid diseases: risk factors and outcome analysis. *Surgery.* (2014) 155:522–8. doi: 10.1016/j.surg.2013.11.005
3. Rubio GA, Koru-Sengul T, Vaghaiwalla TM, Parikh PP, Farra JC, Lew JI. Postoperative outcomes in Graves' disease patients: results from the nationwide inpatient sample database. *Thyroid.* (2017) 27:825–31. doi: 10.1089/thy.2016.0500
4. Dralle H, Sekulla C, Haerting J, Timmermann W, Neumann HJ, Kruse E, et al. Risk factors of paralysis and functional outcome after recurrent laryngeal nerve monitoring in thyroid surgery. *Surgery.* (2004) 136:1310–22. doi: 10.1016/j.surg.2004.07.018
5. Thomusch O, Machens A, Sekulla C, Ukkat J, Lippert H, Gastinger I, et al. Multivariate analysis of risk factors for postoperative complications in benign goiter surgery: prospective multicenter study in Germany. *World J Surg.* (2000) 24:1335–41. doi: 10.1007/s002680010221
6. Gualniera P, Scurria S, Mondello C, Asmundo A, Sapienza D, Gianlorenzo D. Narrative review of proving the causal link of recurrent laryngeal nerve injury and thyroidectomy: a medico legal appraisal. *Gland Surg.* (2020) 9:1564–72. doi: 10.21037/gs-20-203
7. Serpell JW. New operative surgical concept of two fascial layers enveloping the recurrent laryngeal nerve. *Ann Surg Oncol.* (2010) 17:1628–36. doi: 10.1245/s10434-010-0928-0
8. Chiang F-Y, Lu I-C, Chen H-C, Chen H-Y, Tsai C-J, Lee K-W, et al. Intraoperative neuromonitoring for early localization and identification of recurrent laryngeal nerve during thyroid surgery. *Kaohsiung J Med Sci.* (2010) 26:633–9. doi: 10.1016/S1607-551X(10)70097-8
9. Lahey FH, Hoover WB. Injuries to the recurrent laryngeal nerve in thyroid operations: their management and avoidance. *Ann Surg.* (1938) 108:545–62. doi: 10.1097/00000658-193810000-00006
10. Feng AL, Puram SV, Singer MC, Modi R, Kamani D, Randolph GW. Increased prevalence of neural monitoring during thyroidectomy: global surgical survey. *Laryngoscope.* (2020) 130:1097–104. doi: 10.1002/lary.28210
11. Kim J, Graves CE, Jin C, Duh Q-Y, Gosnell JE, Shen WT, et al. Intraoperative nerve monitoring is associated with a lower risk of recurrent laryngeal nerve injury: a national analysis of 17,610 patients. *Am J Surg.* (2021) 221:472–7. doi: 10.1016/j.amjsurg.2020.10.013
12. Gunn A, Oyekunle T, Stang M, Kazaure H, Scheri R. Recurrent laryngeal nerve injury after thyroid surgery: an analysis of 11,370 patients. *J Surg Res.* (2020) 255:42–9. doi: 10.1016/j.jss.2020.05.017
13. Bai B, Chen W. Protective effects of intraoperative nerve monitoring (IONM) for recurrent laryngeal nerve injury in thyroidectomy: meta-analysis. *Sci Rep.* (2018) 8:7761. doi: 10.1038/s41598-018-26219-5
14. Schneider R, Machens A, Sekulla C, Lorenz K, Elwerr M, Dralle H. Superiority of continuous over intermittent intraoperative nerve monitoring in preventing vocal cord palsy. *Br J Surg.* (2021) 108:566–73. doi: 10.1002/bjs.11901
15. Lee M-S, Lee U-Y, Lee J-H, Han S-H. Relative direction and position of recurrent laryngeal nerve for anatomical configuration. *Surg Radiol Anat.* (2009) 31:649–55. doi: 10.1007/s00276-009-0494-y
16. Henry BM, Sanna S, Graves MJ, Vikse J, Sanna B, Tomaszewska IM, et al. The Non-Recurrent Laryngeal Nerve: a meta-analysis and clinical considerations. *PeerJ.* (2017) 5:e3012. doi: 10.7717/peerj.3012
17. Henry BM, Vikse J, Graves MJ, Sanna S, Sanna B, Tomaszewska IM, et al. Variable relationship of the recurrent laryngeal nerve to the inferior thyroid artery: a meta-analysis and surgical implications: recurrent laryngeal nerve to inferior thyroid artery relationship: a meta-analysis. *Head Neck.* (2017) 39:177–86. doi: 10.1002/hed.24582
18. Henry BM, Vikse J, Graves MJ, Sanna S, Sanna B, Tomaszewska IM, et al. Extralaryngeal branching of the recurrent laryngeal nerve: a meta-analysis of 28,387 nerves. *Langenbecks Arch Surg.* (2016) 401:913–23. doi: 10.1007/s00423-016-1455-7
19. Kostek M, Caliskan O, Yanar C, Cakir Y, Uludag M. The most common anatomical variation of recurrent laryngeal nerve: Extralaryngeal branching. *SiSli Etfal Hastan Tip Bul/Med Bull Sisli Hosp.* (2021) 55:294–303. doi: 10.14744/SEMB.2021.93609
20. Henry BM, Sanna B, Graves MJ, Sanna S, Vikse J, Tomaszewska IM, et al. The reliability of the tracheoesophageal groove and the ligament of berry as landmarks for identifying the recurrent laryngeal nerve: a cadaveric study and meta-analysis. *Biomed Res Int.* (2017) 2017:4357591. doi: 10.1155/2017/4357591
21. Randolph GW, Wu CW, Dionigi G, Kamani D, Modi R, Chiang FY, Henry JF, The international RLN anatomic classification system. In: Randolph GW, editor. *The Recurrent and Superior Laryngeal Nerves*. Cham: Springer International Publishing (2018). p. 125–38.
22. Liddy W, Wu C-W, Dionigi G, Donatini G, Giles Senyurek Y, Kamani D, et al. Varied recurrent laryngeal nerve course is associated with increased risk of nerve dysfunction during thyroidectomy: results of the surgical anatomy of the recurrent laryngeal nerve in thyroid surgery study, an international multicenter prospective anatomic and electrophysiologic study of 1000 monitored nerves at risk from the International Neural Monitoring Study Group. *Thyroid.* (2021) 31:1730–40. doi: 10.1089/thy.2021.0155
23. Uludag M, Aygun N, Isgor A. Motor function of the recurrent laryngeal nerve: Sometimes motor fibers are also located in the posterior branch. *Surgery.* (2016) 160:153–60. doi: 10.1016/j.surg.2016.02.003
24. Pelizzo MR, Toniato A, Gemo G. Zuckerkandl's tuberculum: an arrow pointing to the recurrent laryngeal nerve (constant anatomical landmark). *J Am Coll Surg.* (1998) 187:333–6. doi: 10.1016/S1072-7515(98)00160-4
25. Randolph GW, Dralle H. International Intraoperative Monitoring Study Group, Abdullah H, Barczynski M, Bellantone R, et al. Electrophysiologic recurrent laryngeal nerve monitoring during thyroid and parathyroid surgery: international standards guideline statement. *Laryngoscope.* (2011) 121(Suppl 1):S1–16. doi: 10.1002/lary.21119
26. Uludag M, Tanal M, Işgör A. A review of methods for the preservation of laryngeal nerves during thyroidectomy. *SiSli Etfal Hastan Tip Bul/Med Bull Sisli Hosp.* (2018) 52:79–91. doi: 10.14744/SEMB.2018.37928
27. Dionigi G, Wu C-W, Kim HY, Rausei S, Boni L, Chiang F-Y. Severity of recurrent laryngeal nerve injuries in thyroid surgery. *World J Surg.* (2016) 40:1373–81. doi: 10.1007/s00268-016-3415-3
28. Higgins TS, Gupta R, Ketcham AS, Sataloff RT, Wadsworth JT, Sinacori JT. Recurrent laryngeal nerve monitoring versus identification alone on post-thyroidectomy true vocal fold palsy: a meta-analysis. *Laryngoscope*. (2011) 121:1009–17. doi: 10.1002/lary.21578
29. Lombardi CP, Carnassale G, Damiani G et al. "The final countdown": Is intraoperative, intermittent neuromonitoring really useful in preventing permanent nerve palsy? Evidence from a meta-analysis. *Surgery.* (2016) 160:1693–706. doi: 10.1016/j.surg.2016.06.049
30. Barczynski M, Konturek A, Cichon S. Randomized clinical trial of visualization versus neuromonitoring of recurrent laryngeal nerves during thyroidectomy. *Br J Surg.* (2009) 96:240–6. doi: 10.1002/bjs.6417
31. Vasileiadis I, Karatzas T, Charitoudis G, Karakostas E, Tseleni-Balafouta S, Kouraklis G. Association of intraoperative neuromonitoring with reduced recurrent laryngeal nerve injury in patients undergoing total thyroidectomy. *JAMA Otolaryngol Head Neck Surg.* (2016) 142:994–1001. doi: 10.1001/jamaoto.2016.1954
32. Wu C-W, Dionigi G, Sun H, Liu X, Kim HY, Hsiao P-J, et al. Intraoperative neuromonitoring for the early detection and prevention of RLN traction injury in thyroid surgery: a porcine model. *Surgery.* (2014) 155:329–39. doi: 10.1016/j.surg.2013.08.015
33. Schneider R, Sekulla C, Machens A, Lorenz K, Nguyen Thanh P, Dralle H. Postoperative vocal fold palsy in patients undergoing thyroid

surgery with continuous or intermittent nerve monitoring: Intraoperative nerve monitoring in thyroid surgery. *Br J Surg.* (2015) 102:1380–7. doi: 10.1002/bjs.9889

34. Schneider R, Machens A, Sekulla C, Lorenz K, Weber F, Dralle H. Twenty-year experience of paediatric thyroid surgery using intraoperative nerve monitoring: Intraoperative nerve monitoring in paediatric thyroidectomy. *Br J Surg.* (2018) 105:996–1005. doi: 10.1002/bjs.10792
35. Karamanakos SN, Markou KB, Panagopoulos K, Karavias D, Vagianos CE, Scopa CD, et al. Complications and risk factors related to the extent of surgery in thyroidectomy. Results from 2,043 procedures. *Hormones.* (2010) 9:318–25. doi: 10.14310/horm.2002.1283
36. Barczyński M, Konturek A, Pragacz K, Papier A, Stopa M, Nowak W. Intraoperative nerve monitoring can reduce prevalence of recurrent laryngeal nerve injury in thyroid reoperations: results of a retrospective cohort study. *World J Surg.* (2014) 38:599–606. doi: 10.1007/s00268-013-2260-x
37. Wojtczak B, Sutkowski K, Kaliszewski K, Barczyński M, Bolanowski M. Thyroid reoperation using intraoperative neuromonitoring. *Endocrine.* (2017) 58:458–66. doi: 10.1007/s12020-017-1443-x
38. Chiang FY, Lu IC, Chen HC, Chen HY, Tsai CJ, Hsiao PJ, et al. Anatomical variations of recurrent laryngeal nerve during thyroid surgery: how to identify and handle the variations with intraoperative neuromonitoring. *Kaohsiung J Med Sci.* (2010) 26:575–83. doi: 10.1016/S1607-551X(10)70089-9
39. Casella C, Pata G, Nascimbeni R, Mittempergher F, Salerni B. Does extralaryngeal branching have an impact on the rate of postoperative transient or permanent recurrent laryngeal nerve palsy? *World J Surg.* (2009) 33:261–5. doi: 10.1007/s00268-008-9832-1
40. Sancho JJ, Pascual-Damieta M, Pereira JA, Carrera MJ, Fontané J, Sitges-Serra A. Risk factors for transient vocal cord palsy after thyroidectomy. *Br J Surg.* (2008) 95:961–7. doi: 10.1002/bjs.6173
41. Barczyński M, Stopa M, Konturek A, Nowak W. The overwhelming majority but not all motor fibers of the bifid recurrent laryngeal nerve are located in the anterior extralaryngeal branch. *World J Surg.* (2016) 40:629–35. doi: 10.1007/s00268-015-3257-4
42. Serpell JW, Lee JC, Chiu WK, Edwards G. Stressing the recurrent laryngeal nerve during thyroidectomy: RLN stretch during thyroidectomy. *ANZ J Surg.* (2015) 85:962–5. doi: 10.1111/ans.13054

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Surgery

REVIEW
published: 04 May 2022
doi: 10.3389/fsurg.2022.882594

# Improving Voice Outcomes after Thyroid Surgery and Ultrasound-Guided Ablation Procedures

*Pia Pace-Asciak[1], Jon O. Russell[2] and Ralph P. Tufano[3]**

*[1]Department of Otolaryngology – Head and Neck Surgery, University of Toronto, Toronto, Canada, [2]Department of Otolaryngology – Head and Neck Surgery, Johns Hopkins University, Baltimore, Maryland, United States, [3]Sarasota Memorial Health Care System Multidisciplinary Thyroid and Parathyroid Center, Sarasota, Florida, United States*

The field of endocrine surgery has expanded from the traditional open neck approach to include remote access techniques as well as minimally invasive approaches for benign and malignant thyroid nodules. In experienced hands and with careful patient selection, each approach is considered safe, however complications can and do exist. Post-operative dysphonia can have serious consequences to the patient by affecting quality of life and ability to function at work and in daily life. Given the significance of post-procedural dysphonia, we review the surgical and non-surgical techniques for minimizing and treating recurrent laryngeal nerve injury that can be utilized with the traditional open neck approach, remote access thyroidectomy, or minimally invasive thermal ablation.

**Keywords: thyroid surgery, radiofrequency ablation, dysphonia, voice, vocal cord dysfunction**

OPEN ACCESS

**Edited by:**
*KyungTae,*
*Hanyang University, South Korea*

**Reviewed by:**
*Leandro Luongo Matos,*
*Clinical Hospital, Faculty of Medicine, University of São Paulo, São Paulo, Brazil*
*Navid Tabriz,*
*Pius-Hospital Oldenburg, Oldenburg, Germany*

***Correspondence:**
*Ralph P. Tufano*
*Ralph-Tufano@smh.com*

**Speciality section:**
*This article was submitted to Otorhinolaryngology - Head and Neck Surgery, a section of the journal Frontiers in Surgery*

**Received:** *24 February 2022*
**Accepted:** *11 April 2022*
**Published:** *04 May 2022*

**Citation:**
*Pace-Asciak P, Russell JO and Tufano RP (2022) Improving Voice Outcomes after Thyroid Surgery and Ultrasound-Guided Ablation Procedures. Front. Surg. 9:882594. doi: 10.3389/fsurg.2022.882594*

## INTRODUCTION

Thyroid surgery has been performed for thousands of years and still remains one of the more common head and neck procedures (1). With the modernization of thyroid surgery, the mortality rate has significantly dropped to less than 1% compared to 40% when in 1850, the French Medical Society banned these operations (2). The open neck approach that Kocher fathered is still used today, while newer methods to address thyroid nodules have evolved to address specific shortcomings. Such methods involve accessing the thyroid remotely with an endoscope in order to avoid a neck incision, or by minimally invasive techniques such as thermal ablation to avoid removing the thyroid gland at all. Regardless of the surgical approach, complications still exist.

In the hands of an experienced and high volume thyroid surgeon, complication rates may vary by disease pathology. Intraoperative injury to the recurrent laryngeal nerve (RLN) is one of the dreaded complications that can occur with open surgical approaches and less commonly with thermal ablation. Symptoms of unilateral vocal cord paralysis may include hoarseness, choking, dysphagia, and dysphonia with unilateral vocal cord paralysis, or symptoms of airway obstruction and stridor with bilateral vocal cord paralysis (3–6). Changes in the quality of voice or swallowing can significantly diminish a patient's ability to work, socialize and perform many activities of daily living, thus emphasizing the importance of careful handling of the RLN (7, 8).

For open neck approaches to the thyroid, approximately 1 in 10 patients experience temporary RLN injury after surgery, with longer lasting permanent voice problems in up to 1 in 25 (9). Other contributing factors which may lead to temporary dysphonia post-surgery include laryngeal irritation, edema or injury from intubation. Injury to the external branch of the superior laryngeal nerve can also impair a patient's quality of life by reducing the pitch and projection of the voice (10). For thermal ablation, namely radiofrequency ablation (RFA), injury to the RLN can be temporary or less frequently permanent (11–13). Voice changes are less frequently noted (0.94%, 21/2245) in benign nodules treated with RFA compared with recurrent thyroid cancer (7.95%, 14/176) (11). The overall complication rate in RFA treated primary benign nodules is 2.11% compared with 10.98% for malignant thyroid nodules (11).

In this paper, we review the surgical and nonsurgical techniques for minimizing and treating post-operative dysphonia caused by an open approach or remote access thyroidectomy as well as minimally invasive thermal ablation (namely radiofrequency ablation). In addition, we review how intraoperative electromyographic (EMG) changes correlate to post-operative voice changes, and how to treat weakness of the recurrent laryngeal nerve.

## PRACTICE RECOMMENDATIONS TO MINIMIZE DYSPHONIA POST THYROID SURGERY

### Visualization of the Nerve

The gold standard approach for preventing inadvertent injury to the RLN during thyroid surgery has always been meticulous dissection of the nerve in order to visualize its entry into the cricothyroid joint and/or course (14). Many prospective studies have confirmed Lahey's observation in 1938 (15) that clear visualization of the RLN during thyroid surgery significantly lowers the incidence of nerve injury compared to surgery without visualization (16–20). Yet the best method to prevent nerve injury has been greatly debated. Even with a visually intact RLN, function can been compromised (21). Generally, the rate of RLN paralysis is low in experienced hands for open neck approaches (temporary injury 2%–8%, permanent in 0.5%–3%), however the rate tends to be higher for malignant thyroid disease, enlarged goiters, Graves' disease, re-operative cases, anatomic variability and surgeon's inexperience (22–24).

Most often, surgeons take a lateral approach for dissecting the thyroid in order to identify the RLN. Fixed landmarks, such as the cricothyroid joint, is a helpful guide for localizing the entry point of the RLN into the larynx. In certain situations a medial approach can be advantageous in cases with a nonrecurrent RLN, a large Tubercle of Zuckerkandl, or in cases with extrathyroidal extension of cancer along the distal RLN segment (with the exception of cricothyroid junction involvement), or large goiters (25). This approach allows for early and direct access to the RLN once the isthmus is divided and Berry's ligament is exposed (25). Care must be taken to avoid inadvertent injury when localizing the RLN with the medial approach since up to 80% of the time, the RLN is located superficial to Berry's ligament, and below it 15% of the time (26).

### Intraoperative Nerve Monitoring

Over the past few decades, intraoperative nerve monitoring (IONM) has gained acceptance as an adjunct to nerve visualization during thyroid surgery and is used by most high volume thyroid surgeons in North America (27). The American Academy of Otolaryngology – Head and Neck Surgery guidelines have recommended its use, and it has become the standard of care at most institutions. Regardless of whether the surgeon has high-volume or low-volume experience, most would argue that IONM can aid the surgeon through difficult anatomical situations should the surgical field be impaired by bleeding, scarring or tumor infiltration that may complicate a clean dissection. However, IONM does not replace knowledge of the head and neck anatomy.

Whether IONM conveys a real advantage over no monitoring at all continues to be debated by endocrine surgeons (3, 14, 22, 23, 28–31). Barczynski et al. and others have demonstrated statistically lower rates for transient RLN paralysis with IONM compared with visualization alone (32). Whereas, Higgins et al., did not report a statistically significant difference in the overall incidence of true vocal fold palsy (3.52%) for IONM compared with (3.12%) for nerve identification alone (31). In a Cochrane analysis, the rates of permanent RLN palsy (RR 0.77, 95% CI 0.33 to 1.77; $P = 0.54$; 4 trials; 2895 nerves at risk; very low-certainty evidence) and transient RLN palsy (RR 0.62, 95% CI 0.35 to 1.08; $P = 0.09$; 4 trials; 2895 nerves at risk; very low-certainty evidence) when IONM was compared with nerve visualization alone did not conclude firm evidence showing an advantage or disadvantage for prevention of RLN injury (23). However, in Zheng's meta-analysis of over 12 different trials which included 36,487 participants, IONM was found to decrease the risk of transient RLN palsy, but had no significant effect on the permanent rate of injury (32).

The most widely available IONM system is one where two surface electrodes embedded in the endotracheal tube are positioned so they contact the vocal folds during intubation. This allows the surgeon to intermittently monitor the RLN or the vagus nerve with a handheld probe once the nerve has been surgically isolated (3, 27). This system is useful for confirming the localization of the RLN, for identifying whether there is a loss of signal from nerve injury, and to guide decision making for whether to stage the surgery in the case of an ipsilateral loss of signal during a bilateral procedure (3, 27, 33). Intermittent IONM has its limitations, namely the need to maintain constant contact with the surface electrodes on the endotracheal tube and the vocal folds to obtain an accurate EMG recording. Should the endotracheal tube shift during surgical manipulation, a false decrease or loss in the EMG signal can result. Once the surgery is in progress, it can be disruptive for the surgeon or the anesthetist to reposition the tube, particularly during remote access surgeries such as the transoral robotic approach (34). Various newer approaches have emerged to circumvent these limitations (33, 34).

Continuous IONM has evolved to circumvent the limitations of intermittent IONM so that nerve monitoring can occur continuously and in real time. It is beneficial for the early detection and prevention of thermal or traction injuries, thus allowing the surgeon to take immediate action if a change in the EMG is noted (28, 29). Some studies have noted improved outcomes with continuous monitoring relative to intermittent monitoring, which has spurred adoption in some centers (35). In a comparative study, Schneider et al., examined a total of 6029 patients, of whom 3139 underwent continuous and 2890 intermittent IONM (35). Continuous IONM independently reduced early postoperative vocal cord palsy 1.8-fold (OR 0.56) and permanent vocal cord palsy 29.4-fold (OR 0.034) compared with intermittent IONM (35). Early postoperative vocal cord palsies were 17.9-fold less likely to become permanent with continuous IONM than intermittent IONM, demonstrating the advantage for using continuous monitoring in the right clinical scenario (35).

## Hemostasis with Energy Based Devices

With the modernization of thyroid surgery, advances have included the use of energy-based devices (EBD) as an extension from the "clamp-and-tie" technique that Theodore Kocher fathered in the 19th century. Today, hemostasis can be achieved in multiple ways: clamp-and-tie, electrocautery (monopoloar or bipolar), with hemostatic clips, and more advanced EBD that use thermal, ferromagnetic, or ultrasonic energy to ligate, seal and dissect tissue (36). Even though more advanced techniques with EBD have demonstrated reduced pain, wound drainage, decreased rates of neck hematoma and even hypocalcaemia (37–40), the results for EBD are inconsistent in terms of rates of RLN injury compared with conventional approaches (41, 42). Several studies have demonstrated that traction and thermal injury are the first and second most common causes of iatrogenic RLN injury during thyroidectomy (39, 43, 44). As one would expect, the use of EBDs can generate high temperatures that can spread to critical structures such as the RLN causing indirect thermal spread or direct thermal injury (36). Thus, various guidelines are published to ensure that surgeons maintain a safe distance between the activated EBD tip and the surrounding soft tissue (36). It is also recommended that enough time lapses for the tip or blade to cool sufficiently before using the device to dissect tissue or work close to the RLN.

Depending on whether monopolar electrocautery or bipolar cautery is used, a safe distance must be maintained in order to protect critical structures. Care should be taken when using monopolar electrocautery adjacent to the RLN given that thermal spread is diffuse. In a porcine model, Wu et al. demonstrated that an activation distance of 5 mm is required to maintain safety with a cooling time of 1 s for monopolar electrocautery set at 15 Watts (45). For bipolar cautery the recommendations differ since the current is confined to the tissue between the two arms of the tines (forcep-shaped electrode). Wu et al. reported an activation distance of 3 mm from critical structures with a 1 s cooling time set at 30 Watts (45). For advanced bipolar EBDs such as the LigaSure Small Jaw and Ligasure Exact Dissector, Dionigo et al, recommend a safe activation distance of 2 mm with a 2-second interval for cooling the instrument tip before further dissecting tissue (46). Similar distances are noted for EBDs that deliver energy in the form of ultrasonic vibrations (such as the Harmonic) or Ferromagnetic energy (47). Regardless of the EBD used, surgeons should be aware of the device specific recommended distance needed for a safe dissection. The perception of distance may be altered in remote access surgery where the surgical field is closed and visualized via endoscope compared with traditional open neck approaches but is key for minimizing thermal injury and for improving voice outcomes.

Thermal injury to the RLN is more detrimental to voice outcomes than mechanical injury cause by traction or compression. Studies have demonstrated that thermal injury can cause irreversible changes to the nerve, damaging the endoneurium with temperatures at little as 60 Celsius (48). Most EBDs reach temperatures that exceed 200 Celsius when they are activated, and more than 350 Celsius with monopolar electrocautery (36). Additional care should be taken to avoid inadvertent injury to nearby structures when operating in a wet surgical field, as high temperature steam can be generated if the EBD is activated (49). Furthermore, surgeons should be aware and cautious when using EBDs as dissectors post-activation particularly during endoscopic approaches where the field of view can be limited.

Despite meticulous dissection along tissue planes, a slow oozing type of bleeding can still occur often around neural structures that are nourished by smaller vessels. The use of clips, cautery or ties adjacent to the nerve can pose risk. For this reason, various hemostatic agents have been developed in the form of a gel or patch to help mitigate this risk of a hematoma and nerve injury with cauterization. The use of such hemostatic agents, such as topical gels and patches have been shown to be a safe practice and does not put the RLN at risk. In a meta-analysis comparing the use of a topical hemostatic patch or gel to conventional methods for hemostasis, no significant difference between groups (patch 95% CI, 0.28, 5.52; gel 95% CI, 0.20, 2.47) were found in terms of risk to RLN injury (50).

# PRACTICE RECOMMENDATIONS TO MINIMIZE DYSPHONIA POST THERMAL ABLATION WITH RFA

The true rate of RLN injury post thermal ablation is not known since studies examining pre- and post-procedure laryngoscopy are lacking. However, the overall rate of transient or permanent voice change following RFA is 1.44% based on subjective voice assessment (11, 51).

Since RFA is done in an outpatient setting with local anesthesia, temporary voice changes can be noted either during radiofrequency ablation (RFA) or immediately after the procedure. The most important approach for mitigating this potential complication is to carefully map the location of the target nodule by ultrasound in relation to the "danger triangle"; which is localized posterior to the thyroid capsule and adjacent to the trachea where the RLN runs (52). The only study which specifically examined the effects of RFA along the posterior thyroid capsule is found in a recent prospective study. Sinclair et al. demonstrated in thirteen benign nodules that abutted the posterior thyroid capsule, that RFA could safety be performed at a power of up to 40 Watts without laryngeal adductor reflex (LAR) amplitude changes measured by continuous intraoperative neuromonitoring (CIONM) (13). No significant difference between pre- and postoperative laryngoscopy and voice assessments were noted, and after 12 month follow-up, regrowth was not noted at the posterior aspect of the nodule (13). For nodules that extend beyond the posterior thyroid capsule, or for nodules that lack a cuff of normal thyroid tissue, surgery should be considered instead of RFA due to the risk to the RLN and the lack of tissue to buffer thermal spread, especially if the nodule is malignant.

While RFA can be completed under general anesthesia with nerve monitoring, most operators feel that local sedation offers an improved safety profile. One of the benefits of an outpatient procedure is the real-time feedback that patients can give the operator in terms of pain control, change in voice or breathing. An important way to monitor for thermal damage to the RLN during ablation is to maintain communication with the patient during the procedure. Prior to the thermal ablation, perithyroidal lidocaine is injected around the anterior or superficial thyroid capsule to reduce pain. By avoiding anesthesia of the deeper tissues, if pain is experienced during the procedure, it can be an early sign of thermal propagation to the surrounding tissue and the electrode can be moved and then power can be reduced by 5 to 10 Watts before proceeding further (12, 53). If patients note changes to their voice immediately post-procedure, most often it is transient and can be treated with a short course of Prednisone during their recovery period. Furthermore, when using RFA to ablate bilateral thyroid nodules, care should be taken to monitor for voice changes to avoid bilateral RLN paresis. The operator should have a low threshold for staging bilateral procedures should dysphonia be noted during RFA.

Another useful approach for minimizing injury to the surrounding tissue (ie. RLN) prior to ablation is hydro-dissection with 5% dextrose solution along the plane between the target tumor and adjacent critical structures. This creates a thermal barrier as well as a "heat-sink effect" which allows for heat to escape during ablation (54). Dextrose solution is the fluid of choice since it is iso-molar (252 mOsmol/L) and non-ionic in composition, thus safer than normal saline which is anionic and able to conduct electricity. If thermal injury is suspected post-procedure, Lee et al. describe injecting cold 5% dextrose solution into the tracheoesophageal groove post-ablation as an effective method for cooling the tissues and for reducing heat conduction to surrounding structures (55). Compression of the neck is not recommended since it may enhance heat conduction to the surrounding tissue.

The safest technique described for performing RFA is the "moving shot technique", which involves alternating the position of the electrode in the nodule so each theoretical sub-unit is ablated. This limits the frictional heat generated from the electrode tip by intermittent active movement and limits the time of ablation for each subunit to a few seconds compared to a fixed approach used in organs such as the liver (54). By using the trans-isthmic approach, which refers to insertion of a RF electrode through the isthmus, this allows the operator to be able to pivot from a midline to lateral direction to access different angles depending on whether the nodule is situated in the right or left thyroid gland, and enables the operator to ensure that the contents of the "danger triangle" can be protected (54). By inserting the probe in the midline, it allows the operator to effectively monitor the electrode tip using ultrasound guidance and to stabilize the needle should a patient talk or cough during the procedure.

Although multiple sized electrodes are available for targeting different organs, it is important to use thyroid-dedicated internally cooled electrodes for RFA given the superficial and intricate anatomy of the thyroid and neck. Generally, for the thyroid, RFA consists of a 7-cm internally cooled electro (shaft length) with an 18 or 19-gauge active tip that measures either 5 mm, 7 mm, 10 mm or 15 mm) with typical workhorse tips sizes of 7 mm or 10 mm depending on the patient population (54, 56). Depending on where the nodule is located, small active tips (3.8 mm) can allow for a more precise treatment limiting collateral thermal spread to nearby structures (54).

## CORRELATION BETWEEN INTRAOPERATIVE ELECTROPHYSIOLOGICAL CHANGE OF RLN/EBSLN AND VOICE IMPAIRMENT IN THYROID SURGERY

If a loss of signal or a decrease in the EMG amplitude is noted intraoperatively and equipment malfunction or neuromuscular blockage has been ruled out, careful stimulation of the nerve with the probe from distal (the laryngeal nerve entry site) to proximal is recommended to identify the site of neuropraxic injury. This is typically done for open neck procedures compared with closed remote access techniques. Generally, nerve injuries identified through intraoperative neural monitoring are divided into two types: Type I (segmental) or Type II (global) injury (27). Segmental injuries can be corrected if a section of the nerve is entrapped with a clip or a suture, however for global type injuries, where all segments are nonconductive, an intralaryngeal focus is more likely.

Several papers have looked at the correlation between intraoperative EMG responses and postoperative vocal cord mobility. The International Neural Monitoring Study Group Guideline describes an impending adverse EMG even defined as an amplitude decrease of >50% of the initial baseline value, and an adverse EMG event is defined as an amplitude of <100 uV (14, 27). A true negative test is one where the EMG response is within normal limits at the end of surgery with intact vocal cord mobility postoperatively. Several studies have demonstrated that when the EMG has a robust response at the end of surgery, intact post-operative vocal fold functioning (the negative predictive value) is more than 95% (57–64). In a more recent review, Schneider et al., describe an even higher NPV for RLN palsy (97.3%–99.8%) when intermittent, and continuous (99.8%–100%) IONM is used (64). In contrast, if a loss of signal is noted on EMG at the end of surgery combined with immediate post-operative vocal cord paralysis, the outcome is a true positive test (27). However, for PPV, the rate is more variable due to transient versus permanent paresis, with a range of 37.8%–80.5% for intermittent, and 99.8%–100% for continuous IONM (63, 64). These values still translate into excellent outcomes with low rates of post-operative vocal cord palsy in experienced surgical hands, with early transient palsy 0.8%–10.5% for intermittent, and 2.6%–2.9% for continuous IONM (64). For permanent palsy, the rates are lower (0.2%–1.5% for intermittent, and 0%–1.0% for continuous IONM) (64). As a general rule, if there is an intact IONM signal at the end of the case, any post-operative voice changes are unlikely to be related to permanent RLN dysfunction.

## VOICE AND LARYNGEAL ASSESSMENT BEFORE AND AFTER THYROID SURGERY AND THERMAL ABLATION

It is standard of care to assess the patient's voice prior to thyroid surgery or thermal ablation to establish baseline function that can be compared post-surgically. As part of the history, patients should be asked about subjective changes in their pitch, loudness, quality or power of their voice (65). Validated standardized methods can also be employed, such as the Voice Handicap Index. This 30-item questionnaire determines the degree of voice impairment and has been used as a tool to determine pre- and postoperative voice status after thyroid surgery (66, 67). During physical exam, all patients with subjective voice changes should receive a preoperative glottic exam to ensure normal baseline glottic functioning. Approximately 1% of patients with benign thyroid disease have vocal fold paresis or paralysis and in up to 8% of patients with malignant thyroid disease who have not undergone prior thyroid, neck or chest surgery (68). Given that a preoperatively diagnosis for vocal fold paralysis is suspicious for thyroid cancer, such as finding may alter the surgeon's approach to surgical resection as well as how the patient is counselled preoperatively regarding expected voice outcomes.

The most commonly available method for examining the larynx is by flexible nasopharyngoscopy. More traditional methods involve the mirror exam, but have increasingly been replaced by flexible nasopharyngoscopy. Video-strobo-laryngoscopy (VSL) is another way to do a detailed functional examination of the larynx, however is less readily available except in more laryngology-based practices.

## SPEECH THERAPY AND INJECTION LARYNGOPLASTY FOR POST-THYROID PROCEDURE DYSPHONIA (PTD)

When a patient presents with complains of breathiness, dyspnea and/or mild dysphagia post-thyroid surgery, and vocal fold immobility has been confirmed on flexible nasopharyngoscopy, several options that can be offered. The management of symptomatic patients post-thyroid surgery varies from patient to patient but can include speech therapy, vocal fold injection, thyroplasty, reconstructive approaches for unilateral vocal fold paralysis and tracheotomy for bilateral vocal fold paralysis (**Figure 1**).

The clinical practice guidelines for improving voice outcomes after thyroid surgery recommend that assessment of voice is done within 2 weeks to 2 months post-thyroid surgery by the surgeon (65). If voice changes are noted, a laryngeal mirror or flexible nasopharyngoscopy is done to document whether vocal fold paresis is present. If the surgeon does not have the equipment to assess the vocal folds, a referral is made to an Otolaryngologist – Head and Neck surgeon for further management. Once a diagnosis of unilateral vocal fold paresis

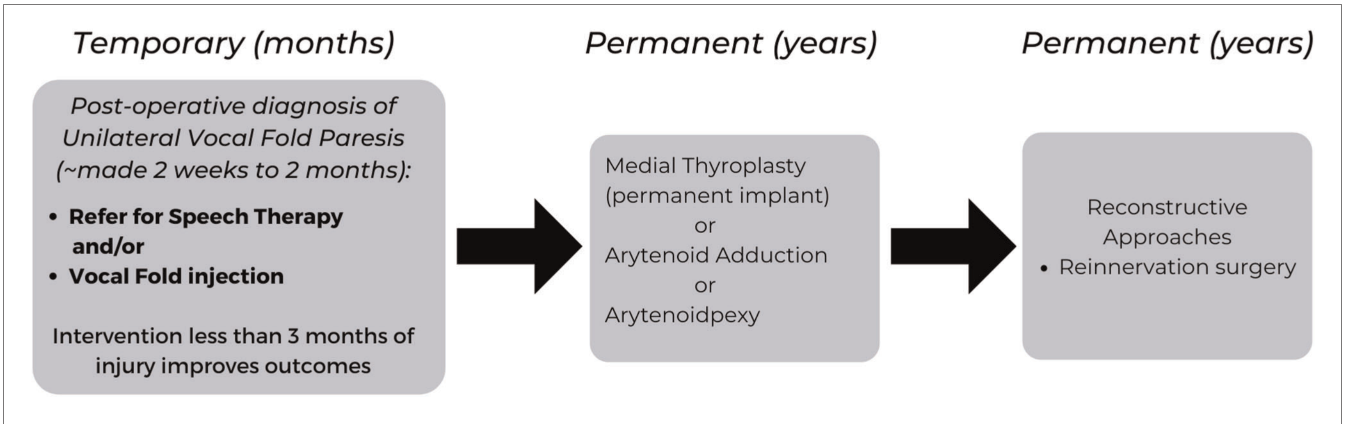



**FIGURE 1** | Flow Chart summarizing the Management for Temporary and Permanent Post-Operative Dysphonia due to Unilateral Vocal Paresis.

is made or suspected, shared decision making with the patient regarding the next steps of management is made. Of note, the earlier the intervention with speech therapy and/or vocal fold injection (less than 3 months), the better the long-term outcomes in voice and swallowing for the patient (65).

Speech therapy focuses on rehabilitation of vocal fold approximation using behavioral approaches. The goal of voice therapy is to improve glottic closure by strengthening the intrinsic muscles of the larynx, rather than developing abdominal support for breathing and supraglottic hyperfunction (65). Procedural approaches include vocal fold injection, which is a temporary method to augment the immobile vocal fold to a more midline position. This outpatient procedure can improve laryngeal function by improving glottic closure during the recovery period, while also reducing the likelihood for permanent medialization laryngoplasty (69). In a retrospective review, Yung et al. demonstrated the benefit of temporary injection medialization in 19 patients with unilateral fold paresis compared with 35 patients who were managed conservatively (69). Those patients injected were significantly less likely to require permanent medialization laryngoplasty ($p = 0.0131$). In terms of the timing for injection medialization, Friedman et al., demonstrated the earlier the intervention, the better (70). In patients that had early injection medialization (less than 6 months from the time of injury to medialization), 62% (20/32) maintained an adequate voice obviating the need for open neck surgical reconstruction, whereas 100% (3/3) that underwent late injection (more than 6 months post paralysis) required surgical reconstruction ($P = 0.03$) (70).

For permanent unilateral vocal fold paralysis, medialization thyroplasty is an option to mobilize the vocal fold to a midline position through a small transcervical incision (71). Other permanent methods involve manipulating the laryngeal cartilage to perform an arytenoid adduction or arytenopexy (72, 73). These more advanced procedures involve an operating room setting and are generally done by surgeons with a laryngology based practice. Laryngeal reinnervation is another advanced procedure which is less commonly done, and typically performed by connecting the ansa cervicalis and the recipient RLN (74). Although there is a delay in voice improvement with this technique, it can partially improve the position of the vocal fold and provide bulk so long-term denervation atrophy of the laryngeal muscles is avoided (74). Often, the delay in voice improvement can be bridged with injection laryngoplasty. Depending on what was noted intraoperatively in terms of tumor involvement around the RLN, or transection of the nerve, decisions can be made to go directly to permanent solutions (such as medial thyroplasty, arytenoid adduction, arytenopexy or reinnervation surgery) if the nerve is deemed unlikely to recover.

## CONCLUSION

Post-operative dysphonia has serious implications and consequences to patients, and thus, every effort should be taken to mitigate this complication. Various surgical and nonsurgical approaches can be taken reduce vocal fold injury during thyroid surgery as well as during thermal ablation. In symptomatic patients with RLN injury, various treatment options can be offered which range in behaviour therapy to more surgical type approaches to improve their quality of life.

## AUTHOR CONTRIBUTIONS

PP-A contributed to the literature review and manuscript writing. JOR contributed to the revisions as well as the manuscript finalization. All authors contributed to the article and approved the submitted version.

## REFERENCES


1. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the american thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid*. (2016) 26(1):1–133. doi: 10.1089/thy.2015.0020
2. Dorairajan N, Pradeep PV. Vignette thyroid surgery: a glimpse into its history. *Int Surg*. (2013) 98(1):70–5. doi: 10.9738/CC185.1
3. Schneider R, Randolph GW, Dionigi G, Wu CW, Barczynski M, Chiang FY, et al. International neural monitoring study group guideline 2018 part I: staging bilateral thyroid surgery with monitoring loss of signal. *Laryngoscope*. (2018) 128(Suppl 3):S1–S17. doi: 10.1002/lary.27359
4. Yu W-HV, Wu C-W. Speech therapy after thyroidectomy. *Gland Surg*. (2017) 6(5):501. doi: 10.21037/gs.2017.06.06
5. Borel F, Tresallet C, Hamy A, Mathonnet M, Lifante J-C, Brunaud L, et al. Self-assessment of voice outcomes after total thyroidectomy using the voice handicap index questionnaire: results of a prospective multicenter study. *Surgery*. (2020) 167(1):129–36. doi: 10.1016/j.surg.2019.05.090
6. Borel F, Christou N, Marret O, Mathonnet M, Caillard C, Bannani S, et al. Long-term voice quality outcomes after total thyroidectomy: a prospective multicenter study. *Surgery*. (2018) 163(4):796–800. doi: 10.1016/ j.surg.2017.09.023
7. Wilson JA, Deary IJ, Millar A, Mackenzie K. The quality of life impact of dysphonia. *Clin Otolaryngol Allied Sci*. (2002) 27(3):179–82. doi: 10.1046/j.1365-2273.2002.00559.x
8. Jones SM, Carding PN, Drinnan MJ. Exploring the relationship between severity of dysphonia and voice-related quality of life. *Clin Otolaryngol*. (2006) 31(5):411–7. doi: 10.1111/j.1749-4486.2006.01291.x
9. Jeannon JP, Orabi AA, Bruch GA, Abdalsalam HA, Simo R. Diagnosis of recurrent laryngeal nerve palsy after thyroidectomy: a systematic review. *Int J Clin Pract*. (2009) 63(4):624–9. doi: 10.1111/j.1742-1241.2008.01875.x
10. Roy N, Smith ME, Dromey C, Redd J, Neff S, Grennan D. Explorating the phonotory effets of external superior laryngeal nerve paralysis: an in vivo model. *Laryngoscope*. (2009) 119(4):816–26. doi: 10.1002/lary.20143
11. Chung SR, Suh CH, Baek JH, Park HS, Choi YJ, Lee JH. Safety of radiofrequency ablation of benign thyroid nodules and recurrent thyroid cancers: a systematic review and meta-analysis. *Int J Hyperthermia*. (2017) 33:920–30. doi: 10.1080/02656736.2017.1337936
12. Baek JH, Lee JH, Shung JY, Bae JI, Kim KT, Sim J, et al. Complications encountered in the treatment of benign thyroid nodules with US-guided

radiofrequency ablation: a multicenter study. Korean Society of Thyroid Radiology. *Radiology*. (2012) 262(1):335–42. doi: 10.1148/radiol.11110416

13. Sinclair CF, Tellez MJ, Pelaez-Cruz R, Diaz-Baamonde A, Ulkatan S. Continous neuromonitoring during radiofrequency ablation of benign thyroid nodules provides objective evidence of laryngeal nerve safety. *Am J Surg*. (2021) 222(2):354–60. doi: 10.1016/j.amjsurg.2020.12.033
14. Maneeprasopchoke P, Chongkolwatana C, Pongsapich W, Iwata AJ, Kamani D, Randolph GW. Intraoperative nerve monitoring in thyroid surgery: Analysis of recurrent laryngeal nerve identification and operative time. *Laryngoscope Investig Otolaryngol*. (2021) 6(2):354–61. doi: 10.1002/lio2.543
15. Lahey FH. Routine dissection and demonstration of recurrent laryngeal nerves in subtotal thyroidectomy. *Surg Gynecol Obstet*. (1938) 66:775–7.
16. Riddel VH. Injury to recurrent laryngeal nerves during thyroidectomy: a comparison between the results of identification and non-identification in 1022 nerves exposed to risk. *Lancet*. (1956) 29:638–41. doi: 10.1016/S0140-6736(56)92333-9
17. Jatzko GR, Lisborg PH, Muller MG, Wette VM. Recurrent nerve palsy after thyroid operations – principal nerve identification and a literature review. *Surgery*. (1994) 115:139–44.
18. Hermann M, Alk G, Roka R, Glaser K, Freissmuth M. Laryngeal recurrent nerve injury in surgery for benign thyroid disease: effect of the nerve dissection and impaction of individual surgeon in more than 27,000 nerves at risk. *Ann Surg*. (2002) 235:261–8. doi: 10.1097/00000658-200202000-00015
19. Steurer M, Passler C, Denk DM, Schneider B, Niederle B, Bigenzahn W. Advantages of recurrent laryngeal nerve identification in thyroidectomy and parathyroidectomy and the importance of preoperative and posteroperative laryngoscopic examination in more than 1000 nerves at risk. *Laryngoscope*. (2002) 112:124–33. doi: 10.1097/00005537-200201000-00022
20. Chiang FY, Wang LF, Huang YF, Lee KW, Kuo WR. Recurrent laryngeal nerve palpsy after thyroidectomy with routine identification of the recurrent laryngeal nerve. *Surgery*. (2005) 137:342–7. doi: 10.1016/j.surg.2004.09.008
21. Serpell JW, Phan D. Safety of total thyroidectomy. *ANZ J Surg*. (2007) 77(1–2):15–9. doi: 10.1111/j.1445-2197.2006.03897.x
22. Calò PG, Pisano G, Medas F, Pittau MR, Gordini L, Demontis R, et al. Identification alone versus intraoperative neuromonitoring of the recurrent laryngeal nerve during thyroid surgery: experience of 2034 consecutive patients. *Am J Otolaryngol Head Neck Surg*. (2014) 43:16. doi: 10.1186/1916-0216-43-16
23. Cirocchi R, Arezzo A, D'Andrea V, Abraha I, Popivanov GI, Avenia N, et al. Intraoperative neuromonitoring versus visual nerve identification for prevention of recurrent laryngeal nerve injury in adults undergoing thyroid surgery. *Cochrane Database Syst Rev*. (2019) 1:CD012483. doi: 10.1002/14651858.CD012483.pub2
24. Snyder SK, Sigmond BR, Lairmore TC, Govednik-Horny CM, Janicek AK, Jupiter DC. The long-term impact of routine intraoperative nerve monitoring during thyroid and parathyroid surgery. *Surgery*. (2013) 154(4):704–11; discussion 711–703. doi: 10.1016/j.surg.2013.06.039
25. Butskiy O, Chang BA, Luu K, McKenzie RM, Anderson DW. A systematic approach to the recurrent laryngeal nerve dissection at the cricothyroid junction. *J Otolaryngol Head Neck Surg*. (2018) 47(57):1–9. doi: 10.1186/s40463-018-0306-7
26. Henry BM, Sanna B, Graves MJ, Sanna S, Vikse J, Tomaszewska IM, et al. The Reliability of the tracheoesophageal groove and the Ligament of Berry as landmarks for identifying the Recurrent Laryngeal Nerve: a cadaveric study and meta-analysis. *BioMed Res Int*. (2017) 2017:1–11. doi: 10.1155/2017/4357591
27. Randolph GW, Dralle H, Abdullah H, Barczynski M, Bellantone R, Brauckhoff M, et al. International intraoperative monitoring study electrophysiologic recurrent laryngeal nerve monitoring during thyroid and parathyroid surgery: international standards guideline statement. *Laryngoscope*. (2011) 121(Suppl 1):S1–S16. doi: 10.1002/lary.21119
28. Phelan E, Schneider R, Lorenz K, Dralle H, Kamani D, Potenza A, et al. Continuous vagal IONM prevents recurrent laryngeal nerve paralysis by revealing initial EMG changes of impending neuropraxic injury: a prospective, multicenter study. *Laryngoscope*. (2014) 124(6):1498–505. doi: 10.1002/lary.24550
29. Dionigi G, Donatini G, Boni L, Rausei S, Rovera F, Tanda ML, et al. Continuous monitoring of the recurrent laryngeal nerve in thyroid surgery: a critical appraisal. *Int J Surg*. (2013) 11(Suppl):S44–6. doi: 10.1016/S1743-9191(13)60014-X
30. Sanabria A, Kowalski LP, Nixon I, Angelos P, Shaha A, Owen RP, et al. Methodological quality of systematic reviews of intraoperative neuromonitoring in thyroidectomy: a systematic review. *JAMA Otolaryngol Head Neck Surg*. (2019) 145:563–73. doi: 10.1001/jamaoto.2019.0092
31. Higgins TS, Gupta R, Ketcham AS, SataloK RT, Wadsworth JT, Sinacori JT. Recurrent laryngeal nerve monitoring versus identification alone on post-thyroidectomy true vocal fold palsy: a meta-analysis. *Laryngoscope*. (2011) 121(5):1009–17. doi: 10.1002/lary.21578
32. Zheng S, Xu Z, Wei Y, Zeng M, He J. Effect of intraoperative neuromonitoring on recurrent laryngeal nerve palsy rates after thyroid surgery - a meta-analysis. *J Formos Med Assoc*. (2013) 112(8):463–72. doi: 10.1016/j.jfma.2012.03.003
33. Sinclair CF, Tellez MJ, Ulkatan S. Continuous laryngeal adductor reflex versus intermittent nerve monitoring in neck endocrine surgery. *Laryngoscope*. (2020) 131:230–6. doi: 10.1002/lary.28710
34. Liu CH, Huang TY, Wu CW, Wang JJ, Wang F, Chan LP, et al. New developments in anterior laryngeal recording technique during neuromonitored thyroid and parathyroid surgery. *Front Endocrinol*. (2021) 12:763170. doi: 10.3389/fendo.2021.763170
35. Schneider R, Machens A, Sekulla C, Lorenz K, Elwerr M, Dralle H. Superiority of continuous over intermittent intraoperative nerve monitoring in preventing vocal cord palsy. *Br J Surg*. (2021) 108(5):566–73. doi: 10.1002/bjs.11901
36. Wang JJ, Huang TY, Wu CW, Lin YC, Tseng HY, Liu CH, et al. Improving voice outcomes after thyroid surgery – review of safety parameters for using energy-based devices near the recurrent laryngeal nerve. *Front Endocrinol*. (2021) 12:793431. doi: 10.3389/fendo.2021.793431
37. Moran K, Grigorian A, Elfenbein D, Schubl S, Jutric Z, Lekawa M, et al. Energy vessel sealant devices are associated with decreased risk of neck hematoma after thyroid surgery. *Updates Surg*. (2020) 72(4):1135–41. doi: 10.1007/s13304-020-00776-9
38. Canu GL, Medas F, Podda F, Tatti A, Pisano G, Erdas E, et al. Thyroidectomy with energy-based devices: surgical outcomes and complications—comparison between harmonic focus, ligasure small jaw and thunderbeat open fine jaw. *Gland Surg*. (2020) 9(3):721. doi: 10.21037/gs.2020.03.31
39. Dionigi G, Wu C-W, Kim H-Y, Liu X, Liu R, Randolph GW, et al. Safety of energy based devices for hemostasis in thyroid surgery. *Gland Surg*. (2016) 5(5):490. doi: 10.21037/gs.2016.09.01
40. Liu C-H, Wang C-C, Wu C-W, Lin Y-C, Lu I, Chang P-Y, et al. Comparison of surgical complications rates between ligasure small jaw and clamp-and tie hemostatic technique in 1,000 neuro-monitored Thyroidectomies. *Front Endocrinol*. (2021) 12:313. doi: 10.3389/fendo.2021.638608
41. Pacilli M, Tartaglia N, Gerundo A, Pavone G, Fersini A, Ambrosi A. Energy based vessel sealing devices in thyroid surgery: a systematic review to clarify the relationship with recurrent laryngeal nerve injuries. *Medicina*. (2020) 56(12):651. doi: 10.3390/medicina56120651
42. Garas G, Okabayashi K, Ashrafian H, Shetty K, Palazzo F, Tolley N, et al. Which hemostatic device in thyroid surgery? a network meta-analysis of surgical technologies. *Thyroid*. (2013) 23(9):1138–50. doi: 10.1089/ thy.2012.0588
43. Dionigi G, Wu CW, Kim HY, Rausei S, Boni L, Chiang FY. Severity of recurrent laryngeal nerve injuries in thyroid surgery. *World J Surg*. (2016) 40(6):1373–81. doi: 10.1007/s00268-016-3415-3
44. Dionigi G, Alesina PF, Barczynski M, Boni L, Chiang FY, Kim HY, et al. Recurrent laryngeal nerve injury in video-assisted thyroidectomy: lessons learned from neuromonitoring. *Surg Endosc*. (2012) 26(9):2601–8. doi: 10.1007/s00464-012-2239-y
45. Wu C-W, Huang T-Y, Chen H-C, Chen H-Y, Tsai T-Y, Chang P-Y, et al. Intra-operative neural monitoring of thyroid surgery in a porcine model. *JoVE*. (2019) 144:e57919. doi: 10.3791/57919
46. Dionigi G, Chiang FY, Kim HY, Randolph GW, Mangano A, Chang PY, et al. Safety of ligasure in recurrent laryngeal nerve dissection-porcine model using continuous monitoring. *Laryngoscope*. (2017) 127(7):1724–9. doi: 10.1002/lary.26271

47. Wu CW, Chai YJ, Dionigi G, Chiang FY, Liu X, Sun H, et al. Recurrent laryngeal nerve safety parameters of the H armonic focus during thyroid surgery: porcine model using continuous monitoring. *Laryngoscope*. (2015) 125(12):2838–45. doi: 10.1002/lary.25412
48. Lin YC, Dionigi G, Randolph GW, Lu IC, Chang PY, Tsai SY, et al. Electrophysiologic monitoring correlates of recurrent laryngeal nerve heat thermal injury in a porcine model. *Laryngoscope*. (2015) 125(8):E283–90. doi: 10.1002/lary.25362
49. Hayami M, Watanabe M, Mine S, Imamura Y, Okamura A, Yuda M, et al. Steam induced by the activation of energy devices under a wet condition may cause thermal injury. *Surg Endoscopy*. (2020) 34(5):2295–302. doi: 10.1007/s00464-019-07312-w
50. Khadra H, Bakeer M, Hauch A, Hu T, Kandil E. *Gland Surg*. (2018) 7(Suppl 1):S34–S41. doi: 10.21037/gs.2018.03.02
51. Orloff L, Noel JE, Stack Jr BC, Russell MD, Angelos P, Baek JH, et al. Radiofrequency ablation and related ultrasound-guided ablation technologies for for treatment of benign and malignant thyroid disease: An international multidisciplinary consensus statement of the American Head and Neck Society Endocrine Surgery Section with the Asia Pacific Society of Thyroid Surgery, Associazione Medici Endocrinologi, British Association of Endocrine and Thyroid Surgeons, Europoean Thyroid Association, Italian Thyroid Radiology, Latin American Thyroid Society and Thyroid Nodules Therapies Association. *Head & Neck*. (2021) 44(3): 633–660. doi: 10.1002/hed.26960
52. Ha EJ, Baek JH, Lee JH. Ultrasonography-based thyroidal and perithyroidal anatomy and its clinical significance. *Korean J Radiol*. (2015) 16:749–66. doi: 10.3348/kjr.2015.16.4.749
53. Park HS, Baek JH, Park AW, Chung SR, Choi YJ, Lee JH. Thyroid radiofrequency ablation: updates on innovative devices and techniques. *Korean J Radiol*. (2017) 18(4):615–23. doi: 10.3348/kjr.2017.18.4.615
54. Park HS, Baek JH, Choi YJ, Lee JH. Innovative techniques for image-guided ablation of benign thyrid nodules: combined ethanol and radiofrequency ablation. *Korean J Radiol*. (2017) 18(3):461–9. doi: 10.3348/kjr.2017.18.3.461
55. Lee MK, Baek JH, Chung SR, Choi YJ, Lee YM, Kim TY, et al. Effectiveness of injection cold 5% Dextrose into patients with nerve damage symptoms during thyroid Radiofrequency Ablation. *Endocrinol Metab*. (2020) 35:407–15. doi: 10.3803/EnM.2020.35.2.407
56. Jeong SY, Baek JH, Choi YJ, Lee JH. Ethanol and thermal ablation for malignant thyroid tumours. *Int J Hyperthermia*. (2017) 33:938–45 doi: 10.1080/02656736.2017.1361048
57. Tomoda C, Hirokawa Y, Uruno T, Takamura Y, Ito Y, Miya A, et al. Sensitivity and specificity of intraoperative recurrent laryngeal nerve stimulation test for predicting vocal cord palsy after thyroid surgery. *World J Surg*. (2006) 30:1230–3. doi: 10.1007/s00268-005-0351-z
58. Hamelmann WH, Meyer T, Timm S, Timmermann W. A critical estimation of intraoperative neuromonitoring (IONM) in thyroid surgery. *Zentralbl Chir*. (2002) 127:409–13. doi: 10.1055/s-2002-31982
59. Chan WF, Lang BH, Lo CY. The role of intraoperative neuromonitoring of recurrent laryngeal nerve during thyroidectomy: a comparative study on 1000 nerves at risk. *Surgery*. (2006) 140:866–72; discussion 872–873. doi: 10.1016/j.surg.2006.07.017
60. Thomusch O, Sekulla C, Machens A, Neumann HJ, Timmermann W, Dralle H. Validity of intraoperative neuromonitoring signals in thyroid surgery. *Langenbecks Arch Surg*. (2004) 389:499–503. doi: 10.1007/s00423-003-0444-9
61. Beldi G, Kinsbergen T, Schlumpf R. Evaluation of intraoperative recurrent nerve monitoring in thyroid surgery. *World J Surg*. (2004) 28:589–91. doi: 10.1007/s00268-004-7226-6
62. Hermann M, Hellebart C, Freissmuth M. Neuromonitoring in thyroid surgery: prospective evaluation of intraoperative electrophysiological responses for the prediction of recurrent laryngeal nerve injury. *Ann Surg*. (2004) 240:9–17. doi: 10.1097/01.sla.0000132260.34503.02
63. Dralle H, Sekulla C, Lorenz K, Brauckhoff M, Machens A. German IONM Study Group: Intraoperative monitoring of the recurrent laryngeal nerve and thyroid surgery. *World J Surg*. (2008) 32:1358–66. doi: 10.1007/s00268-008-9483-2
64. Schneider R, Machens A, Lorenz K, Dralle H. Intraoperative nerve monitoring in thyroid surgery – shifting current paradigms. *Gland Surg*. (2020) 9(Suppl 2):S120–8.
65. Chandrasekhar SS, Randolph GW, Seidman MD, Rosenfeld RM, Angelos P, Barkmeier-Kraemer J, et al. Clinical practice guideline: improving voice outcomes after thyroid surgery. *Otolaryngol Head Neck Surg*. (2013) 148(6S): S1–S37. doi: 10.1177/0194599813487301
66. Stojadinovic A, Henry LR, Howard RS, Gurevich-Uvena J, Makashay MJ, Coppit GL, et al. Prospective trial of voice outcomes after thyroidectomy: evaluation of patient-reported and clinician-determined voice assessments in identifying post-thyroidectomy dysphonia. *Surgery*. (2008) 143(6): 732–42. doi: 10.1016/j.surg.2007.12.004
67. Jacobson BH, Johnson A, Grywalski C, Silbergleit A, Jacobson G. The voice handicap index (VHI): development and validation. *Am J Speech Lang Pathol*. (1997) 6(3):66–70. doi: 10.1044/1058-0360.0603.66
68. Row-Jones JM, Leighton SEJ, Rosswick RO. Benign thyroid disease and vocal cord palsy. *Ann RCS Eng*. (1993) 75:241–4. PMID: 8379624 PMCID: PMC2497920.
69. Yung KC, Likhterov I, Courey MS. Effect of temporary vocal fold injection medialization on the rate of permanent medialization laryngoplasty in unilateral vocal fold paralysis patients. *Laryngoscope*. (2011) 121(10): 2191–4. doi: 10.1002/lary.21965
70. Friedman AD, Burns JA, Heaton JT, Zeitels SM. Early versus late injection medialization for unilateral vocal cord paralysis. *Laryngoscope*. (2010) 120 (10):2191–4. doi: 10.1002/lary.21097
71. Isshiki N, Okamura H, Ishikawa T. Thyroplasty type I (lateral compression) for dysphonia due to vocal cord paralysis or atrophy. *Acta Otolaryngol*. (1975) 80(5–6):465–73. doi: 10.3109/00016487509121353
72. Isshiki N, Tanabe M, Sawada M. Arytenoid adduction for unilateral vocal cord paralysis. *Arch Otolaryngol*. (1978) 104(10):555–8. doi: 10.1001/archotol.1978.00790100009002
73. Zeitels SM, Mauri M, Dailey SH. Adduction arytenopexy for vocal fold paralysis: indications and technique. *J Laryngol Otol*. (2004) 118(7):508–16. doi: 10.1258/0022215041615263
74. Aynehchi BB, McCoul ED, Sundaram K. Systematic review of laryngeal reinnervation techniques. *Otolaryngol Head Neck Surg*. (2010) 143(6): 749–59. doi: 10.1016/j.otohns.2010.09.031

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Frontiers in Endocrinology

ORIGINAL RESEARCH
published: 24 May 2022
doi: 10.3389/fendo.2022.886924

# Treatment Options and Voice Outcomes for Patients With Unilateral Vocal Fold Paralysis After Thyroidectomy

*Ming-Hsun Wen*[1] *and Chi-Te Wang*[1,2,3]*

[1] *Department of Otolaryngology Head and Neck Surgery, Far Eastern Memorial Hospital, Taipei, Taiwan,* [2] *Department of Electrical Engineering, Yuan Ze University, Taoyuan, Taiwan,* [3] *Department of Special Education, University of Taipei, Taipei, Taiwan*

OPEN ACCESS

**Edited by:**
*Che-Wei Wu,*
*Kaohsiung Medical University, Taiwan*

**Reviewed by:**
*Gianlorenzo Dionigi,*
*University of Milan, Italy*
*Erivelto Martinho Volpi,*
*Centro de referencia no ensino do diagnóstico por imagem (CETRUS), Brazil*

***Correspondence:**
*Chi-Te Wang*
*drwangct@gmail.com*

**Specialty section:**
*This article was submitted to Thyroid Endocrinology, a section of the journal Frontiers in Endocrinology*

**Received:** *01 March 2022*
**Accepted:** *19 April 2022*
**Published:** *24 May 2022*

**Citation:**
*Wen M-H and Wang C-T (2022) Treatment Options and Voice Outcomes for Patients With Unilateral Vocal Fold Paralysis After Thyroidectomy. Front. Endocrinol. 13:886924. doi: 10.3389/fendo.2022.886924*

**Objectives:** This study investigated the treatment options and clinical outcomes of voice therapy (VT), hyaluronic acid (HA) injection, autologous fat injection (FI), and medialization thyroplasty (MT) in patients with unilateral vocal fold paralysis (UVFP) after thyroidectomy.

**Study Design:** Retrospective case series.

**Setting:** A tertiary teaching hospital.

**Methods:** This study included 51 patients with post-thyroidectomy UVFP who underwent VT (*n* = 20), HA injection (*n* = 14), FI (*n* = 12), or MT (*n* = 5) from January 2016 to June 2021. The treatment outcomes were evaluated using 10-item voice handicap index (VHI-10), maximal phonation time (MPT), and auditory perceptual rating using GRB scales (i.e., grade, roughness, and breathiness) before and 3 to 6 months after treatment.

**Results:** Patients received HA injection presented a significantly shorter interval after thyroidectomy (mean: 4.6 months), followed by VT (6.7 months), FI (12.3 months), and MT (22.4 months). The results exhibited improvement in most of the outcomes after all of the four treatments. Additional comparisons indicated that VHI-10 scores improved the most among patients receiving MT, followed by HA, FI, and VT. The differences of MPT and GRB scores among the 4 treatment groups were non-significant.

**Conclusions:** The results revealed that VT, HA, FI, and MT can all improve the voice outcomes of patients with post-thyroidectomy UVFP. The optimal treatment approach should be individualized according to the patient's preference and vocal demand, and the interval between thyroidectomy and intervention.

**Keywords: vocal palsy, hoarseness, aspiration, laryngoplasty, injection**

**Abbreviations:** VT, Voice therapy; HA, Hyaluronic acid; FI, Fat injection; MT, Medialization thyroplasty; UVFP, Unilateral vocal fold paralysis; VHI-10, 10-item Voice Handicap Index; MPT, Maximal phonation time; GRB, Grade, Roughness, Breathiness; RLN, Recurrent laryngeal nerve; GEE, Generalized estimating equation.

# INTRODUCTION

Unilateral vocal fold paralysis (UVFP) is a common laryngeal disorder that may cause hoarseness, dysphagia, and even aspiration, leading to considerable impairment of quality of life (1). It commonly results from dysfunction of the recurrent laryngeal nerve (RLN) innervating the intrinsic muscles of the larynx. The etiologies of UVFP include iatrogenic, neoplastic, idiopathic, neurologic, nonsurgical trauma, and other factors (2). Iatrogenic surgical injury has become the most common cause of UVFP because of the rising number of surgeries involving RLN pathway being performed. Thyroidectomy remains the leading cause of surgery-related UVFP (2, 3).

A systematic review of 27 articles and 25,000 patients revealed that the average incidence rates of temporary and permanent UVFP after thyroidectomy are 9.8% and 2.3%, respectively (4). In a large multi-institutional study, RLN injury occurred in nearly 6% of thyroid surgeries (5). The incidence of RLN palsy after thyroid surgery is up to 8% for transient palsy and ranges from 0.3% to 3% for permanent palsy (6–8).

Multiple treatment modalities have been proposed for UVFP. For example, voice therapy (VT) may be applied as a conservative and noninvasive treatment with documented clinical effectiveness (9). Injection laryngoplasty (IL), which was first introduced by Dr. Bruening in 1911, is another common treatment option for UVFP (10). Owing to advances in endoscopic technology, various injection approaches may be used in the treatment of UVFP according to the patient's tolerance and the surgeon's preference. Depending on the longevity of the injection materials used, IL can be performed as a temporary or long-lasting means of improving glottal insufficiency. The list of injection materials may include collagen, hyaluronic acid (HA), calcium hydroxylapatite, and other synthetic materials (11, 12). Autologous fat injection (FI) is another well-established procedure for UVFP. Lipoinjection requires overinjection by some degree to correct for the expected resorption of fat in the first 4 to 6 weeks after the procedure (13).

In contrast to IL, of which the sustainability depends on the materials used, medialization thyroplasty (MT) is considered a definite long-term treatment for UVFP. MT is performed by creating a window in the thyroid cartilage and pushing the paralyzed vocal fold medially by an implant, such as a silicone block, Gore-Tex strip, or titanium plate (14–16). Similar to IL, MT is mostly performed under local anesthesia to facilitate real-time audio feedback. It can be performed in conjunction with arytenoid adduction to further improve posterior glottal closure (17).

Although some studies have compared the surgical outcomes of patients with UVFP (18), few have focused specifically on the management and effectiveness of post-thyroidectomy UVFP. Therefore, this study investigated the voice outcomes associated with different treatment options for patients with UVFP after thyroid surgery. Our research goal was to elucidate the effectiveness of clinical treatment options for this specific clinical scenario.

# MATERIALS AND METHODS

## Study Setting

We retrospectively reviewed the medical charts of patients who were diagnosed with UVFP after thyroidectomy and visited the voice clinic of a tertiary teaching hospital from January 2016 to June 2021. UVFP was clinically diagnosed on the basis of an immobile vocal fold with an atrophic, bowing appearance. Patients who did not receive active intervention, who received preceding treatments at another hospital, who were lost to follow-up or who received voice therapy less than three sessions were excluded (**Figure 1**). This study protocol was approved by the Research Ethics Review Committee of Far Eastern Memorial Hospital (FEMH No. 111032-E).

## Procedures

VT sessions were conducted by a senior therapist with more than 10 years of clinical experience. All the participants were scheduled for one session of individual VT per week and were instructed to perform further practice at home after each session. The treatment strategies, which included vocal function exercise, pushing exercise, water resistant therapy, and hard glottal attacks (19, 20), were tailored according to clinical judgement. To ensure a sufficient treatment effect, patients who attended fewer than three sessions of VT were excluded from the study.

Vocal fold HA injection was conducted under local anesthesia in an office setting. A 10% lidocaine solution was sprayed on the pharynx, tonsils, vallecula, and epiglottis, followed by laryngeal gargling of a 2% lidocaine solution (21). We injected HA into the vocal folds *via* a transcutaneous or a transoral approach (22), and the injection locations were (1) lateral to the vocal process and (2) the middle third of the vocal fold at the depth of the vocalis muscle (**Figure 2**). The required amount of augmentation was determined according to acoustic feedback and usually ranged from 0.5 to 1.0 mL. The entire procedure was completed within 15 minutes in cooperative patients.

We performed FI under general anesthesia. Autologous fat was obtained from the lower abdomen through liposuction *via* a small peri-umbilical incision. After infiltrating tumescent solution, we aspirated 10 to 20 mL of subcutaneous adipose tissue. We further rinsed the fat tissue with normal saline to remove blood clots, and the purified fat globules were loaded into a 1-cc insulin syringe. The autologous fat was then injected into vocal folds under the guidance of a direct suspension laryngoscope (**Figure 3**), and the target area was the posterior third of the vocalis muscle, just lateral to the vocal process. To compensate for fat loss or reabsorption, we generally overinjected 20% to 30% of the fat (23).

All the MT procedures were performed under local anesthesia combined with light intravenous sedation. A horizontal skin incision was made at the level of the mid-height of the thyroid cartilage. After we elevated the platysma and retracted the strap muscle, the thyroid cartilage was exposed. The thyrotomy window was created 3–4 mm above the lower margin of the thyroid cartilage, 6–8 mm lateral to the midline of the thyroid cartilage (**Figure 4**). The window was approximately 3–4 mm

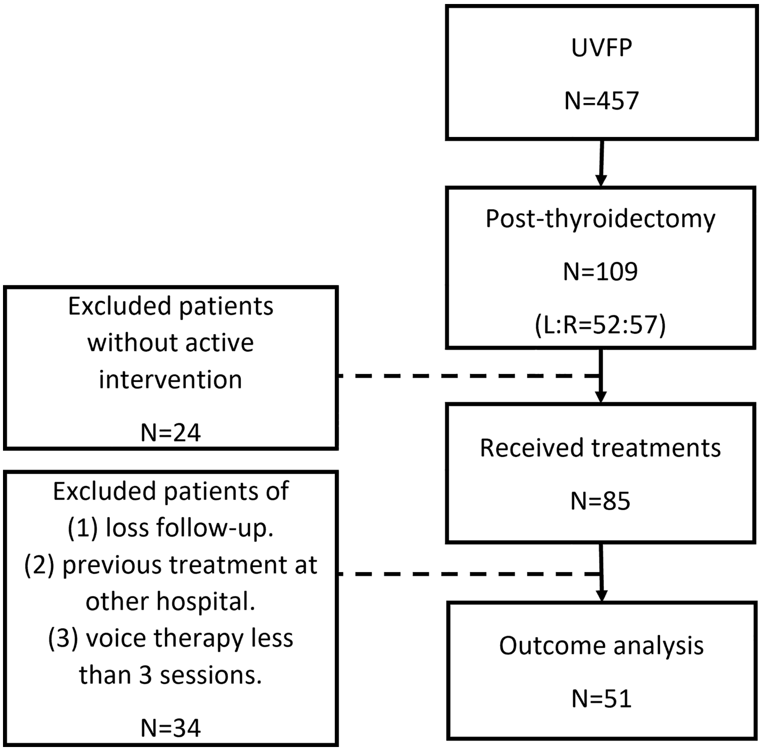



**FIGURE 1** | Flow chart of study cohort.

high and 5–8 mm wide depending on the size of the thyroid cartilage (24). We inserted a Gore-Tex sheet to medialize the paralytic vocal fold, and adjusted the depth of medialization according to auditory feedback by asking the patient to phonate intra-operatively. Once the voice quality was tuned, the implant was sutured to the thyrotomy window and closed using a small piece of bone wax. After careful hemostasis, the wound was closed in layers without the need to place a drain.

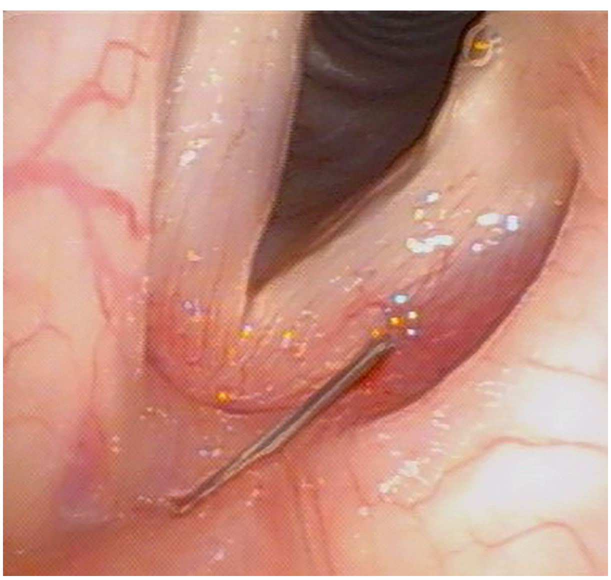


**FIGURE 2** | A 40-year-old woman with left UVFP received HA injection *via* transcutaneous approach under local anesthesia 3 months after thyroidectomy.

## Outcomes and Statistics

Treatment outcomes were investigated using the following parameters: (1) the 10-item Voice Handicap Index (VHI-10), (2) Maximum Phonation Time (MPT), and (3) perceptual rating of voice quality using GRB (Grade, Roughness, Breathiness) scales (rated 0=normal, 1=mildly deviated, 2=moderately deviated, or 3=severely deviated. Post-operative outcome were measured between 3-6 months after the treatments. One-way ANOVA and Chi-square test were used to compare the difference between the four treatment groups. Treatment outcomes of various modalities was analyzed by Generalized Estimating Equations (GEE). $P<0.05$ was considered statistically significant.

# RESULTS

## Population

We screened 457 patients with UVFP and identified 109 patients who developed UVFP after thyroidectomy. The right and left vocal folds were involved in 57 and 52 cases, respectively.

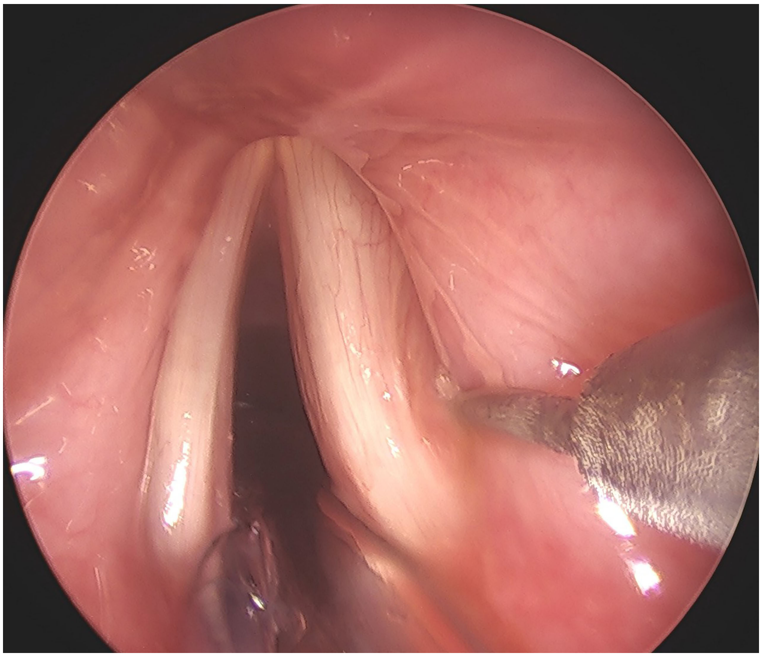


**FIGURE 3** | A 56-year-old woman with right UVFP received FI under general anesthesia 9 months after thyroidectomy.

We excluded 24 patients who did not receive active intervention and 34 patients who were lost to follow-up, who were already treated at another hospital, or who had received fewer than three sessions of VT. Ultimately, 51 patients were included in subsequent analyses. (**Figure 1**).

Of the 51 patients, 20, 14, 12, and 5 received VT, HA, FI, and MT, respectively. The age range was 20 to 81 years, without significant differences among the treatment groups. Other demographics, namely sex, smoking, and alcohol consumption were also not significantly different among four groups (**Table 1**). The time interval between thyroidectomy and intervention for UVFP was significantly shorter in patients receiving HA and VT, compared with patients receiving MT and FI ($p<0.01$, ANOVA). The average interval between VT and subsequent treatment modalities was 3.4 months (standard deviation 0.8 months), corresponding to a mean of 9.5 VT sessions (standard deviation: 4 sessions).

## Treatment Outcomes

Almost all treatment outcome parameters improved significantly after treatment in all the four groups (**Table 2**). Improvement of MPT in the FI group and GRB scores in the MT group exhibited borderline significance.

Examining the VHI-10 scores before and after interventions, the MT group exhibited the greatest improvement (**Figure 5**, $p<0.01$, GEE), followed by the HA, FI, and VT groups. Regarding MPT, generalized estimating equation analysis revealed significant improvement after treatment (**Figure 6**, $p<0.01$), but no differences were identified among the treatment groups ($p=0.59$). Similarly, the patients' GRB scores all improved significantly after treatment (**Figure 7**, $p<0.01$), but no significant differences were identified among the treatment groups ($p=0.56$).

# DISCUSSION

Treatment for UVFP after thyroidectomy is a perennial challenge. In fact, RLN injury after thyroidectomy is a common allegation in malpractice litigations (25). According to our clinical experience, timely intervention can substantially attenuate the negative impact of UVFP after thyroidectomy and reduce patients' willingness to file law suits. In the present study, all the treatment modalities resulted in significant voice improvement in patients with UVFP after thyroidectomy, which is consistent with the conclusions of a systematic review (18). Nevertheless, the optimal treatment strategy should be individualized according to the time interval after thyroidectomy, vocal demand, severity of complications, compliance, and expectations.

During thyroid surgery, the RLN may undergo stretch injury or accidental transection (26). In clinical practice, when vocal palsy is identified after surgery, thorough and regular follow-up every 3 to 4 weeks until the patient recovers is recommended. For patients with high vocal demand and strong motivation, VT can be applied as the first-line treatment (27). Voice training minimizes the impact of UVFP on daily life and helps patients endure the recovery period. Previous studies had documented that early referral often leads to a superior VT outcome (28). The treatment methodologies employed (e.g., the glissando maneuver to activate the cricothyroid muscles, hard glottal attacks to

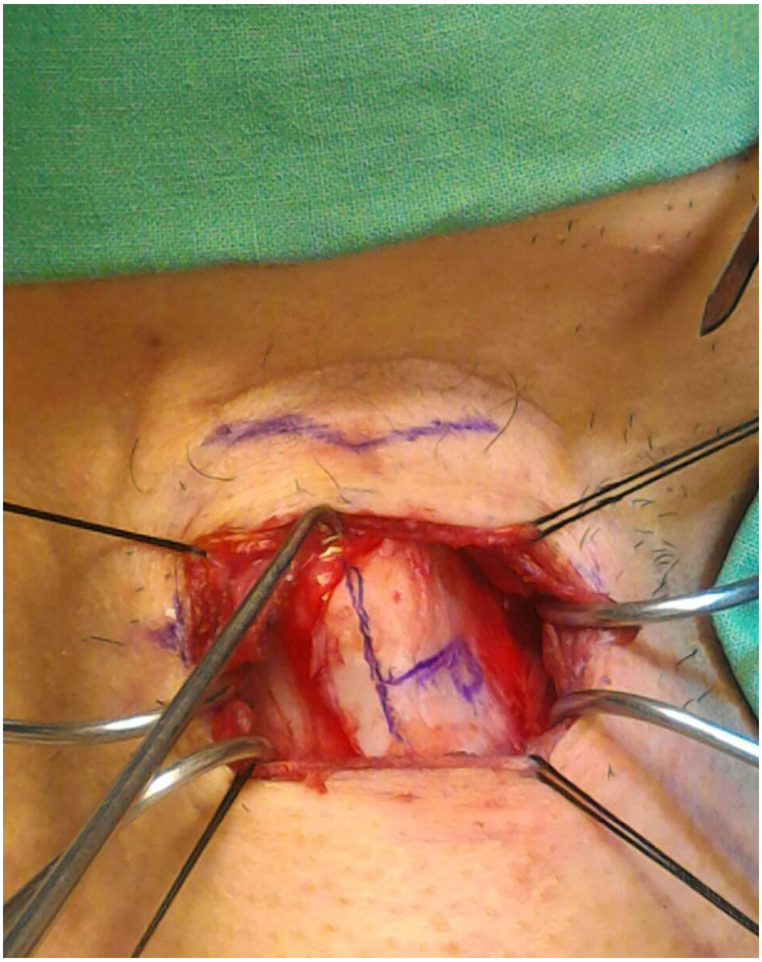


**FIGURE 4** | Measuring the thyrotomy window during MT for left UVFP.

strengthen the adductor muscles, and resonant VT) may vary among speech pathologists. Most of these approaches are intended to enhance the laryngeal compensatory mechanisms from the healthy side. Our study results also indicated that although the degree of voice improvement associated with VT was slightly lower than that associated with the other surgical modalities, VT is still effective and well tolerated. VT remains the most common treatment for post-thyroidectomy UVFP in our routine practice (**Table 1**).

For patients who failed to improve after VT or presented with active dysphagia shortly after thyroidectomy, IL is the most practical choice for temporary intervention. Our practice mostly uses HA in IL procedures because of its high tissue compatibility and easy access. Our previous study showed that symptomatic

**TABLE 1** | Characteristics of the 51 patients with post-thyroidectomy UVFP receiving various treatments.

| | VT (N=20) | HA (N=14) | FI (N=12) | MT (N=5) | p-value |
|---|---|---|---|---|---|
| **Age** | 57.1 ± 10.2 | 51.5 ± 18.7 | 57.5 ± 12.8 | 51.4 ± 15.1 | 0.61* |
| **Sex** | | | | | |
| Female/Male | 18/2 | 11/3 | 10/2 | 4/1 | 0.82# |
| **Smoking** | | | | | |
| Active/Others | 0/20 | 0/14 | 0/12 | 0/5 | – |
| **Alcohol** | | | | | |
| Active/Others | 0/20 | 1/13 | 0/12 | 1/4 | 0.16# |
| **Time Interval (Month)** | 6.7 ± 6.7 | 4.6 ± 2.3 | 12.3 ± 8.1 | 22.1 ± 14.4 | <0.01* |

**: One-way ANOVA.*
*#: Chi Square Test.*

**TABLE 2** | Voice outcomes of the 4 different treatment groups.

| Parameters | VT (N=20) | | p-value+ | HA (N=14) | | p-value+ | FI (N=12) | | p-value+ | MT (N=5) | | p-value+ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Pre Mean ± SD | Post Mean ± SD | | Pre Mean ± SD | Post Mean ± SD | | Pre Mean ± SD | Post Mean ± SD | | Pre Mean ± SD | Post Mean ± SD | |
| VHI-10 | 30.8 ± 6.1 | 22.9 ± 9.2 | <0.01 | 33.2 ± 4.4 | 14.1 ± 11.0 | <0.01 | 30.9 ± 5.9 | 16.3 ± 7.2 | <0.01 | 30.8 ± 13.7 | 7.6 ± 4.6 | 0.04 |
| MPT | 5.0 ± 2.6 | 6.8 ± 3.5 | 0.03 | 4.2 ± 2.3 | 9.4 ± 5.5 | <0.01 | 4.3 ± 1.7 | 8.3 ± 7.0 | 0.06 | 6.0 ± 4.3 | 10.3 ± 4.9 | 0.05 |
| GRB(sum) | 5.2 ± 1.8 | 3.9 ± 1.3 | <0.01 | 6.0 ± 0.9 | 2.9 ± 2.2 | <0.01 | 5.2 ± 1.3 | 3.1 ± 1.9 | <0.01 | 5.4 ± 1.5 | 2.2 ± 2.3 | 0.08 |

+: *Paired t test.*

relief could last for 9–14 months after HA injection (22), indicating that HA is a suitable material for temporary correction of UVFP (29). Early HA injection might promote a more proper vocal fold position with improved outcomes (30), which explains why only a small fraction of the patients in the present study underwent definite MT. The greatest advantage of HA injection is that it can be performed in the clinic under local anesthesia, meaning patients do not require an additional procedure in the operating room to correct complications from the preceding thyroidectomy. HA injection can also provide rapid (sometimes immediate) voice recovery, which is beneficial for patients with high vocal demand. In addition, early HA injection can reduce the anxiety of uncertain voice recovery and ease the tension between the thyroid surgeon and the patient.

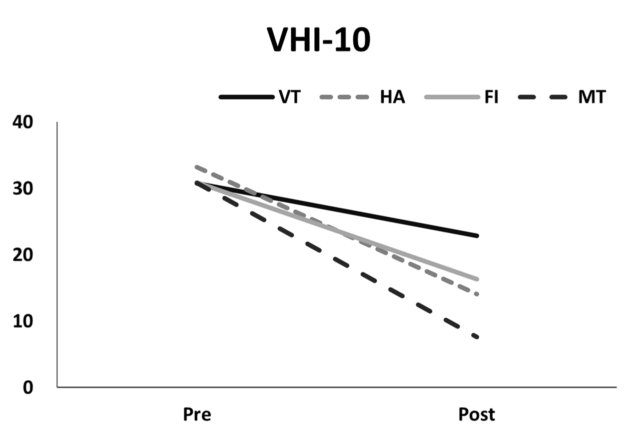



**FIGURE 5** | Pre- and post-measurements of VHI-10 in different treatment groups.

When functional recovery of phonation and swallowing is absent after 9-12 months of observation, treatment modalities with longer-lasting effects (e.g., FI and MT) are indicated. Despite the wide acceptability and tissue compatibility of autologous fat, clinical practitioners must account for the uncertain survival rates of fat grafts. Studies have reported high failure rates following FI, and patients may require revision surgery (31, 32). The variability in the clinical outcomes of the procedure can be explained by the different techniques for fat harvesting and injection. In the present study, the effects of IL with HA and fat remained similar for up to 6 months. Limited by the lack of long-term follow-up records, we are unable to determine whether fat may sustain as a long-term filler, as suggested in other studies (33).

MT is widely applied as a permanent treatment for patients with UVFP and provide satisfactory outcomes on experienced hands. However, performing an additional open surgery to correct vocal palsy caused by a previous thyroidectomy can induce substantial psychological stress for the patient. In the

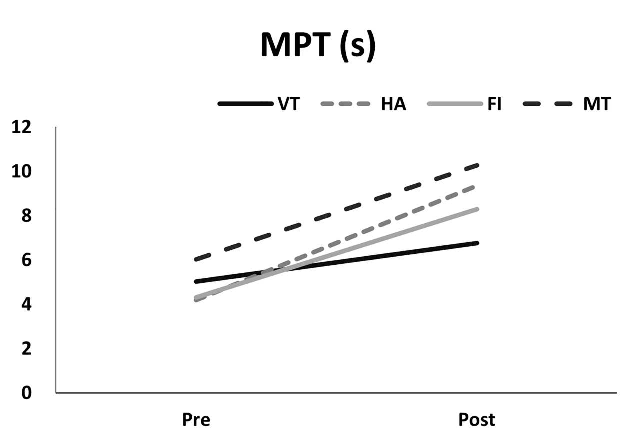



**FIGURE 6** | Pre- and post-measurements of MPT (seconds) in different treatment groups.

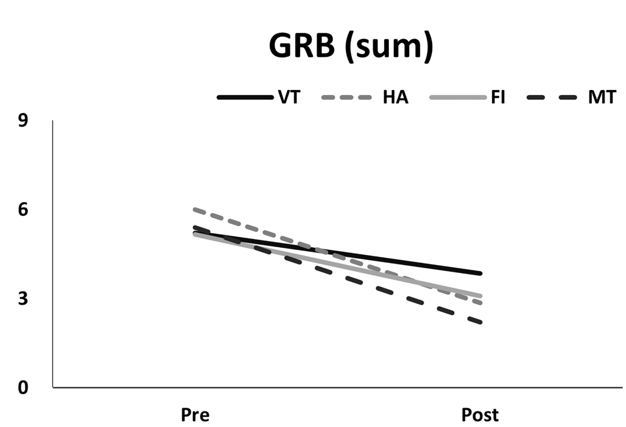



**FIGURE 7** | Pre- and post-measurements of the summation of GRB scores in different treatment groups.

present study, only five of the patients agreed to undergo MT after thyroidectomy. Nevertheless, our results indicated that the voice outcomes associated with MT were superior to the other treatment modalities, especially in terms of patient-reported VHI-10 scores. A likely explanation for this trend is that MT is performed under local anesthesia, thereby enabling the patient to actively participate in the vocal tuning process.

Our study has several limitations. First, the treatment modalities were not randomized but based on shared decision between the otolaryngologist and the patient. Second, the short follow-up period limits the interpretation for long-term treatment outcomes. In addition, the treatment results of UVFP strongly depend on the surgeon's experience, and outcomes of VT may also be influenced by the patient's motivation and active adherence (34). Further studies with longer follow-up periods and larger samples are warranted to evaluate and compare the long-term effects of different treatment modalities for thyroidectomy-related UVFP.

## CONCLUSION

UVFP is common after thyroidectomy, and common treatments include VT, HA, FI, and MT. Our results indicated significant improvements of voice outcomes associated with all these treatments. Clinical decisions may be tailored according to the surgeon's experience, the patient's preference and vocal demand, and the interval between thyroidectomy and intervention.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Research Ethics Review Committee of Far Eastern Memorial Hospital (FEMH No. 111032-E). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

M-HW: Manuscript preparing and drafting, data analysis, C-TW: Study conceptualization, data analysis, manuscript drafting and proof reading. All authors contributed to the article and approved the submitted version.


## FUNDING

This work was supported by grants from the Far Eastern Memorial Hospital (FEMH-2022-C-067 and FEMH-2022-C-068).


## REFERENCES


1. Spector BC, Netterville JL, Billante C, Clary J, Reinisch L, Smith TL, et al. Quality-of-Life Assessment in Patients With Unilateral Vocal Cord Paralysis. *Otolaryngol - Head Neck Surg* (2001) 125(3):176–82. doi: 10.1067/mhn.2001.117714
2. Rosenthal LH, Benninger MS, Deeb RH. Vocal Fold Immobility: A Longitudinal Analysis of Etiology Over 20 Years. *Laryngoscope* (2007) 117 (10):1864–70. doi: 10.1097/MLG.0b013e3180de4d49
3. Spataro EA, Grindler DJ, Paniello RC. Etiology and Time to Presentation of Unilateral Vocal Fold Paralysis. *Otolaryngol Head Neck Surg* (2014) 151 (2):286–93. doi: 10.1177/0194599814531733
4. Jeannon JP, Orabi AA, Bruch GA, Abdalsalam HA, Simo R, et al. Diagnosis of Recurrent Laryngeal Nerve Palsy After Thyroidectomy: A Systematic Review. *Int J Clin Pract* (2009) 63(4):624–9. doi: 10.1111/j.1742-1241.2008.01875.x
5. Gunn A, Oyekunle T, Stang M, Kazaure H, Scheri R. Recurrent Laryngeal Nerve Injury After Thyroid Surgery: An Analysis of 11,370 Patients. *J Surg Res* (2020) 255:42–9. doi: 10.1016/j.jss.2020.05.017
6. Chiang F-Y, Wang LF, Huang YF, Lee KW, Kuo WR, et al. Recurrent Laryngeal Nerve Palsy After Thyroidectomy With Routine Identification of the Recurrent Laryngeal Nerve. *Surgery* (2005) 137(3):342–7. doi: 10.1016/j.surg.2004.09.008
7. Echternach M, Maurer CA, Mencke T, Schilling M, Verse T, Richter B, et al. Laryngeal Complications After Thyroidectomy: Is It Always the Surgeon? *Arch Surg* (2009) 144(2):149–53; discussion 153. doi: 10.1001/archsurg.2008.530
8. Efremidou EI, Papageorgiou MS, Liratzopoulos N, Manolas KJ. The Efficacy and Safety of Total Thyroidectomy in the Management of Benign Thyroid Disease: A Review of 932 Cases. *Can J Surg* (2009) 52(1):39–44.
9. Busto-Crespo O, Uzcanga-Lacabe M, Abad-Marco A, Berasategui I, García L, Maraví E, et al. Longitudinal Voice Outcomes After Voice Therapy in Unilateral Vocal Fold Paralysis. *J Voice* (2016) 30(6):767.e9–767.e15. doi: 10.1016/j.jvoice.2015.10.018
10. Courey MS, Naunheim MR. Injection Laryngoplasty for Management of Neurological Vocal Fold Immobility. *Adv Otorhinolaryngol* (2020) 85:68–84. doi: 10.1159/000456684
11. Kwon TK, Buckmire R. Injection Laryngoplasty for Management of Unilateral Vocal Fold Paralysis. *Curr Opin Otolaryngol Head Neck Surg* (2004) 12 (6):538–42. doi: 10.1097/01.moo.0000144393.40874.98
12. Carroll TL. *Ideal Material Selection for Vocal Fold Augmentation, in Vocal Fold Injection*. Singapore: Springer (2021). p. 73–8.
13. Mikaelian DO, Lowry LD, Sataloff RT. Lipoinjection for Unilateral Vocal Cord Paralysis. *Laryngoscope* (1991) 101(5):465–8. doi: 10.1288/00005537-199105000-00003
14. Isshiki N, Kojima H, Shoji K, Hirano S. Vocal Fold Atrophy and its Surgical Treatment. *Ann Otol Rhinol Laryngol* (1996) 105(3):182–8. doi: 10.1177/000348949610500303
15. McCulloch TM, Hoffman HT. Medialization Laryngoplasty With Expanded Polytetrafluoroethylene: Surgical Technique and Preliminary Results. *Ann Otol Rhinol Laryngol* (1998) 107(5):427–32. doi: 10.1177/000348949810700512
16. Schneider B, Denk DM, Bigenzahn W. Functional Results After External Vocal Fold Medialization Thyroplasty With the Titanium Vocal Fold Medialization Implant. *Laryngoscope* (2003) 113(4):628–34. doi: 10.1097/00005537-200304000-00008
17. Netterville JL, Stone RE, Civantos FJ, Luken ES, Ossoff RH. Silastic Medialization and Arytenoid Adduction: The Vanderbilt Experience: A Review of 116 Phonosurgical Procedures. *Ann Otol Rhinol Laryngol* (1993) 102(6):413–24. doi: 10.1177/000348949310200602
18. Siu J, Tam S, Fung K. A Comparison of Outcomes in Interventions for Unilateral Vocal Fold Paralysis: A Systematic Review. *Laryngoscope* (2016) 126(7):1616–24. doi: 10.1002/lary.25739

19. Angadi V, Croake D, Stemple J. Effects of Vocal Function Exercises: A Systematic Review. *J Voice* (2019) 33(1):124.e13–34. doi: 10.1016/j.jvoice.2017.08.031
20. Stemple JC, Roy N, Klaben BK. *Clinical Voice Pathology Theory and Management*. San Diego: Plural Publishing (2014).
21. Wang CT, Liao LJ, Huang TW, Cheng PW. Preliminary Report of Vocal Fold Augmentation With Cross-Linked Porcine Collagen. *Otolaryngol Head Neck Surg* (2012) 146(4):606–10. doi: 10.1177/0194599811434003
22. Wen MH, Cheng PW, Liao LJ, Chou HW, Wang CT. Treatment Outcomes of Injection Laryngoplasty Using Cross-Linked Porcine Collagen and Hyaluronic Acid. *Otolaryngol Head Neck Surg* (2013) 149(6):900–6. doi: 10.1177/0194599813508082
23. Shaw GY, Szewczyk MA, Searle J, Woodroof J. Autologous Fat Injection Into the Vocal Folds: Technical Considerations and Long-Term Follow-Up. *Laryngoscope* (1997) 107(2):177–86. doi: 10.1097/00005537-199702000-00008
24. Rosen CA, Simpson CB. *Operative Techniques in Laryngology*. Berlin: Springer (2008).
25. Abadin SS, Kaplan EL, Angelos P. Malpractice Litigation After Thyroid Surgery: The Role of Recurrent Laryngeal Nerve Injuries, 1989–2009. *Surgery* (2010) 148(4):718–23. doi: 10.1016/j.surg.2010.07.019
26. Chiang F-Y, Lu I-C, Kuo W-R, Lee K-W, Chang N-C, Wu C-W, et al. The Mechanism of Recurrent Laryngeal Nerve Injury During Thyroid Surgery—the Application of Intraoperative Neuromonitoring. *Surgery* (2008) 143 (6):743–9. doi: 10.1016/j.surg.2008.02.006
27. Schindler A, Bottero A, Capaccio P, Ginocchio D, Adorni F, Ottaviani F, et al. Vocal Improvement After Voice Therapy in Unilateral Vocal Fold Paralysis. *J Voice* (2008) 22(1):113–8. doi: 10.1016/j.jvoice.2006.08.004
28. Ruoppolo G, Mariani L, Quaglieri S, Longo L, Pescerelli P, Cilfone A, et al. Unilateral Vocal Fold Paralysis Post-Thyroidectomy: Does Early Intervention Allow for Better Voice Recovery? *Eur Rev Med Pharmacol Sci* (2021) 25 (3):1177–84. doi: 10.26355/eurrev_202102_24820
29. Wang C-C, Wu S-H, Tu Y-K, Lin W-J, Liu S-A, et al. Hyaluronic Acid Injection Laryngoplasty for Unilateral Vocal Fold Paralysis—A Systematic Review and Meta-Analysis. *Cells* (2020) 9(11):2417. doi: 10.3390/cells9112417
30. Marques JAS, Marronnier A, Crampon F, Lagier A, Marie JP. Early Management of Acute Unilateral Vocal Fold Paralysis: Update of the Literature. *J Voice* (2021) 35(6):924–6. doi: 10.1016/j.jvoice.2020.02.021
31. McCulloch TM, Andrews BT, Hoffman HT, Graham SM, Karnell MP, Minnick C, et al. Long-Term Follow-Up of Fat Injection Laryngoplasty for Unilateral Vocal Cord Paralysis. *Laryngoscope* (2002) 112(7 Pt 1):1235–8. doi: 10.1097/00005537-200207000-00017
32. Laccourreye O, Papon JF, Kania R, Crevier-Buchman L, Brasnu D, Hans S, et al. Intracordal Injection of Autologous Fat in Patients With Unilateral Laryngeal Nerve Paralysis: Long-Term Results From the Patient's Perspective. *Laryngoscope* (2003) 113(3):541–5. doi: 10.1097/00005537-200303000-00027
33. Umeno H, Shirouzu H, Chitose S-I, Nakashima T. Analysis of Voice Function Following Autologous Fat Injection for Vocal Fold Paralysis. *Otolaryngol Head Neck Surg* (2005) 132(1):103–7. doi: 10.1016/j.otohns.2004.09.016
34. Portone C, Johns MM III, Hapner ER. A Review of Patient Adherence to the Recommendation for Voice Therapy. *J Voice* (2008) 22(2):192–6. doi: 10.1016/j.jvoice.2006.09.009

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Endocrinology

ORIGINAL RESEARCH
published: 25 May 2022
doi: 10.3389/fendo.2022.849065

# Radiomics Analysis of Computed Tomography for Prediction of Thyroid Capsule Invasion in Papillary Thyroid Carcinoma: A Multi-Classifier and Two-Center Study

*Xinxin Wu[1,2†], Pengyi Yu[1,2†], Chuanliang Jia[1,2†], Ning Mao[3], Kaili Che[3], Guan Li[3], Haicheng Zhang[4], Yakui Mou[1,2*] and Xicheng Song[1,2*]*

*[1] Department of Otorhinolaryngology, Head and Neck Surgery, Yantai Yuhuangding Hospital, Qingdao University, Yantai, China, [2] Shandong Provincial Clinical Research Center for Otorhinolaryngologic Diseases, Yantai, China, [3] Department of Radiology, Yantai Yuhuangding Hospital, Qingdao University, Yantai, China, [4] Big Data and Artificial Intelligence Laboratory, Yantai Yuhuangding Hospital, Qingdao University, Yantai, China*

**Objective:** To investigate the application of computed tomography (CT)-based radiomics model for prediction of thyroid capsule invasion (TCI) in papillary thyroid carcinoma (PTC).

**Methods:** This retrospective study recruited 412 consecutive PTC patients from two independent institutions and randomly assigned to training (n=265), internal test (n=114) and external test (n=33) cohorts. Radiomics features were extracted from non-contrast (NC) and artery phase (AP) CT scans. We also calculated delta radiomics features, which are defined as the absolute differences between the extracted radiomics features. One-way analysis of variance and least absolute shrinkage and selection operator were used to select optimal radiomics features. Then, six supervised machine learning radiomics models (k-nearest neighbor, logistic regression, decision tree, linear support vector machine [L-SVM], Gaussian-SVM, and polynomial-SVM) were constructed. Univariate was used to select clinicoradiological risk factors. Combined models including optimal radiomics features and clinicoradiological risk factors were constructed by these six classifiers. The prediction performance was evaluated using the receiver operating characteristic (ROC) curve, calibration curve, and decision curve analysis (DCA).

**Results:** In the internal test cohort, the best combined model (L-SVM, AUC=0.820 [95% CI 0.758–0.888]) performed better than the best radiomics model (L-SVM, AUC = 0.733 [95% CI 0.654–0.812]) and the clinical model (AUC = 0.709 [95% CI 0.649–0.783]). Combined-L-SVM model combines 23 radiomics features and 1 clinicoradiological risk factor (CT-reported TCI). In the external test cohort, the AUC was 0.776 (0.625–0.904) in the combined-L-SVM model, showing that the model is stable. DCA demonstrated that the combined model was clinically useful.

OPEN ACCESS

**Edited by:**
*Che-Wei Wu,*
*Kaohsiung Medical University, Kaohsiung, Taiwan*

**Reviewed by:**
*Carlotta Giani,*
*University of Pisa, Italy*
*Tzu-Yen Huang,*
*Kaohsiung Medical University, Taiwan*

***Correspondence:**
*Xicheng Song*
*drxchsong@163.com*
*Yakui Mou*
*muykmd@126.com*

*†These authors have contributed equally to this work and share first authorship*

**Specialty section:**
*This article was submitted to Thyroid Endocrinology, a section of the journal Frontiers in Endocrinology*

***Received:*** *05 January 2022*
***Accepted:*** *20 April 2022*
***Published:*** *25 May 2022*

**Citation:**
*Wu X, Yu P, Jia C, Mao N, Che K, Li G, Zhang H, Mou Y and Song X (2022) Radiomics Analysis of Computed Tomography for Prediction of Thyroid Capsule Invasion in Papillary Thyroid Carcinoma: A Multi-Classifier and Two-Center Study. Front. Endocrinol. 13:849065. doi: 10.3389/fendo.2022.849065*

**Conclusions:** Our combined model based on machine learning incorporated with CT radiomics features and the clinicoradiological risk factor shows good predictive ability for TCI in PTC.

**Keywords: papillary thyroid carcinoma, radiomics, machine learning, computed tomography, thyroid capsule invasion**

## INTRODUCTION

Thyroid cancer is the most frequent endocrine malignancy, and papillary thyroid carcinoma (PTC) accounts for about 80%–90% of all cases and the most common histological subtype (1, 2). PTC has a slow disease progression, excellent prognosis, and high survival rate; thus, most patients with PTC are ambivalent in choosing a treatment modality (3). However, surgery is necessary for some rapidly progressing thyroid tumors, such as those with extrathyroidal extension (ETE) and lymph node metastasis (LNM) (4). Therefore, the identification of PTC with ETE or LNM is important.

Thyroid capsule invasion (TCI) is the infiltration of a tumor into the continuous fibrous thyroid capsule without extension into the surrounding soft tissues or the sternothyroid muscle. Indeed, TCI is the premise of ETE (5). Many studies found that TCI is one of the independent risk factors for LNM in the central and lateral cervical regions, whether in papillary thyroid microcarcinoma or PTC (6–9). Mazzaferri suggested that TCI is associated with increased tumor recurrence and distant metastases (10). Early studies demonstrated that TCI contributes to poor prognostic (11–13). Therefore, predicting TCI in PTC is important to assess tumor progression.

However, accurate preoperative assessment of TCI in PTC remains challenging. Although surgical histopathology image analysis serves as the gold standard for diagnosing TCI, it is invasive and cannot predict TCI preoperatively. Computed tomography (CT), a common imaging examination method, has great auxiliary value in preoperatively evaluating and determining the extent, localization, and lymph node (LN) status of the tumor (14, 15).

However, up to now, most diagnostic information from CT is based on visual inspection by a radiologist, who may miss critical diagnostic information. Thus, conventional CT is still not effective in diagnosing TCI. Radiomics, which is the quantitative analysis of a large amount of data in medical images using computer technology, has received increasing attention because of its improved diagnosis and prediction accuracy (16, 17). Moreover, no studies have been conducted to predict TCI in PTC using radiomics analysis.

Therefore, this study aimed to propose and validate a machine learning-based method to preoperatively predict TCI in PTC by combining CT-based radiomics features and clinicoradiological characteristics.

**Abbreviations:** AP, artery phase; AUC, area under the receiver operating characteristic curve; CI, confidence interval; CT, computed tomography; CT-MTD, CT-reported maximum tumor diameter; DCA, decision curve analysis; DT, decision tree; ETE, extrathyroidal extension; G-SVM, Gaussian support vector machine; ICCs, inter- and intra-correlation coefficients; KNN, k-nearest neighbor; LASSO, least absolute shrinkage and selection operator; LN, lymph node; LNM, lymph node metastasis; LR, logistic regression; L-SVM, linear support vector machine; NC, non-contrast CT; PTC, papillary thyroid carcinoma; P-SVM, polynomial support vector machine; ROC, receiver operating characteristic; VOI, volume of interest; TCI, thyroid capsule invasion; TSH, thyroid-stimulating hormone.

## MATERIALS AND METHODS

### Patients

This retrospective study was approved by the clinical institutional review boards of the two selected institutions, and patient informed consent was waived. A total of 412 consecutive patients were recruited. The 379 eligible patients recruited from Yantai Yuhuangding Hospital (Institution I) from March 2018 to March 2020 were divided into the training cohort (n=265) and internal test cohort (n=114) at a ratio of 7:3. The 33 eligible patients recruited from Qilu Hospital of Shandong University (Institution II) from September 2020 to December 2020 served as the external test cohort.

The inclusion criteria were as follows: (a) patients who preoperatively underwent non-enhanced and contrast-enhanced CT scans for <2 weeks; (b) patients who had pathologically confirmed PTC after surgical resection; (c) patients who had pathologically confirmed capsular status after surgery; and (d) patients with well-preserved clinical data, imaging data, and pathological specimens. The exclusion criteria were as follows: (a) patients who received preoperative radiofrequency ablation, radiotherapy, chemotherapy, or other antitumor treatments; (b) patients who received prior treatment in other institutions; (c) patients who presented with multiple primary carcinomas or concurrent malignancy; (d) patients with Hashimoto's thyroiditis; (e) patients whose maximum tumor diameter < 0.5 cm or had poor quality of CT images. The patient recruitment pathway is depicted in **Figure 1**.

### Clinicoradiological Characteristics

Clinicoradiological characteristics, including age, sex, thyroid-stimulating hormone (TSH), tumor location (left lobe, right lobe, and isthmus), CT-reported maximum tumor diameter (CT-MTD), CT-reported TCI (positive and negative), and CT-reported LN status (positive, negative, and suspicious) were collected. A laboratory analysis of TSH was performed <2 weeks before surgery. The preoperative CT scans of all patients were retrospectively reviewed and verified by two radiologists (Radiologist 1 has 12 years of experience in thyroid imaging and Radiologist 2 has 10 years of experience in thyroid imaging) who did not have knowledge of the histopathological findings.

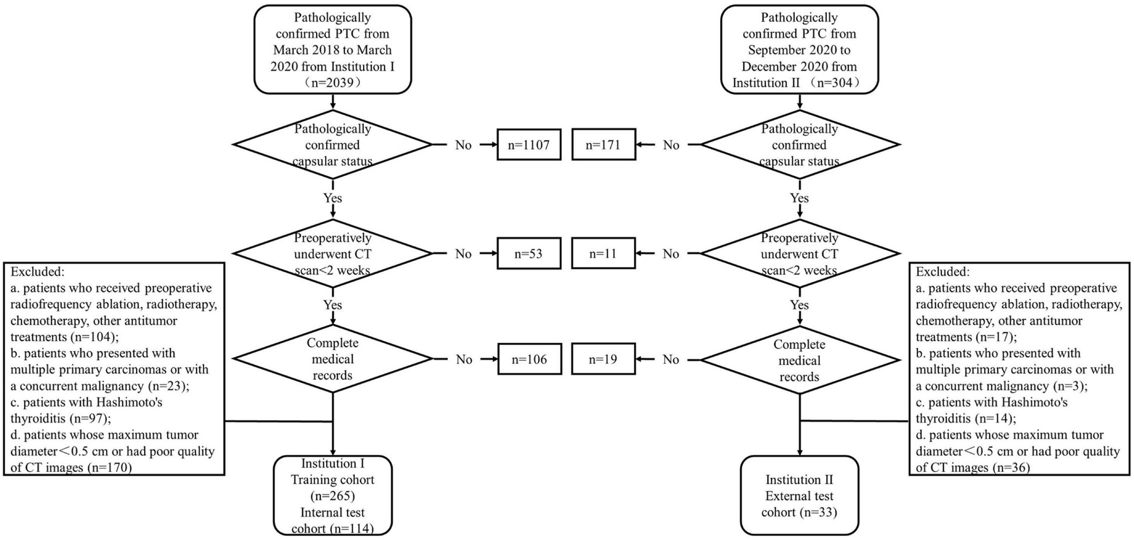



**FIGURE 1** | The patient recruitment pathway in the two-center study.

The radiologists recorded the tumor location, CT-MTD, TCI status, and LN status in the CT images. CT-MTD was recorded as the mean value. In CT images, tumor with an irregular shape, tumor that breaks through the thyroid capsule, a contact area with the thyroid margin > 25% of the tumor circumference, and the presence of a reduction/blurring of the focal extent after enhancement were considered to have CT-reported TCI (positive). Based on the National Comprehensive Cancer Network guidelines (18), relevant literature (14, 19), and diagnostic experience, the CT diagnostic criteria for LNM in patients with PTC were as follows: (a) LN maximal short-axis diameter > 10 mm; (b) round or irregular shape; (c) rough margin, fuzzy boundary, and/or invasion into adjacent tissues; (d) calcification or cystic and/or necrotic change; (e) strong enhancement (similar to or stronger than that of the pharyngeal mucosa); and (f) heterogeneous enhancement. A patient's CT-reported LN status was classified as positive if one or more LNs found in the CT images met any one of the above criteria. LN was considered suspicious when LN did not meet the above criteria but had a short-axis diameter > 5 mm at cervical region VI (20, 21). A LN that did not meet the above criteria was considered to have a negative LN statis. Any disagreements were resolved by consensus or the consultation with a third radiologist who had 20 years of experience. κ-statistic was calculated to determine the inter-observer agreement between two radiologists, where $0<\kappa\leq0.4$ indicates poor agreement, $0.4<\kappa<0.75$ indicates good agreement, and $0.75\leq\kappa<1$ indicates high agreement.

## CT Acquisition Parameters

Preoperative non-contrast (NC) and contrast-enhanced CT scans were performed for each patient at the two institutions. Institution I performed CT scans using two CT scanners: a 64-slice spiral CT scanner (Siemens, Germany) or a 256-slice spiral CT scanner (Philips, Netherlands). Institution II performed CT scans using four CT scanners: a 16-slice spiral CT scanner (Siemens, Germany), a 64-slice spiral CT scanner (GE, USA), a 64-slice spiral CT scanner (Toshiba, Japan), or a 256-slice spiral CT scanner (Philips, Netherlands).

The parameters for the CT scan were as follows: tube voltage, 100 or 120 kV; tube current, 180–400 mA·s; reconstruction section thickness, 1.25–5.00 mm; pitch, 0.97–1.5; and matrix, 512×512. The scan range was from the skull base to the subclavian region. After routine plain CT scans, contrast-enhanced CT scans were performed after a delay of 20–30 s (arterial phase [AP]) following an intravenous administration of 80–100 mL of iodinated nonionic contrast agent at a rate of 3.0–3.5 mL/s using a high-pressure syringe. The nonionic contrast agent used was iohexol (Yangtze River, China; GE Healthcare, Ireland).

## Image Segmentation

All CT images were retrieved from the Picture Archiving and Communication System with the data format of Digital Imaging and Communications in Medicine and then loaded into a radiomics cloud platform (http://radcloud.cn/) for manual segmentation. All clinical and pathological information was hidden when the data was uploaded to the platform. Volume of interest (VOI) segmentation was manually drawn slice by slice on the entire tumor's boundary by radiologist 1. A sample of the segmentation process is presented in **Figure 2**.

## Image Preprocessing

The image data analyzed in this study were obtained from various CT scanners. As highlighted by many previous studies, voxels were diverse if acquired from different scanners (21–23). The diversity of voxels leads to variability in feature values. Therefore, the images were preprocessed to extract robust radiomics features as follows:

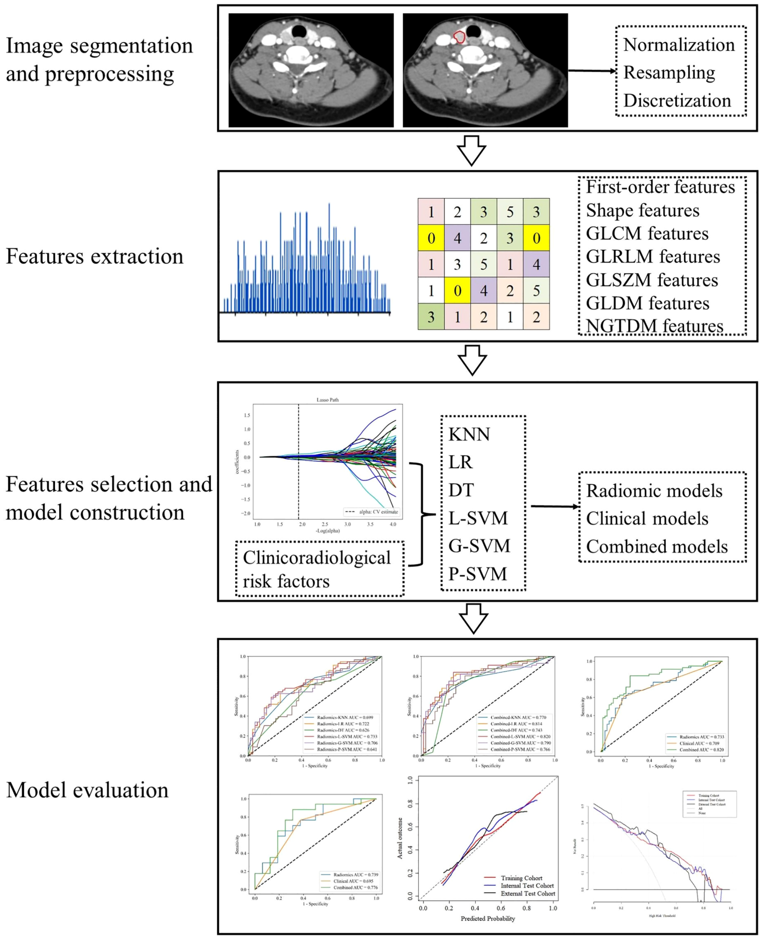



**FIGURE 2** | Workflow of data analysis. The workflow illustrates image segmentation and preprocessing, radiomics features extraction and selection, models construction and evaluation.

(1) voxel density normalization ( ± 3σ technique), (2) voxel size resampling (1×1×1 mm$^3$, and (3) voxel intensity discretization (64 bins).

## Radiomics Feature Extraction and Selection

Radiomics features were automatically extracted from the VOIs of the non-contrast (NC) and arterial phase (AP) images of each patient based on the "pyradiomics" package in Python (version 3.6). Delta radiomics features (AP–NC), which are defined as the absolute differences between the radiomics features extracted from AP and NC phases, were also computed. Before the radiomics features selection process, Z-scores were used to standardize each radiomics feature to eliminate the differences between features. The features in the internal test and external test cohorts were normalized according to the mean and standard deviation (SD) of the training cohort.

The extracted features were divided into four categories: (1) first-order statistics features, which describe the distribution of voxel intensities within the image region defined through commonly used and basic metrics, such as mean, maximum, minimum, median, energy, entropy, skewness, and kurtosis; (2) shape features, which reflect the shape and size of the region, such as surface area, sphericity, compactness, and maximum diameter; (3) texture features, which were calculated from the Gray-level Co-occurrence Matrix (GLCM), Gray-level Run Length Matrix (GLRLM), Gray-level Size Zone Matrix (GLSZM), Gray-level Dependence Matrix (GLDM), and neighborhood gray tone difference matrix (NGTDM); and (4) higher-order statistical features, which include the first-order statistics and texture features obtained through the wavelet transformation and filter transformation of the original images, such as logarithm, square, square root, wavelet, exponential, and gradient.

Sixty patients were randomly selected from the training cohort by statistical software to evaluate the inter-and intra-observer agreement of the extracted radiomics features. Radiologist 2 used the same tool and method for tumor segmentation. After 3 months, tumor segmentation was repeated by radiologist 1. Inter- and intra-correlation coefficients (ICCs) were calculated to determine the reproducibility of radiomics features. ICCs > 0.75 represent good agreement (24, 25).

The following features selection strategies were used to reduce the dimensionality and select the best subset of features. First, features with ICCs > 0.75 were retained. Second, features with p < 0.05 were selected after one-way analysis of variance (ANOVA). Then, the least absolute shrinkage and selection operator algorithm (LASSO) with penalty tuning conducted by 10-fold cross-validation was applied to select the key radiomics features with nonzero coefficients.

## Clinicoradiological Risk Factor Selection

Univariate analysis was applied to the clinicoradiological characteristics of the training cohort to select the clinicoradiological risk factor associated with TCI. Odds ratios (ORs) as estimates of relative risk with 95% confidence intervals (CIs) were calculated for each risk factor.

## Model Construction

Most previous thyroid-related radiomics studies used logistic regression (LR) as a classifier (26–28). K-nearest neighbor (KNN), decision tree (DT), linear support vector machine (L-SVM), Gaussian support vector machine (G-SVM), and polynomial support vector machine (P-SVM) are also commonly used machine learning classifiers in radiomics studies. In this study, based on these six classifiers, models based on the optimal radiomics features (radiomics model), the clinicoradiological risk factor (clinical model), and combined model were constructed, respectively. LR, KNN, DT, and SVM were performed using Python (version 3.6) with scikit-learn package (https://scikit-learn.org/).

In the training process, the hyperparameters of each classifier were tuned by an iterative grid search procedure to avoid overfitting and maximize the performance of the model. A 5-fold cross-validation was applied to tune the model parameters.

## Model Evaluation

All models were trained in the training cohort, performance was assessed by 5-fold cross-validation, and the process was repeated 10 times to calculate the mean of performance estimates. The prediction performance was evaluated by using receiver operating characteristic (ROC) curve and calculating the area under the ROC curve (AUC). The calibration curves of the optimal combined model were used to evaluate the agreement between the observed results and the predicted probabilities. Decision curve analysis (DCA) was used to calculate the net benefits for threshold probabilities determine the clinical usefulness of the optimal combined model.

## Statistical Analysis

Normally distributed data are expressed as mean ± SD, and non-normally distributed data are presented as median (interquartile range). Continuous characteristics were compared by two-sample t-test or Mann-Whitney U test, whereas categorical characteristics were analyzed by chi-square test or Fisher's exact test. Statistical analysis was performed in R software (version 4.0.3) and Python (version 3.6). "rms," "rmda," and "irr," packages in R were used. Python scikit-learn package was employed to select radiomics features and construct and evaluate models. "selectKbest," "LassoCV," "LogisticRegression," "svm," "neighbors," "tree," and "roccurve," packages were used. All statistical tests were two-sided, and p<0.05 was considered a statistically significant difference.

# RESULTS

## Patients and Clinicoradiological Characteristics

A total of 412 patients were divided into pTCI+ (pathological positive TCI) and pTCI− (pathological negative TCI) based on postoperative pathological findings. Inter-observer agreement for CT-reported TCI was good (κ=0.734, 95% confidence interval [CI] =0.658–0.829). Inter-observer agreement for CT-reported LN status was high (κ=0.819, 95% CI=0.776–0.900). The clinicoradiological characteristics of patients in the training, internal test, and external test cohorts are summarized in **Table 1**.

## Radiomics Features Extraction and Selection

1409 radiomics features were extracted from each CT phase, followed by a calculation of delta radiomics features. A total of 4227 (1409 × 3) radiomics features were extracted from each patient. The inter-observer ICCs calculated based on radiologist 1's first-extracted features and those of radiologist 2 ranged from 0.766 to 0.897. The intra-observer ICCs calculated based on radiologist 1's twice features extraction ranged from 0.821 to 0.943. These results showed that features extraction within and between observers had good repeatability. Then, 640 features (p<0.05) were further selected by ANOVA. Finally, 23 optimal radiomics features were selected through the LASSO method with all features from the NC (6 first-order statistical feature, 4 shape-based feature, and 13 textural features [GLDM, n = 4; GLRLM, n = 3; GLSZM, n = 6]; **Figure 3**). The most predictive radiomics features are described in detail in **Supplementary Material Table S1**.

## Clinicoradiological Risk Factors Selection

In the training cohort, CT-reported TCI (OR=1.80, 95% CI 1.60–2.02, p < 0.001) was identified as the clinicoradiological risk factor of TCI in PTC (**Table 2**).

## Predictive Performance of Models

Radiomics models based on the optimal radiomics features alone were constructed. In the training cohort, radiomics-G-SVM model achieved the most satisfactory results with AUC 0.786 (95%CI 0.736–0.832). In the internal test cohort, radiomics-L-SVM model achieved the most satisfactory results with AUC 0.733 (95%CI 0.654–0.812) (**Figures 4A, B**).

Clinical model based on the clinicoradiological risk factor (CT-reported TCI) alone was constructed. The AUC of the clinical model was 0.734 (95% CI 0.688-0.776) and 0.709 (95% CI 0.649-0.783) in the training and internal test cohorts, respectively.

Combined models that comprise the optimal radiomics features and the clinicoradiological risk factor were

**TABLE 1** | Clinicoradiological characteristics of the training, internal test, and external test cohorts.

| | Training cohort (n=265) | | | Internal test cohort (n=114) | | | External test cohort (n=33) | | |
|---|---|---|---|---|---|---|---|---|---|
| | pTCI + (n=130) | pTC I– (n=135) | *p* value | pTCI + (n=56) | pTCI – (n=58) | *p* value | pTCI + (n=17) | pTCI – (n=16) | *p* value |
| **Gender** | | | 0.692 | | | 0.035 | | | 0.389 |
| Male | 30/23.1 | 35/25.9 | | 38/67.9 | 50/86.2 | | 4/23.5 | 7/43.8 | |
| Female | 100/76.9 | 100/74.1 | | 18/32.1 | 8/13.8 | | 13/76.5 | 9/56.3 | |
| Age (years)[a] | 45.52 ± 11.88 | 43.87 ± 11.14 | 0.246 | 46.20 ± 11.01 | 44.60 ± 11.77 | 0.635 | 46.05 ± 13.41 | 44.88 ± 11.77 | 0.789 |
| TSH (mIU/L)[a] | 2.60 ± 2.76 | 2.44 ± 1.18 | 0.551 | 2.41 ± 1.70 | 2.38 ± 1.17 | 0.915 | 2.28 ± 1.35 | 2.04 ± 0.92 | 0.927 |
| CT-MTD (cm)[a] | 1.01 ± 0.58 | 0.99 ± 0.55 | 0.807 | 1.04 ± 0.48 | 0.95 ± 0.44 | 0.345 | 1.32 ± 0.50 | 1.08 ± 0.65 | 0.242 |
| **Location** | | | <0.001 | | | 0.451 | | | <0.001 |
| Left | 66/50.8 | 60/44.4 | | 27/48.2 | 23/39.7 | | 5/29.4 | 3/18.75 | |
| Right | 59/45.4 | 73/54.1 | | 29/51.8 | 35/60.3 | | 12/70.6 | 12/75.0 | |
| Isthmus | 5/3.8 | 2/1.5 | | 0 | 0 | | 0/0.0 | 1/6.25 | |
| **CT-reported TCI** | | | <0.001 | | | <0.001 | | | 0.037 |
| Yes | 80/61.5 | 20/14.8 | | 34/60.7 | 11/19.0 | | 13/76.5 | 6/37.5 | |
| No | 50/38.5 | 115/85.2 | | 22/39.3 | 47/81.0 | | 4/23.5 | 10/62.5 | |
| **CT-reported LN status** | | | <0.001 | | | <0.001 | | | 0.001 |
| Positive | 29/22.3 | 17/12.6 | | 11/19.6 | 10/17.2 | | 7/41.2 | 4/25.0 | |
| Negative | 79/60.8 | 92/68.1 | | 32/57.2 | 39/67.3 | | 9/52.9 | 12/75.0 | |
| Suspicious | 22/16.9 | 26/19.3 | | 13/23.2 | 9/15.5 | | 1/5.9 | 0/0.0 | |

*The data are displayed as n/% except otherwise noted.*
*[a]Mean ± standard deviation*
*pTCI+, pathologically positive thyroid capsule invasion; pTCI–, pathologically negative thyroid capsule invasion; TSH, thyroid-stimulating hormone; CT, computed tomography; CT-MTD, CT-reported maximum tumor diameter;TCI, thyroid capsule invasion; LN, lymph node.*

constructed. In the training cohort, combined-P-SVM model achieved the most satisfactory results with AUC 0.905 (95%CI 0.871–0.934). In the internal test cohort, the highest AUC was 0.820 (95%CI 0.758–0.888) in combined-L-SVM model (**Figures 4C, D**). The parameters for the models' predictive performances were summarized in detail in **Supplementary Material Table S2**.

The three models constructed by the L-SVM classifier to be evaluated in the training, the internal test, and the external test cohorts, respectively (**Figure 5**). The combined-L-SVM model performed better than radiomics and clinical models. Among them, in the external test cohort, the AUC was 0.776 (0.625–0.904) showing that the model is stable.

The lesions close to the thyroid capsule was examined using the combined-L-SVM model. The AUC was 0.794 (95% CI 0.701-0.912) and 0.830 (95% CI 0.620-0.983) in internal test and external test cohorts, respectively (**Figures 6A, B**).

We grouped lesions locations in the internal test and external test cohorts according to different adjacent structures: posterior (esophagus), medial (trachea), lateral (carotid sheath), anterior (strap muscle), and performed stratified analysis using the combined-L-SVM model. In both cohorts, the model performed relatively well in lesions close to the medial and posterior, with AUCs of 0.938 and 1.000 in the internal test cohort and 1.000 and 1.000 in the external test cohort, respectively (**Figures 6C, D**).

The calibration curves of the combined-L-SVM model indicated good calibration between predictive outcome and observation in the training, internal test, and external test cohorts (**Figure 6E**). The DCA showed that the combined-L-SVM model to predict TCI could provide more benefit than the treat-all-patients scheme or the treat-all-none scheme, when the threshold probability range from 0.20–0.86 in the training and internal test cohorts, 0.20–0.74 in the external test cohort (**Figure 6F**).

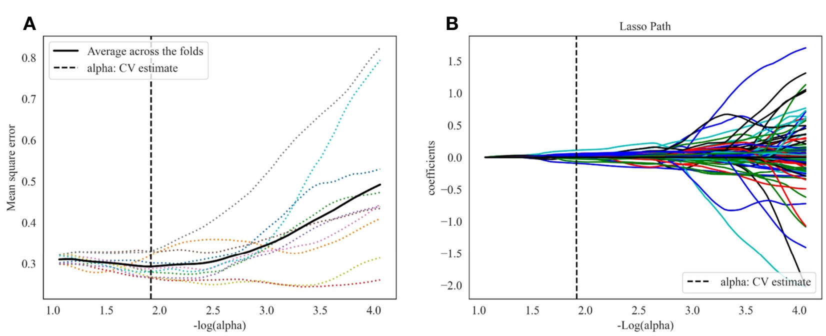



**FIGURE 3** | LASSO algorithm for radiomics features selection. **(A)** Mean square error path using 10-fold cross validation. **(B)** LASSO coefficient profiles of the radiomics features.

**TABLE 2** | Univariate analysis of clinicoradiological characteristics in the training cohort.

| | Univariate analysis | |
|---|---|---|
| | **OR (95%CI)** | ***p* value** |
| **Sex** | 1.04 (0.90-1.20) | 0.592 |
| **Age (years)** | 1.00 (0.99-1.01) | 0.245 |
| **TSH (mIU/L)** | 1.01 (0.98-1.04) | 0.527 |
| **CT-MTD (cm)** | 1.01 (0.91-1.13) | 0.807 |
| **Location** | 0.97 (0.87-1.08) | 0.558 |
| **CT-reported TCI** | 1.80 (1.60-2.02) | <0.001 |
| **CT-reported LN status** | 1.02 (0.94-1.10) | 0.601 |

*TSH, thyroid-stimulating hormone; CT, computed tomography; CT-MTD, CT-maximum tumor diameter; TCI, thyroid capsule invasion; LN, lymph node; OR, odds ratio; CI, confidence interval.*

## DISCUSSION

We established combined models based on machine learning incorporated with CT radiomics features and the clinicoradiological risk factor to individualize the prediction of TCI in PTC. Moreover, we tested the models using internal and independent external test cohorts. The combined-L-SVM model demonstrated good predictive ability and clinical usefulness in the training and test cohorts, which indicates that the combined model could be an effective, non-invasive, and safe tool for preoperative prediction of TCI in PTC.

Akbulut et al. (29) found that patients with TCI are younger on average than those with non-invasive tumors (p=0.035). Luo et al. (30) suggested that TCI and patient age do not correlate (p=0.863). Our study fits with the findings of Luo et al., that is, age may not be associated with TCI (p=0.245). A consensus on whether TSH level is an independent predictive factor of TCI in PTC has not yet been established. A previous study reported that patients with TCI have remarkably higher TSH levels than those without TCI (31). However, some studies believed that TSH level is not a predictor of tumor aggressiveness. In our study, TSH level may not be associated with TCI (p=0.527). Previous studies have shown that PTC with TCI is associated with location and tumor size. Pontieri G et al. (32) and Zhang et al. (33) reported that PTC localized in the isthmus had a high rate of TCI. Furlan et al. (34) reported that PTC with capsular invasion is associated with larger tumors than PTC without capsular invasion. However, our study did not obtain the above results in terms of the correlation between capsule invasion and tumor size/location (P=0.807/0.558). The reasons may be the differences in the selection of sample and the size of sample. Besides, Luo et al. (30) revealed that there was no correlation between LNM and with/without TCI of PTC, which was similar to our study (P=0.601).

Notably, many previous studies on radiomics have only provided an internal test cohort, and all data were obtained from a single piece of equipment in a single center. However, studies have confirmed that equipment from different manufacturers leads to differences in scanning parameter settings and post-processing reconstruction algorithms, which

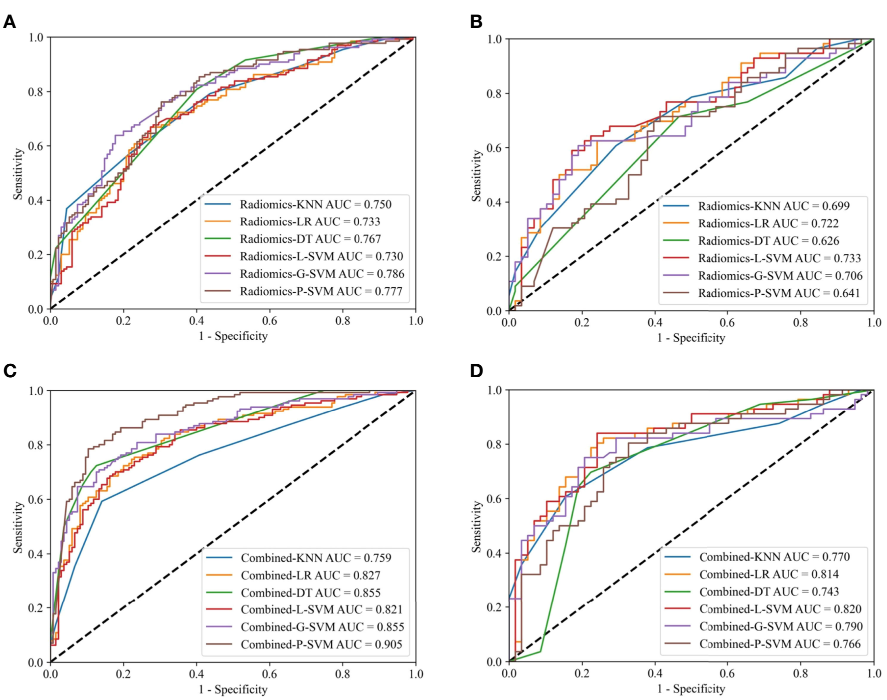



**FIGURE 4** | ROC curves for the radiomics models in the training **(A)** and internal test **(B)** cohorts; ROC curves for the combined models in the training **(C)** and internal test **(D)** cohorts.

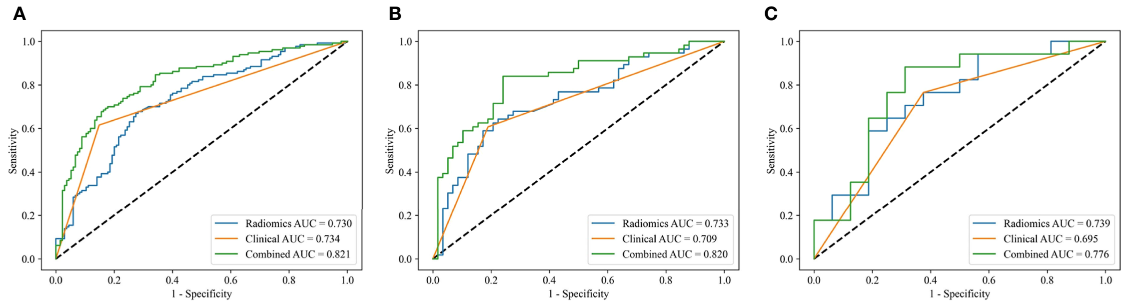



**FIGURE 5** | ROC curves of the radiomics models, clinical models and combined models constructed by L-SVM in the training **(A)**, internal test **(B)** and external test **(C)** cohorts.

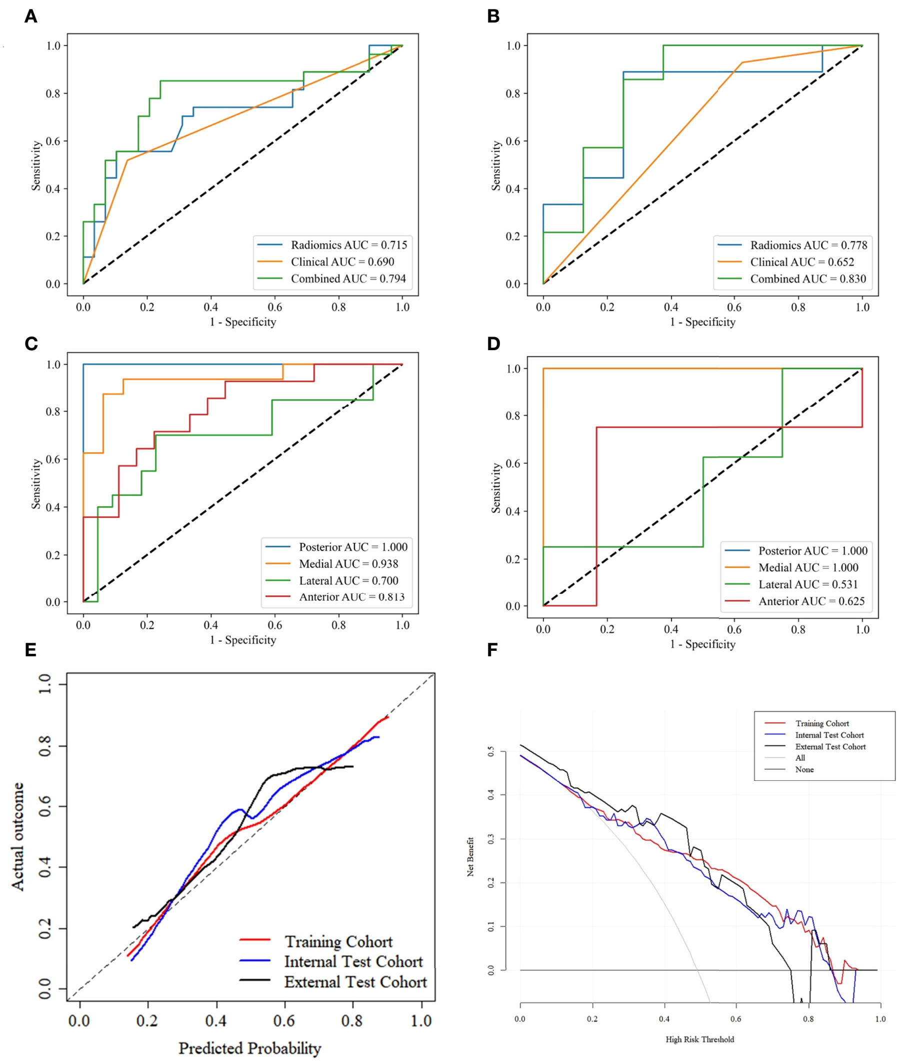



**FIGURE 6** | ROC curves of PTCs close to thyroid capsule in the internal test **(A)** and external test **(B)** cohorts. ROC curves for predicting lesions close to different adjacent structures using the combined L-SVM model in the internal test **(C)** and external test **(D)** cohorts. Calibration curves of the combined-L-SVM models in the training, internal test and external test cohorts **(E)**. DCA of the combined-L-SVM models in the training, internal test and external test cohorts **(F)**.

result in remarkable differences in radiomics features (23, 35, 36). Although some studies have achieved good results, the generalizability of the models was not confirmed because the studies were conducted in single centers. Therefore, single-center studies have their limitations (37). This problem was addressed in the present study by including an external test cohort to assess model performance. In addition, image preprocessing was performed before feature extraction to reduce the dependency on image specifications. Our results showed that the prediction performance of the model in the external test cohort was still good, which illustrates the generalizability of our model.

The model construction methods used in many studies were relatively simple, and the differences in models constructed by different classifiers were not adequately discussed. For example, in our previous study, we only used the LR-based model to identify <1 cm benign and malignant thyroid lesions, and the model performed excellently in the training and test sets with AUCs of 0.853 and 0.851, respectively (38). However, Lambin et al. (16) showed that studies on radiomics should use multiple machine learning methods. LR is a regression method that eliminates the selected features with little contribution to the linear model. However, the potential relationship between the radiomics features and lesions is complex and may be non-linear during radiomics analysis. Masataka et al. (39) applied six machine learning classifiers to distinguish uterine sarcomas from leiomyomas using image texture analysis, and the resulting AUCs ranged from 0.68 to 0.93. These results suggest that the diagnostic performance of radiomics analysis is highly dependent on the selection of machine learning classifiers. Six types of supervised machine learning classifiers (i.e., LR, KNN, DT, L-SVM, G-SVM, and P-SVM) were used in model construction to improve the performance of the models in the current study. The results showed that the L-SVM-based model had the best performance. SVM is a powerful and robust machine learning classifier that has been used to solve a range of high-dimensional, non-linear problems (40).

Our study was performed on the VOIs of NC and AP images rather than on the VOI of a single CT scan. At the same time, the delta radiomics features of tumors were also calculated. Interestingly, only features from NC images were used in our model, which suggests that these features may be more helpful in identifying thyroid TCI than AP and delta radiomics features. In our previous study, most of the radiomics features used in identifying <1 cm benign and malignant thyroid lesions were also extracted from NC images (38).

Our study has several limitations. First, although this study was based on two centers (both from Northern China), prospective studies with more centers should be involved to provide more diverse data to interpret tumor heterogeneity and construct models with greater stability and accuracy. Second, fully automatic or semi-automatic image segmentation techniques are still immature for the irregular shape and uncertain contour of thyroid tumors; therefore, automatic and semi-automatic segmentation techniques will be further explored in our future study. Third, previous studies have suggested that TCI may be closely associated with B-Raf proto-oncogene serine/threonine kinase (*BRAF*) mutations (5, 41). However, this variable was not included in our study because of a lack of *BRAF* information in some patients. In addition, although stratified analysis of tumor location by posterior, medial, lateral, and anterior revealed that the model performed relatively well at posterior and medial locations in this study, the results may not be very stable due to the small sample size of the subgroup. Finally, although radiomics features can manifest tumor heterogeneity, tumor heterogeneity may be comprehensively quantified through a combination of pathological imaging, proteomics, and genomic sequencing.

In conclusion, our combined model based on machine learning incorporated with CT radiomics features and the clinicoradiological risk factor shows good predictive ability for TCI in PTC. Further studies using large sample size, multiple centers, multi-modes, different ethnic groups, and different geographical locations should be performed to improve the model efficiency.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Yantai Yuhuangding Hospital and Qilu Hospital of Shandong University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

XW, PY and CJ contributed to the data analysis and the manuscript preparation. XS, YM, NM, XW contributed to the conception and design of the study. PY, KC, GL, HZ contributed to data acquisition and analysis. PY, XS and YM contributed to the manuscript revision. All authors contributed to the article and approved the submitted version.

## FUNDING

This work was supported by Taishan Scholars Project (No. ts20190991).

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2022.849065/full#supplementary-material

## REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. *CA Cancer J Clin* (2021) 71:7–33. doi: 10.3322/caac.21654
2. Schneider DF, Chen H. New Developments in the Diagnosis and Treatment of Thyroid Cancer. *CA Cancer J Clin* (2013) 63:374–94. doi: 10.3322/caac.21195
3. Brito JP, Hay ID, Morris JC. Low Risk Papillary Thyroid Cancer. *BMJ (Clinical Res ed)* (2014) 348:g3045. doi: 10.1136/bmj.g3045
4. McLeod DS, Sawka AM, Cooper DS. Controversies in Primary Treatment of Low-Risk Papillary Thyroid Cancer. *Lancet (London England)* (2013) 381:1046–57. doi: 10.1016/s0140-6736(12)62205-3
5. Basolo F, Torregrossa L, Giannini R, Miccoli M, Lupi C, Sensi E, et al. Correlation Between the BRAF V600E Mutation and Tumor Invasiveness in Papillary Thyroid Carcinomas Smaller Than 20 Millimeters: Analysis of 1060 Cases. *J Clin Endocrinol Metab* (2010) 95:4197–205. doi: 10.1210/jc.2010-0337
6. Heng Y, Yang Z, Zhou L, Lin J, Cai W, Tao L. Risk Stratification for Lateral Involvement in Papillary Thyroid Carcinoma Patients With Central Lymph Node Metastasis. *Endocrine* (2020) 68:320–8. doi: 10.1007/s12020-020-02194-8
7. Li M, Zhu XY, Lv J, Lu K, Shen MP, Xu ZL, et al. Risk Factors for Predicting Central Lymph Node Metastasis in Papillary Thyroid Microcarcinoma (CN0): A Study of 273 Resections. *Eur Rev Med Pharmacol Sci* (2017) 21:3801–7.
8. Luo Y, Zhao Y, Chen K, Shen J, Shi J, Lu S, et al. Clinical Analysis of Cervical Lymph Node Metastasis Risk Factors in Patients With Papillary Thyroid Microcarcinoma. *J Endocrinol Invest* (2019) 42:227–36. doi: 10.1007/s40618-018-0908-y
9. Vasileiadis I, Karakostas E, Charitoudis G, Stavrianaki A, Kapetanakis S, Kouraklis G, et al. Papillary Thyroid Microcarcinoma: Clinicopathological Characteristics and Implications for Treatment in 276 Patients. *Eur J Clin Invest* (2012) 42:657–64. doi: 10.1111/j.1365-2362.2011.02633.x
10. Mazzaferri EL. Thyroid Remnant 131I Ablation for Papillary and Follicular Thyroid Carcinoma. *Thyroid* (1997) 7:265–71. doi: 10.1089/thy.1997.7.265
11. Hay ID, Bergstralh EJ, Goellner JR, Ebersold JR, Grant CS. Predicting Outcome in Papillary Thyroid Carcinoma: Development of a Reliable Prognostic Scoring System in a Cohort of 1779 Patients Surgically Treated at One Institution During 1940 Through 1989. *Surgery* (1993) 114:1050–7; discussion 7-8.
12. Hay ID. Papillary Thyroid Carcinoma. *Endocrinol Metab Clin North Am* (1990) 19:545–76. doi: 10.1016/S0889-8529(18)30310-4
13. Treseler PA, Clark OH. Prognostic Factors in Thyroid Carcinoma. *Surg Oncol Clin North Am* (1997) 6:555–98. doi: 10.1016/S1055-3207(18)30317-X
14. Kim E, Park JS, Son KR, Kim JH, Jeon SJ, Na DG. Preoperative Diagnosis of Cervical Metastatic Lymph Nodes in Papillary Thyroid Carcinoma: Comparison of Ultrasound, Computed Tomography, and Combined Ultrasound With Computed Tomography. *Thyroid* (2008) 18:411–8. doi: 10.1089/thy.2007.0269
15. Yang TT, Huang Y, Jing XQ, Gai XJ, Li WW. CT-Detected Solitary Thyroid Calcification: An Important Imaging Feature for Papillary Carcinoma. *Onco Targets Ther* (2016) 9:6273–9. doi: 10.2147/ott.S113369
16. Lambin P, Leijenaar RTH, Deist TM, Peerlings J, de Jong EEC, van Timmeren J, et al. Radiomics: The Bridge Between Medical Imaging and Personalized Medicine. *Nat Rev Clin Oncol* (2017) 14:749–62. doi: 10.1038/nrclinonc.2017.141
17. Bi WL, Hosny A, Schabath MB, Giger ML, Birkbak NJ, Mehrtash A, et al. Artificial Intelligence in Cancer Imaging: Clinical Challenges and Applications. *CA Cancer J Clin* (2019) 69:127–57. doi: 10.3322/caac.21552
18. Haddad RI, Nasr C, Bischoff L, Busaidy NL, Byrd D, Callender G, et al. NCCN Guidelines Insights: Thyroid Carcinoma, Version 2.2018. *J Natl Compr Cancer Netw* (2018) 16:1429–40. doi: 10.6004/jnccn.2018.0089
19. Cooper JS, Porter K, Mallin K, Hoffman HT, Weber RS, Ang KK, et al. National Cancer Database Report on Cancer of the Head and Neck: 10-Year Update. *Head Neck* (2009) 31:748–58. doi: 10.1002/hed.21022
20. Randolph GW, Duh QY, Heller KS, LiVolsi VA, Mandel SJ, Steward DL, et al. The Prognostic Significance of Nodal Metastases From Papillary Thyroid Carcinoma can be Stratified Based on the Size and Number of Metastatic Lymph Nodes, as Well as the Presence of Extranodal Extension. *Thyroid* (2012) 22:1144–52. doi: 10.1089/thy.2012.0043
21. Zhao Y, Li X, Li L, Wang X, Lin M, Zhao X, et al. Preliminary Study on the Diagnostic Value of Single-Source Dual-Energy CT in Diagnosing Cervical Lymph Node Metastasis of Thyroid Carcinoma. *J Thorac Dis* (2017) 9:4758–66. doi: 10.21037/jtd.2017.09.151
22. Shafiq-Ul-Hassan M, Zhang GG, Latifi K, Ullah G, Hunt DC, Balagurunathan Y, et al. Intrinsic Dependencies of CT Radiomic Features on Voxel Size and Number of Gray Levels. *Med Phys* (2017) 44:1050–62. doi: 10.1002/mp.12123
23. Mackin D, Fave X, Zhang L, Fried D, Yang J, Taylor B, et al. Measuring Computed Tomography Scanner Variability of Radiomics Features. *Invest Radiol* (2015) 50:757–65. doi: 10.1097/rli.0000000000000180
24. Barry WT, Kernagis DN, Dressman HK, Griffis RJ, Hunter JD, Olson JA, et al. Intratumor Heterogeneity and Precision of Microarray-Based Predictors of Breast Cancer Biology and Clinical Outcome. *J Clin Oncol* (2010) 28:2198–206. doi: 10.1200/jco.2009.26.7245
25. Yan R, Hao D, Li J, Liu J, Hou F, Chen H, et al. Magnetic Resonance Imaging-Based Radiomics Nomogram for Prediction of the Histopathological Grade of Soft Tissue Sarcomas: A Two-Center Study. *J Magn Reson Imaging* (2021) 53:1683–96. doi: 10.1002/jmri.27532
26. Chen B, Zhong L, Dong D, Zheng J, Fang M, Yu C, et al. Computed Tomography Radiomic Nomogram for Preoperative Prediction of Extrathyroidal Extension in Papillary Thyroid Carcinoma. *Front Oncol* (2019) 9:829. doi: 10.3389/fonc.2019.00829
27. Jiang M, Li C, Tang S, Lv W, Yi A, Wang B, et al. Nomogram Based on Shear-Wave Elastography Radiomics Can Improve Preoperative Cervical Lymph Node Staging for Papillary Thyroid Carcinoma. *Thyroid* (2020) 30:885–97. doi: 10.1089/thy.2019.0780
28. Wang X, Agyekum EA, Ren Y, Zhang J, Zhang Q, Sun H, et al. A Radiomic Nomogram for the Ultrasound-Based Evaluation of Extrathyroidal Extension in Papillary Thyroid Carcinoma. *Front Oncol* (2021) 11:625646. doi: 10.3389/fonc.2021.625646
29. Akbulut D, Kuz ED, Kursun N, Dizbay Sak S. Capsular Invasion Matters Also in "Papillary Patterned" Tumors: A Study on 121 Cases of Encapsulated Conventional Variant of Papillary Thyroid Carcinoma. *Endocr Pathol* (2021) 32:357–67. doi: 10.1007/s12022-020-09650-1
30. Luo H, Yan F, Lan L, Ma B, Zhao H, He Y, et al. Ultrasonographic Features, Nodule Size, Capsular Invasion, and Lymph Node Metastasis of Solitary Papillary Carcinoma of Thyroid Isthmus. *Front Oncol* (2020) 10:558363. doi: 10.3389/fonc.2020.558363
31. Li C, Yu W, Fan J, Li G, Tao X, Feng Y, et al. Thyroid Functional Parameters and Correlative Autoantibodies as Prognostic Factors for Differentiated Thyroid Cancers. *Oncotarget* (2016) 7:49930–8. doi: 10.18632/oncotarget.10236
32. Pontieri G, Urselli F, Peschi L, Liccardi A, Ruggiero AR, Vergara E, et al. Is the Isthmus Location an Additional Risk Factor for Indeterminate Thyroid Nodules? Case Report and Review of the Literature. *Front Endocrinol* (2018) 9:750. doi: 10.3389/fendo.2018.00750
33. Zhang L, Wei WJ, Ji QH, Zhu YX, Wang ZY, Wang Y, et al. Risk Factors for Neck Nodal Metastasis in Papillary Thyroid Microcarcinoma: A Study of 1066 Patients. *J Clin Endocrinol Metab* (2012) 97:1250–7. doi: 10.1210/jc.2011-1546
34. Furlan JC, Bedard YC, Rosen IB. Significance of Tumor Capsular Invasion in Well-Differentiated Thyroid Carcinomas. *Am Surg* (2007) 73:484–91. doi: 10.1177/000313480707300514
35. Parmar C, Grossmann P, Bussink J, Lambin P, Aerts H. Machine Learning Methods for Quantitative Radiomic Biomarkers. *Sci Rep* (2015) 5:13087. doi: 10.1038/srep13087
36. Balagurunathan Y, Gu Y, Wang H, Kumar V, Grove O, Hawkins S, et al. Reproducibility and Prognosis of Quantitative Features Extracted From CT Images. *Trans Oncol* (2014) 7:72–87. doi: 10.1593/tlo.13844
37. Orlhac F, Frouin F, Nioche C, Ayache N, Buvat I. Validation of A Method to Compensate Multicenter Effects Affecting CT Radiomics. *Radiology* (2019) 291:53–9. doi: 10.1148/radiol.2019182023
38. Wu X, Li J, Mou Y, Yao Y, Cui J, Mao N, et al. Radiomics Nomogram for Identifying Sub-1 Cm Benign and Malignant Thyroid Lesions. *Front Oncol* (2021) 11:580886. doi: 10.3389/fonc.2021.580886
39. Nakagawa M, Nakaura T, Namimoto T, Iyama Y, Kidoh M, Hirata K, et al. Machine Learning to Differentiate T2-Weighted Hyperintense Uterine

Leiomyomas From Uterine Sarcomas by Utilizing Multiparametric Magnetic Resonance Quantitative Imaging Features. *Acad Radiol* (2019) 26:1390–9. doi: 10.1016/j.acra.2018.11.014

40. Emblem KE, Pinho MC, Zöllner FG, Due-Tonnessen P, Hald JK, Schad LR, et al. A Generic Support Vector Machine Model for Preoperative Glioma Survival Associations. *Radiology* (2015) 275:228–34. doi: 10.1148/radiol.14140770
41. Ugolini C, Giannini R, Lupi C, Salvatore G, Miccoli P, Proietti A, et al. Presence of BRAF V600E in Very Early Stages of Papillary Thyroid Carcinoma. *Thyroid* (2007) 17:381–8. doi: 10.1089/thy.2006.0305

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Publisher's Note:** All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 08 August 2022
DOI 10.3389/fendo.2022.875597



# A comparison between cisatracurium and rocuronium-induced neuromuscular block on laryngeal electromyography recovery after neostigmine reversal in a porcine model

I-Cheng Lu[1,2], Hao Tan[1], Sheng-Hua Wu[2,3], Tzu-Yen Huang[2,4], Hsin-Yi Tseng[4], Jia-Joanna Wang[4], Gianlorenzo Dionigi[5,6], Young Jun Chai[7], Feng-Yu Chiang[8], Pi-Ying Chang[3]* and Che-Wei Wu[2,4]*

[1]Department of Anesthesiology, Kaohsiung Municipal Siaogang Hospital, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan, [2]Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan, [3]Department of Anesthesiology, Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan, [4]Department of Otorhinolaryngology, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan, [5]Division of General Surgery, Endocrine Surgery Section, Istituto Auxologico Italiano, Istituto di ricovero e cura a carattere scientifico, Milan, Italy, [6]Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy, [7]Department of Surgery, Seoul National University College of Medicine, Seoul Metropolitan Government—Seoul National University Boramae Medical Center, Transdisciplinary Department of Medicine & Advanced Technology, Seoul National University Hospital, Seoul, South Korea, [8]Department of Otolaryngology, E-Da Hospital, I-Shou University, Kaohsiung, Taiwan

**Background:** Inducing and reversing neuromuscular block is essential to a positive outcome of thyroid surgery, with intraoperative neuromonitoring (IONM) being used to decrease recurrent and superior laryngeal nerve injuries and improve vocal outcome. Neostigmine is a non-specific broad-spectrum and inexpensive reversal agent for neuromuscular blocking agents (NMBAs). The aim of this porcine study was to explore the effect of neostigmine on electromyography (EMG) signal recovery profile following the commonly used NMBAs, cisatracurium and rocuronium.

**Methods:** Twelve piglets were allocated into two groups with six piglets in each group. When stable baseline EMG signals were obtained, a neuromuscular block was induced by intravenous cisatracurium 0.2 mg/kg (group C) or rocuronium 0.6 mg/kg (group R) for each piglet. We compared laryngeal EMG tracing with spontaneous recovery (control) and neostigmine (0.04 mg/kg) reversal for each group. The time course of real-time laryngeal EMG signals was observed for 30 min from NMBA injection. Effects of neostigmine on EMG signal were assessed at 50% EMG recovery and by the maximum neuromuscular block recovery degree from the baseline value.

OPEN ACCESS

EDITED BY
Paolo Miccoli,
University of Pisa, Italy

REVIEWED BY
Erivelto Martinho Volpi,
Centro de referencia no ensino do diagnóstico por imagem (CETRUS), Brazil
Ki Tae Jung,
Chosun University, South Korea
Federico Barbariol,
Azienda Sanitaria Universitaria Friuli Centrale (ASU FC), Italy

*CORRESPONDENCE
Pi-Ying Chang
annabelle69@gmail.com
Che-Wei Wu
cwwu@kmu.edu.tw

SPECIALTY SECTION
This article was submitted to Thyroid Endocrinology, a section of the journal Frontiers in Endocrinology

RECEIVED 14 February 2022
ACCEPTED 29 June 2022
PUBLISHED 08 August 2022

CITATION
Lu I-C, Tan H, Wu S-H, Huang T-Y, Tseng H-Y, Wang J-J, Dionigi G, Chai YJ, Chiang F-Y, Chang P-Y and Wu C-W (2022) A comparison between cisatracurium and rocuronium-induced neuromuscular block on laryngeal electromyography recovery after neostigmine reversal in a porcine model.
*Front. Endocrinol.* 13:875597.
doi: 10.3389/fendo.2022.875597

**Results:** Neostigmine shortened the recovery time to 50% EMG amplitude in both group C (16.5 [2.5] vs. 29.0 [2.0] min, *P*<0.01) and group R (16.5[2.5] vs. 26.5 [1.5] min, *P*<0.05) compared to spontaneous recovery, respectively. Neostigmine reversal also enhanced the maximum degree of EMG amplitude recovery in both group C (83.6 [5.1] vs. 47.2 [6.1] %, *P*<0.01) and group R (85.6 [18.2]vs. 57.1 [6.3] %, *P*<0.05) compared to spontaneous recovery, respectively. The reversal effect of neostigmine did not differ significantly between cisatracurium and rocuronium.

**Conclusions:** This porcine model demonstrated that neostigmine provides an adequate and timely IONM signal suppressed by both cisatracurium and rocuronium. These results can potentially expand the options for precision neuromuscular block management during IONM to improve vocal outcomes in thyroid surgery patients.

KEYWORDS

**intraoperative neuromonitoring (IONM), thyroid surgery, laryngeal electromyography (EMG), neostigmine, neuromuscular blocking agent (NMBA), recurrent laryngeal nerve (RLN), voice, precision medicine**

# Introduction

For decades, thyroid surgeons have been improving vocal outcomes after thyroid surgery through the use of intraoperative neuromonitoring (IONM). IONM is used to prevent or predict recurrent laryngeal nerve (RLN) injury as it provides RLN identification, variant nerve detection, and nerve injury differentiation (1–9). A key factor to ensure functional IONM is the correct management of the degree of neuromuscular block (NMB). An ideal NMB degree is complete to profound for tracheal intubation during anesthesia induction, and moderate to shallow for electromyography (EMG) signals during IONM (10, 11).

With respect to NMB management for IONM during thyroid surgery, most trials have investigated a combination of rocuronium and sugammadex. Rocuronium protocols for IONM have been established as: standard dose, one-effective dose, or in combination with sugammadex (12–14). Sugammadex is produced as a specific reversal agent for aminosteroidal NMBAs (15, 16). Sugammadex can be effectively titrated to restore EMG signals suppressed by rocuronium-induced NMB from deep to shallow block degrees (17, 18). However, this combination is not available everywhere and very expensive. Neostigmine is a broad-spectrum and inexpensive reversal agent to non-depolarizing NMBAs. Neostigmine may be an alternative option for IONM. Recently, neostigmine has been successfully used to facilitate IONM under rocuronium-induced NMB (19).

Cisatracurium is the most widely used non-depolarizing NMBA with an isoquinoline structure and has two major advantages in clinical applications. First, it has a stable hemodynamic profile. Cisatracurium does not induce histamine release as do other isoquinoline agents (ex. atracurium), which may cause hypotension. Second, it has a favorable metabolism profile. The metabolism is *via* Hoffman elimination, which is dependent on body temperature and independent of liver or renal function. Hence, cisatracurium is also feasible for patients with organ failure or the elderly (20, 21). Only a limited of studies have investigated the application of cisatracurium in IONM during thyroid surgery (22).

To the best of our knowledge, there are no studies comparing cisatracurium with rocuronium during IONM. The purpose of this study was to explore the effect of neostigmine on EMG recovery profile in pigs receiving either cisatracurium or rocuronium during thyroid surgery. It was hypothesized that neostigmine may be effective for reversing both cisatracurium- and rocuronium-induced neuromuscular block and consequently allowing functional IONM. We compared neostigmine reversal to spontaneous recovery at an institutional intubation dose of cisatracurium (0.2 mg/kg) and rocuronium (0.6 mg/kg).

# Methods

## Animal preparations and anesthesia

The prospective animal study was approved by the Institutional Animal Care and Use Committee of Kaohsiung Medical University (protocol No: 109121). Twelve male piglets aged 3–4 months and weighing 18–22 kg were obtained from the Laboratory Animal Center of Kaohsiung Medical University. All porcine experiments were performed according to institutional guidelines that strictly followed international regulations and national policy. Electromyography of the porcine experiment, consisting of threshold, latency, amplitude, and evoked potentials, were comparable to human data in established animal models (23–25).

All piglets were fasted for 8 h, but allowed water 2 h before the experiments. Premedication included intramuscular azaperone (4 mg/kg) and zoletil (5 mg/kg) 30 min before general anesthesia. Anesthesia induction was performed in the ventrodorsal position by inhalation of 1%–2% isoflurane *via* a hollow plastic bottle connected to an anesthetic machine. After cannulation of a 24-gauge catheter into the peripheral vein on the ear, each piglet was intubated with an EMG endotracheal tube with an inner diameter of 6.0 mm (Medtronic, Jacksonville, FL, USA) under direct laryngoscopy. General anesthesia was maintained with isoflurane 1%–1.3%, and the piglets were control-ventilated with a minute volume of 2–3 L/min. Standard physiological monitoring (electrocardiography, pulse oximetry, noninvasive blood pressure, and capnography) was recorded by a Vista 120 monitor (Drager, Lubeck, Germany) until the experiment ended.

## Surgical procedures and neural monitoring setup

After skin disinfection in the dorsoventral position, a transverse collar incision was made to expose the neck and larynx of each piglet. The strap muscles were removed to reveal the trachea and target nerves (vagus nerve and RLN). Both the vagus nerve and RLN were identified and dissected free from the overlying soft tissue and fascia. The subplatysmal flap was raised cranially from the clavicle to the hyoid bone. Monopolar and bipolar electrocautery were used to facilitate dissection and hemostasis.

To accurately observe real-time EMG changes, continuous intraoperative neuromonitoring (C-IONM) *via* vagus nerve stimulation using an Automatic Periodic Stimulating (APS, Medtronic) accessory was applied (26) to provide seamless monitoring of the functional status along the entire vagus–RLN axis in real time. Stimulation frequency and current for C-IONM was set once per second (1Hz) at 1 mA. After connecting the APS electrode with the Nerve Integrity Monitor system (NIM-Response 3.0, Medtronic), baselines for the latency and amplitude of the evoked response were calibrated automatically. The monitor was set with a response threshold of 100 μV, stimulation rejection artifact at 2.6 ms, and a rectangular pulse negative stimulus of 100 μs duration. Continuous EMG tracings were recorded and analyzed by an NIM-Response 3.0 System (Medtronic) during all animal experiments to continuously evaluate real-time RLN function (27, 28).

## Outcome analysis

Twelve piglets were allocated into group C or group R according to different neuromuscular blocking agents with six piglets in each group. The experimental flowchart (Figure 1) shows both placebo control and neostigmine reversal pigs within each group. When stable EMG signals were obtained, a neuromuscular block was induced by cisatracurium (0.2 mg/kg) or rocuronium (0.6 mg/kg) for group C and group R, respectively. After a 10-min interval, an intravenous bolus of neostigmine (0.04 mg/kg) was given to reverse NMB in four piglets in both groups. In the remaining two piglets in each group, saline was injected as a placebo to observe spontaneous recovery of EMG signal after cisatracurium or rocuronium. Laryngeal EMG signals were continuously recorded during a 30-min interval from administration of cisatracurium or rocuronium. The main outcomes of neostigmine were assessed by time to a 50% recovery of baseline EMG amplitude and maximum recovery of EMG amplitude within a 30-min interval compared to the baseline value. The secondary outcome was adverse cardiovascular events caused by neostigmine. A 20% decrease in heart rate or blood pressure was defined as bradycardia or hypotension. If bradycardia or hypotension occurred, it was treated with atropine or ephedrine.

## Statistical analysis

This study is a preliminary study on a porcine model and estimation of sample size has not been performed. Assuming a non-normal distribution of the data due to small sample size, non-parametric tests were used. Continuous data are presented as median and interquartile range [IQR] values and nominal data are presented as no (%). Statistical analysis of continuous variables without normal distribution between groups was compared using the Mann–Whitney U-test. All statistical tests were two-tailed. Categorical nominal variables were analyzed using Fisher's exact test. Statistical significance was set at $P < 0.05$.

# Results

In all 12 piglets, EMG amplitude was undetectable (<100 μV) immediately after injection of cisatracurium (0.2 mg/kg) or rocuronium (0.6 mg/kg) (Figure 2). Figure 2 shows the effect of neostigmine reversal on typical EMG tracing after cisatracurium- and rocuronium-induced neuromuscular block. Neostigmine significantly shortened recovery time to 50% EMG amplitude in piglets receiving both cisatracurium and

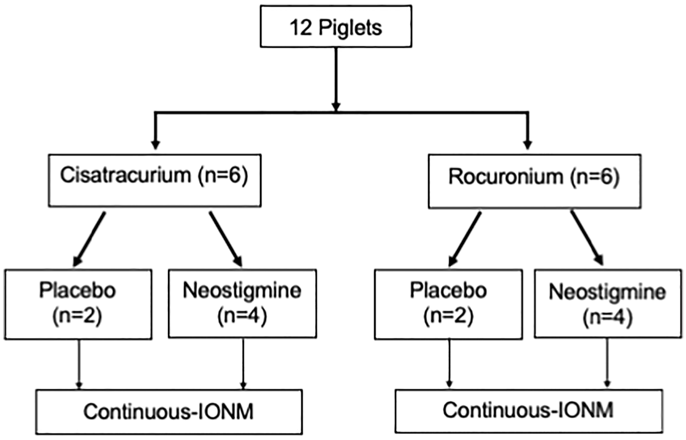



FIGURE 1
Study Flowchart Of 12 enrolled piglets, eight were reversed by neostigmine (0.04 mg/kg) and four underwent spontaneous recovery with saline (placebo). IONM, intraoperative neuromonitoring.

rocuronium compared to spontaneous recovery (Table 1). Recovery time did not differ significantly between cisatracurium and rocuronium either by spontaneous recovery or neostigmine reversal (both $P$>0.05). Neostigmine reversal enhanced the maximum degree of EMG amplitude recovery in both group C and group R compared to spontaneous recovery, respectively (Table 2). Maximum recovery degree did not differ significantly between cisatracurium and rocuronium either by spontaneous recovery or neostigmine reversal (both $P$>0.05).

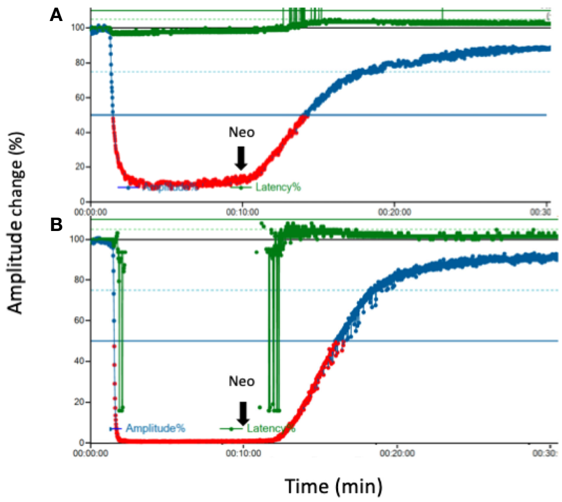



FIGURE 2
Effect of neostigmine on EMG tracing after neuromuscular block. **(A)** Typical tracing after cisatracurium (0.2 mg/kg) for neuromuscular block **(B)**. Typical tracing after rocuronium (0.6 mg/kg) for neuromuscular block. Ten minutes later, neostigmine (0.04 mg/kg) was injected for each group. An overall observation time was 30 min in each experiment. EMG, electromyography; Neo, neostigmine.

Figure 3 shows the hemodynamic status of all 12 piglets within 30 min. Eight piglets received neostigmine and four piglets received saline at 10 min. In the eight piglets that received neostigmine, heart rate and mean arterial pressure remained unchanged, compared to the four piglets that received saline. There was only a minimal decrease in heart rate ($P$>0.05) when neostigmine was administrated at 10 minute (Figure 3). None of animals were given atropine or a vasopressor for bradycardia or hypotension.

## Discussion

The porcine model in this study demonstrated that neostigmine shortened recovery time and enhanced recovery degree of EMG amplitude after cisatracurium- or rocuronium-induced NMB. Recovery time to 50% EMG amplitude after neostigmine administration in group C and group R was near 16.5 min respectively. Maximum recovery degree of EMG amplitude in group C and R was near 86% respectively. Our previous porcine model with sugammadex (0.5 mg/kg) reported a 50% recovery time of 16.8±1.9 min and a maximum recovery degree of 86.8±10.4% (18). In the current study, we confirmed that Neostigmine 0.04 mg/kg provided a similar EMG recovery profile to a low dose of sugammadex. This may explain the recent clinical finding by Oh et al. (19) showing the feasibility of neostigmine reversal of rocuronium in monitored thyroid surgery.

To the best of our knowledge, this study is the first model comparing the reversal effect of neostigmine between cisatracurium and rocuronium for IONM. We demonstrated that neostigmine provided an adequate and timely IONM signal that was suppressed by both cisatracurium and rocuronium. The results expand the

TABLE 1 Recovery time to 50% EMG amplitude.

| | Spontaneous recovery (n = 2) | Neostigmine reversal (n = 4) | *P*-value |
|---|---|---|---|
| Group C (min) | 29.0 [2.0] | 16.5 [2.5] | <0.01 |
| Group R (min) | 26.5 [1.5] | 16.5 [2.5] | <0.05 |

EMG, electromyography; Group C received cisatracurium (0.2mg/kg), Group R received rocuronium (0.6 mg/kg). Data are presented as median [IQR].

options of precision neuromuscular block management during IONM, especially for patients with organ failure or extreme old age. In those population, the use of cisatracurium is more favorable than rocuronium, but cisatracurium-induced NMB is not possible to be reversed by sugammadex. Figure 2 depicted that cisatracurium 0.2 mg/kg did not completely abolish laryngeal EMG. This occurrence may be explained by suboptimal storage of cisatracurium. Cisatracurium should be refrigerated between 2~8° C strictly to preserve the potency. We lacked refrigerator during transport and in the laboratory to ensure the standard temperature. This might lead to partial loss of predicted potency.

Though several NMB reversal regimens have been suggested, there is still a lack of consensus on NMB management for IONM during thyroid surgery. The management of NMB consists of two aspects: neuromuscular monitoring and NMB reversal. First, neuromuscular monitoring provides a guide to reversal agents based on the degree of NMB. NMB degree during IONM can be quantitatively obtained *via* stimulation on the adductor pollicis muscle with train-of-four (**TOF**), post-tetanic counts mode (11, 29). However, neuromuscular monitoring is not always available even at medical centers in developed countries. Therefore, investigations regarding a universal NMB reversal regimen are valuable for clinical practice. Second, NMB reversal for IONM was aimed at a high-quality EMG signal rather than complete recovery of neuromuscular function. Many studies recount the combination of rocuronium and sugammadex for successful IONM during thyroid surgery (14, 17, 18, 30–32). There is growing evidence that a low dose of sugammadex provides high IONM quality without complete NMB reversal. In two studies investigating 0.5, 1, and 2 mg/kg of sugammadex, it was demonstrated that all doses provided comparable EMG signals and the lower doses (0.5 or 1 mg/kg) were associated with less unwanted movements such as bucking (17, 18).

Since merely partial reversal of NMB is sufficient for IONM, it may be possible to use the non-specific reversal agent neostigmine as an alternative to the selective binding reversal agent sugammadex (19). Neostigmine is also a broad-spectrum reversal agent for all non-depolarizing NMBAs. It may be feasible for both cisatracurium (isoquinoline structure) and rocuronium (aminosteroid structure).

A recent report using neostigmine (2 mg) obtained a sufficient EMG signal with less bucking events in 4% (2/50) of patients than low dose sugammadex (13.7%; 7/51) (17, 19). For this experienced team, time from neostigmine to skin incision and initial EMG signal of the vagus nerve (V1) was 7.7±3.2 and 26.1± 5.5 min, respectively. The longer the waiting period, the higher the EMG amplitude. Hence, the time sequence of this neostigmine protocol is feasible for most thyroid surgery.

Cisatracurium is the commonly used NMBA for general anesthesia but is rarely discussed in association with IONM during thyroid surgery. Most trials focus on the rocuronium-sugammadex regimen because of its effectiveness and stability for successful IONM. Because neostigmine has been shown to be feasible for rocuronium-induced NMB during IONM (19), it should be also feasible for cisatracurium. We compared neostigmine reversal between cisatracurium and rocuronium in a porcine model and found comparable IONM outcomes in recovery time and degree. Thus, we established the feasibility of neostigmine for IONM in thyroid surgeries with two commonly used NMBAs in a porcine model. Further clinical trials are needed to compare cisatracurium-neostigmine between published regimens in clinical practice.

The cisatracurium-neostigmine combination possesses several benefits. Firstly, cisatracurium is well-tolerated in most patients even those in extreme old age or with critical illness (20, 21, 33). Cisatracurium does not induce histamine release and is metabolized by Hoffman elimination which bypasses the liver and kidneys.

There is also an option of using short-acting NMBAs, such as suxamethonium without using neostigmine. This regimen may cause possible disadvantages (e.g., unwanted movements after short term NMB and suxamethonium-induced adverse events). Those disadvantages could be avoided with cisatracurium regimen. Secondly, neostigmine induces adequate EMG amplitude with

TABLE 2 Maximum EMG amplitude recovery.

| | Spontaneous recovery (n = 2) | Neostigmine reversal (n = 4) | *P*-value |
|---|---|---|---|
| Group C (%) | 47.2 [6.1] | 83.6 [5.1] | <0.01 |
| Group R (%) | 57.1 [6.3] | 85.6 [18.2] | <0.05 |

EMG, electromyography; Group C received cisatracurium (0.2mg/kg), Group R received rocuronium (0.6mg/kg). Data are presented as median [IQR].

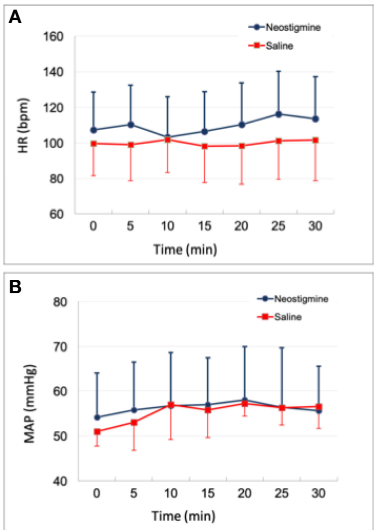



FIGURE 3
Time course of hemodynamic status. **(A)** Heart rate change **(B)** mean arterial pressure change. Either neostigmine or saline was given to each piglet at 10 min. There was no significant difference between neostigmine (n=8) and saline (n=4) in both heart rate and blood pressure (all *P* >0.05). HR = heart rate; MAP = mean arterial pressure.

much less unwanted movement compared with sugammadex. An initial high EMG amplitude is important to identify potential signal reduction (34). In clinical IONM practice, an EMG amplitude > 500 µV is considered as adequate enough for initial vagal stimulation (35). Neostigmine acts as a cholinesterase inhibitor which was very different from sugammadex as a selective relaxant binding agent. Therefore, neostigmine is not as effective as sugammadex to reverse muscle relaxation. Lastly, the cost of cisatracurium-neostigmine is much lower than that of rocuronium-sugammadex. The high price of sugammadex limits its popularity and availability in many healthcare systems (36, 37). Hence, cisatracurium-neostigmine has great potential for IONM because of its effectiveness and accessibility. Recently, cisatracurium titration with spontaneous recovery has been used to facilitate IONM during thyroid surgery (22, 38). A superior IONM outcome of cisatracurium with neostigmine reversal is expected in clinical practice.

There were several limitations in this study. First, this was a prospective animal study with a small sample size. Within each group, four animals were used to test cisatracurium or rocuronium, and saline was used as a placebo in only two animals. The statistical validity of this study is greatly reduced by this. The results of statistical analyses conducted by comparing 2 groups of 2-4 elements each cannot be considered reliable, regardless of whether p is significant or not. However, we found a good reproducibility between experimental animals. The EMG recovery profile was similar in all piglets. The variation between recovery time and degree was relatively small. Secondly, a comparison between neostigmine and sugammadex was not performed in this study. This was because the feasibility of a sugammadex dose from 0.5 to 4 mg/kg has been established in a previous porcine IONM model (14, 18). Our aim was to investigate the feasibility of neostigmine for IONM under different NMBAs. Furthermore, we did not observe significant change of either hemodynamic nor respiratory status due to neostigmine alone in porcine model. However, it should be cautious that cholinesterase inhibitor may lead to not only bradycardia but also more secretion causing fatal problems during mechanical ventilation or postoperatively. Thirdly, it lacks quantitative neuromuscular transmission monitoring such as train-of-four (TOF) to compare the IONM data. We did not use TOF monitor in this study because it is difficult to set up in the porcine model and it will be easy to apply in further clinical study. Finally, caution should be taken in the interpretation and application of the current results. None of the animals experienced significant bradycardia when neostigmine was administered without anticholinergics. Moreover, results of healthy animals undergoing experimental protocols may not be representative of humans with various systemic diseases.

## Conclusions

Neostigmine allowed adequate and timely IONM signal suppression by both cisatracurium and rocuronium in a porcine model. Our results may expand the options of precision NMB management during IONM to improve vocal outcomes in thyroid surgery patients. The EMG recovery profile of cisatracurium-neostigmine or rocuronium-neostigmine was feasible for IONM during thyroid surgery. Although neostigmine (0.04 mg/kg) did not cause significant cardiovascular adverse events in animals, caution should be used when implementing this protocol in a clinical setting.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The animal study was reviewed and approved by Institutional Animal Care and Use Committee of Kaohsiung Medical University.

## Author contributions

C-WW had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. P-YC and C-WW contributed equally to this work. Concept and design: I-CL, C-WW, Acquisition, analysis, or interpretation of data: T-YH, H-YT, J-JW. Drafting of the manuscript: I-CL, P-YC, C-WW Critical revision of the manuscript and final approval: All authors Statistical analysis: I-CL, HT Obtained funding: I-CL, T-YH, C-WW Administrative, technical, or material support: S-HW, GD, YC, F-YC Supervision: P-YC, C-WW. All authors contributed to the article and approved the submitted version.

## Funding

This study was supported by grants from the Kaohsiung Medical University Hospital (KMUH110-OR52), the Kaohsiung Municipal Siaogang Hospital (H-109-001, Kmhk-110-08), the Ministry of Science and Technology, Taiwan (MOST 109-2314-B-037-059, MOST 110-2314-B-037-104 -MY2).

## Acknowledgments

The authors express gratitude to Hsiu-Ya Chen, Jung-Yen Hu (nurse anesthetist, Department of Anesthesiology, KMUH, KMU), Hui-Chun Chen (clinical nurse specialist, Department of Nursing, KMUH, KMU), and Pao-Chu Hun (veterinarian, Laboratory Animal Center, KMU) for their excellent technical assistance.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

## References

1. Choi SY, Son YI. Intraoperative neuromonitoring for thyroid surgery: The proven benefits and limitations. *Clin Exp Otorhinolaryngol* (2019) 12:335–6. doi: 10.21053/ceo.2019.00542

2. Malik R, Linos D. Intraoperative neuromonitoring in thyroid surgery: A systematic review. *World J Surg* (2016) 40:2051–8. doi: 10.1007/s00268-016-3594-y

3. Randolph GW, Dralle HInternational Intraoperative Monitoring Study G, , Abdullah H, Barczynski M, Bellantone R, et al. Electrophysiologic recurrent laryngeal nerve monitoring during thyroid and parathyroid surgery: international standards guideline statement. *Laryngoscope* (2011) 121(Suppl 1): S1–16. doi: 10.1002/lary.21119

4. Sun H, Tian W, Jiang K, Chiang F, Wang P, Huang T, et al. Clinical guidelines on intraoperative neuromonitoring during thyroid and parathyroid surgery. *Ann Transl Med* (2015) 3:213. doi: 10.3978/j.issn.2305-5839.2015.08.21

5. Wu CW, Dionigi G, Barczynski M, Chiang FY, Dralle H, Schneider R, et al. International neuromonitoring study group guidelines 2018: Part II: Optimal recurrent laryngeal nerve management for invasive thyroid cancer-incorporation of surgical, laryngeal, and neural electrophysiologic data. *Laryngoscope* (2018) 128 (Suppl 3):S18–s27. doi: 10.1002/lary.27360

6. Chiang FY, Lu IC, Kuo WR, Lee KW, Chang NC, Wu CW. The mechanism of recurrent laryngeal nerve injury during thyroid surgery–the application of intraoperative neuromonitoring. *Surgery* (2008) 143:743–9. doi: 10.1016/j.surg.2008.02.006

7. Wu CW, Wang MH, Chen CC, Chen HC, Chen HY, Yu JY. Loss of signal in recurrent nerve neuromonitoring: causes and management. *Gland Surg* (2015) 4:19–26. doi: 10.3978/j.issn.2227-684X.2014.12.03

8. Dionigi G, Wu CW, Kim HY, Rausei S, Boni L, Chiang FY. Severity of recurrent laryngeal nerve injuries in thyroid surgery. *World J Surg* (2016) 40:1373–81. doi: 10.1007/s00268-016-3415-3

9. Wu CW, Randolph GW, Barczyński M, Schneider R, Chiang FY, Huang TY. Training courses in laryngeal nerve monitoring in thyroid and parathyroid surgery- the INMSG consensus statement. *Front Endocrinol (Lausanne)* (2021) 12:705346. doi: 10.3389/fendo.2021.705346

10. Lu IC, Wu SH, Wu CW. Neuromuscular blockade management for intraoperative neural monitoring. *Kaohsiung J Med Sci* (2020) 36:230–5. doi: 10.1002/kjm2.12153

11. Naguib M, Brull SJ, Johnson KB. Conceptual and technical insights into the basis of neuromuscular monitoring. *Anaesthesia* (2017) 72(Suppl 1):16–37. doi: 10.1111/anae.13738

12. Chu KS, Wu SH, Lu IC, Tsai CJ, Wu CW, Kuo WR. Feasibility of intraoperative neuromonitoring during thyroid surgery after administration of nondepolarizing neuromuscular blocking agents. *World J Surg* (2009) 33:1408–13. doi: 10.1007/s00268-009-0049-8

13. Lu IC, Tsai CJ, Wu CW, Cheng KI, Wang FY, Tseng KY, et al. A comparative study between 1 and 2 effective doses of rocuronium for intraoperative neuromonitoring during thyroid surgery. *Surgery* (2011) 149:543–8. doi: 10.1016/j.surg.2010.11.006

14. Lu IC, Wu CW, Chang PY, Chen HY, Tseng KY, Randolph GW, et al. Reversal of rocuronium-induced neuromuscular blockade by sugammadex allows for optimization of neural monitoring of the recurrent laryngeal nerve. *Laryngoscope* (2016) 126:1014–9. doi: 10.1002/lary.25577

15. de Boer HD, van Egmond J, van de Pol F, Bom A, Booij LH. Reversal of profound rocuronium neuromuscular blockade by sugammadex in anesthetized rhesus monkeys. *Anesthesiology* (2006) 104:718–23. doi: 10.1097/00000542-200604000-00016

16. Welliver M, McDonough J, Kalynych N, Redfern R. Discovery, development, and clinical application of sugammadex sodium, a selective relaxant binding agent. *Drug Des Devel Ther* (2009) 2:49–59. doi: 10.2147/dddt.s2757

17. Chai YJ, Lee JM, Won D, Lee J, Hwang JY, Kim TK. Comparison of sugammadex dose for intraoperative neuromonitoring in thyroid surgery: A randomized controlled trial. *Laryngoscope* (2021) 131:2154–9. doi: 10.1002/lary.29515

18. Lu IC, Wu SH, Chang PY, Ho PY, Huang TY, Lin YC. Precision neuromuscular block management for neural monitoring during thyroid surgery. *J Invest Surg* (2021) 34:1389–96. doi: 10.1080/08941939.2020.1805055

19. Oh MY, Lee JM, Won D, Huang TY, Wu CW, Dionigi G. Investigation of potential neuropharmacological activity of neostigmine-glycopyrrolate for intraoperative neural monitoring in thyroid surgery. *Kaohsiung J Med Sci* (2022) 38:59–64. doi: 10.1002/kjm2.12448

20. Szakmany T, Woodhouse T. Use of cisatracurium in critical care: a review of the literature. *Minerva Anestesiol* (2015) 81:450–60.

21. Lee LA, Athanassoglou V, Pandit JJ. Neuromuscular blockade in the elderly patient. *J Pain Res* (2016) 9:437–44. doi: 10.2147/JPR.S85183

22. Li X, Zhang B, Xu G, Song Y, Yu L, Yang J, et al. Dosage effect of cisatracurium on intubation and intraoperative neuromonitoring during thyroidectomy: a randomized controlled trial. *Gland Surg* (2021) 10:2150–8. doi: 10.21037/gs-21-109

23. Wu CW, Lu IC, Randolph GW, Kuo WR, Lee KW, Chen CL, et al. Investigation of optimal intensity and safety of electrical nerve stimulation during intraoperative neuromonitoring of the recurrent laryngeal nerve: a prospective porcine model. *Head Neck* (2010) 32:1295–301. doi: 10.1002/hed.21324

24. Lu IC, Chang PY, Hsu HT, Tseng KY, Wu CW, Lee KW, et al. A comparison between succinylcholine and rocuronium on the recovery profile of the laryngeal muscles during intraoperative neuromonitoring of the recurrent laryngeal nerve: a prospective porcine model. *Kaohsiung J Med Sci* (2013) 29:484–7. doi: 10.1016/j.kjms.2013.01.002

25. Wu CW, Huang TY, Chen HC, Chen HY, Tsai TY, Chang PY, et al. Intra-operative neural monitoring of thyroid surgery in a porcine model. *J Vis Exp* (2019) 11: 144. doi: 10.3791/57919

26. Dionigi G, Chiang FY, Hui S, Wu CW, Xiaoli L, Ferrari CC, et al. Continuous intraoperative neuromonitoring (C-IONM) technique with the automatic periodic stimulating (APS) accessory for conventional and endoscopic thyroid surgery. *Surg Technol Int* (2015) 26:101–14.

27. Lin YC, Dionigi G, Randolph GW, Lu IC, Chang PY, Tsai SY, et al. Electrophysiologic monitoring correlates of recurrent laryngeal nerve heat thermal injury in a porcine model. *Laryngoscope* (2015) 125:E283–90. doi: 10.1002/lary.25362

28. Wu CW, Dionigi G, Sun H, Liu X, Kim HY, Hsiao PJ, et al. Intraoperative neuromonitoring for the early detection and prevention of RLN traction injury in thyroid surgery: A porcine model. *Surgery* (2014) 155:329–39. doi: 10.1016/j.surg.2013.08.015

29. Fuchs-Buder T, Meistelman C, Raft J. Sugammadex: clinical development and practical use. *Korean J Anesthesiol* (2013) 65:495–500. doi: 10.4097/kjae.2013.65.6.495

30. Kontoudi M, Gouliami M, Loizou C, Kristoloveanou K, Pandazi A. Intraoperative rocuronium reversion by low doses of sugammadex, in thyroid surgery, with monitoring of the recurrent laryngeal nerves. *ARC J Anesthesiol* (2016) 1:19–28. doi: 10.20431/2455-9792.0103003

31. Empis de Vendin O, Schmartz D, Brunaud L, Fuchs-Buder T. Recurrent laryngeal nerve monitoring and rocuronium: A selective sugammadex reversal protocol. *World J Surg* (2017) 41:2298–303. doi: 10.1007/s00268-017-4004-9

32. Gunes ME, Dural AC, Akarsu C, Guzey D, Sahbaz NA, Tulubas EK, et al. Effect of intraoperative neuromonitoring on efficacy and safety using sugammadex in thyroid surgery: randomized clinical trial. *Ann Surg Treat Res* (2019) 97:282–90. doi: 10.4174/astr.2019.97.6.282

33. Needham CJ, Brindley PG. Best evidence in critical care medicine: The role of neuromuscular blocking drugs in early severe acute respiratory distress syndrome. *Can J Anaesth* (2012) 59:105–8. doi: 10.1007/s12630-011-9615-2

34. Wu CW, Hao M, Tian M, Dionigi G, Tufano RP, Kim HY, et al. Recurrent laryngeal nerve injury with incomplete loss of electromyography signal during monitored thyroidectomy-evaluation and outcome. *Langenbecks Arch Surg* (2017) 402(4):691–9. doi: 10.1007/s00423-016-1381-8

35. Lu IC, Hsu CD, Chang PY, Wu SH, Huang TY, Lin YC, et al. A surgeon-centered neuromuscular block protocol improving intraoperative neuromonitoring outcome of thyroid surgery. *Front Endocrinol (Lausanne).* (2022) 13:817476. doi: 10.3389/fendo.2022.817476

36. O'Reilly-Shah VN, Wolf FA, Jabaley CS, Lynde GC. Using a worldwide in-app survey to explore sugammadex usage patterns: a prospective observational study. *Br J Anaesth* (2017) 119:333–5. doi: 10.1093/bja/aex171

37. de Boer HD, Carlos RV, Brull SJ. Is lower-dose sugammadex a cost-saving strategy for reversal of deep neuromuscular block? facts and fiction. *BMC Anesthesiol* (2018) 18:159. doi: 10.1186/s12871-018-0605-6

38. Sun X, Chang T, Xu Y, Jing Q, Cao S, Tian L, et al. Effects of different doses of cisatracurium on intraoperative nerve monitoring in thyroid surgery: a randomised controlled trial. *Br J Anaesth* (2021) 127:e67–9. doi: 10.1016/j.bja.2021.05.011

frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 11 August 2022
DOI 10.3389/fendo.2022.888381



OPEN ACCESS

EDITED BY
Kang Dae Lee,
Kosin University Gospel Hospital,
South Korea

REVIEWED BY
Byungjoo Lee,
Pusan National University Hospital,
South Korea
Kyung Tae,
Hanyang, University, South Korea
Yong Bae Ji,
Hanyang University, South Korea

*CORRESPONDENCE
Tzu-Yen Huang
tyhuang.ent@gmail.com
Feng-Yu Chiang
fychiang@kmu.edu.tw

SPECIALTY SECTION
This article was submitted to
Thyroid Endocrinology,
a section of the journal
Frontiers in Endocrinology

RECEIVED 02 March 2022
ACCEPTED 27 June 2022
PUBLISHED 11 August 2022

CITATION
Chiu K-L, Lien C-F, Wang C-C,
Wang C-C, Hwang T-Z, Shih Y-C,
Yu W-HV, Wu C-W, Dionigi G,
Huang T-Y and Chiang F-Y (2022)
Intraoperative EMG recovery patterns
and outcomes after RLN traction-related amplitude decrease during
monitored thyroidectomy.
*Front. Endocrinol.* 13:888381.
doi: 10.3389/fendo.2022.888381



# Intraoperative EMG recovery patterns and outcomes after RLN traction-related amplitude decrease during monitored thyroidectomy

Kuan-Lin Chiu[1], Ching-Feng Lien[1,2], Chih-Chun Wang[1,2], Chien-Chung Wang[1], Tzer-Zen Hwang[1,2], Yu-Chen Shih[3], Wing-Hei Viola Yu[4], Che-Wei Wu[4], Gianlorenzo Dionigi[5,6], Tzu-Yen Huang[4]* and Feng-Yu Chiang[1,2]*

[1]Department of Otolaryngology-Head and Neck Surgery, E-Da Hospital, Kaohsiung, Taiwan, [2]School of Medicine, College of Medicine, I-Shou University, Kaohsiung, Taiwan, [3]Department of Otolaryngology, E-Da Cancer Hospital, Kaohsiung, Taiwan, [4]Department of Otorhinolaryngology-Head and Neck Surgery, International Thyroid Surgery Center, Kaohsiung Medical University Hospital, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan, [5]Division of General Surgery, Endocrine Surgery Section, Istituto Auxologico Italiano IRCCS, Milan, Italy, [6]Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy

**Objectives:** Traction injury is the most common type of recurrent laryngeal nerve (RLN) injury in thyroid surgery. Intraoperative neuromonitoring (IONM) facilitates early detection of adverse electromyography (EMG) effect, and this corrective maneuver can reduce severe and repeated nerve injury. This study aimed to evaluate intraoperative patterns and outcomes of EMG decrease and recovery by traction injury.

**Methods:** 644 patients received nerve monitored thyroidectomy with 1142 RLNs at risk were enrolled. Intermittent IONM with stimulating dissecting instrument (real-time during surgical procedure) and trans-thyroid cartilage EMG recording method (without electrode malpositioning issue) were used for nerve stimulation and signal recording. When an EMG amplitude showed a decrease of >50% during RLN dissection, the surgical maneuver was paused immediately. Nerve dissection was restarted when the EMG amplitude was stable.

**Results:** 44/1142 (3.9%) RLNs exhibited a >50% EMG amplitude decrease during RLN dissection and all (100%) showed gradual progressive amplitude recovery within a few minutes after releasing thyroid traction (10 recovered from LOS; 34 recovered from a 51-90% amplitude decrease). Three EMG recovery patterns were noted, A-complete EMG recovery (n=14, 32%); B-incomplete EMG recovery with an injury point (n=16, 36%); C-incomplete EMG recovery without an injury point (n=14, 32%). Patients with postoperative weak or fixed vocal cord mobility in A, B, and C were 0(0%), 7(44%), and 2(14%), respectively.

Complete EMG recovery was found in 14 nerves, and incomplete recovery was found in another 30 nerves. Temporary vocal cord palsy was found in 6 nerves due to unavoidable repeated traction.

**Conclusion:** Early detection of traction-related RLN amplitude decrease allows monitoring of intraoperative EMG signal recovery during thyroid surgery. Different recovery patterns show different vocal cord function outcomes. To elucidate the recovery patterns can assist surgeons in the intraoperative decision making and postoperative management.

KEYWORDS

**recurrent laryngeal nerve (RLN), intraoperative neuromonitoring (IONM), thyroid surgery, electromyography (EMG), traction injury**

# Introduction

Routine identification of the recurrent laryngeal nerve (RLN) has been accepted as the gold standard of care during thyroid surgery to decrease RLN palsy rates (1–4). During the RLN identification and dissection phase, the RLN can be injured by the surgical maneuvers of traction, clamping, electrocauterization, mechanical trauma, and transection. However, traction injury is the most common cause of RLN injury, with a rate of up to 70-80% among all maneuvers (5–8). Medial traction of the thyroid lobe is a necessary step in the surgical procedure to identify RLN. The RLN can be overstretched and injured by a dense fibrous band or surrounding blood vessels at the region of Berry's ligament during medial thyroid traction. Loss of signal (LOS) was found after nerve dissection with the application of intraoperative neuromonitoring (IONM) in thyroid surgery, even though visual anatomical integrity of the RLN was confirmed intraoperatively (8–10).

For stimulating methods, intermittent IONM (I-IONM) applied with a hand-held stimulating probe is still mainstream internationally due to its convenience and inexpensiveness. However, it is challenging to detect early between the intervals of nerve stimulation using the conventional I-IONM, the adverse electromyography (EMG) change, and LOS is consistently recognized after the occurrence of traction injury (5–8). Animal and clinical studies of RLN traction injury with the application of continuous IONM (C-IONM) (11–14) revealed an EMG amplitude decrease during RLN traction and progressive recovery after releasing traction stress. C-IONM is reported to be helpful for the early detection of EMG amplitude decreases caused by traction distress (15–17). Stimulating dissecting instrument (SDI) is a novel and real-time I-IONM stimulating method during surgical procedure. It can maximally reduce the intervals of the nerve stimulation while maintaining the advantages of I-IONM convenience, simplicity and affordability. For recording methods, unstable and variable EMG amplitudes during operation have been reported using traditional EMG tubes for EMG recoding (18, 19). It will be challenging to differentiate an actual decrease in EMG signal caused by traction stress on the RLN from a false decrease caused by EMG tube displacement. The trans-thyroid cartilage EMG recording method can avoid the electrode malpositioning issue and obtain high-quality EMG signals.

IONM facilitates early detection of adverse EMG effect, and the corrective maneuver can reduce severe and repeated nerve injury. However, intraoperative patterns and outcomes of EMG recovery are less studied in the literature. In this study, SDI and the trans-thyroid cartilage EMG recording method were used for nerve stimulation and signal recording. With these two new IONM techniques, we aimed to determine the feasibility of early detection of a significant EMG amplitude decrease during the phase of RLN dissection and the possibility of intraoperative EMG recovery after releasing thyroid traction, which might be helpful for avoiding signal deterioration to complete LOS and postoperative vocal cord (VC) palsy.

# Materials and methods

## Patients

This retrospective study was conducted at a tertiary referral academic medical center, Kaohsiung Medical University Hospital, Taiwan. The data were collected from Oct. 2015 to Oct. 2019 regarding 664 patients (118 men and 546 women; ages ranging from 19 to 81 years; mean age, 50.9 years) who underwent operations for various thyroid diseases treated by the same surgeon (F.-Y. Chiang). There were 173 thyroid lobectomies and 491 total thyroidectomies (397 benign and 267 malignant thyroid diseases). Thirteen nerves were excluded from this study due to preoperative cord palsy (9 nerves) and intentional sacrifice due to cancer encasement (4 nerves). Thus, 1142 nerves at risk were enrolled in this study. (Figure 1)

## IONM setup and procedures

General anesthesia was induced with lidocaine (1 mg/kg), propofol (2–3 mg/kg), a single dose of rocuronium (0.3 mg/kg), and a bolus of fentanyl (50 μg) as necessary. Regular oral endotracheal tubes were used for all patients. Anesthesia was maintained with sevoflurane and propofol target-controlled infusion. We routinely elevated the skin flap to the upper level of the thyroid cartilage and dissected the pyramidal lobe and prelaryngeal lymph nodes to place the electrodes correctly. Two paired subdermal electrodes (length, 12.0 mm; diameter, 0.4 mm; Medtronic, Jacksonville, FL) were inserted into the subperichondrium of the middle thyroid lamina for EMG recording (Figure 2A). The conventional dissecting forceps was connected by the stimulation wire to use it as SDI (Figures 2B, C), which was used for vagus nerve (VN) and RLN stimulation.

During the operation, standard IONM procedures (20) were strictly followed. The VN (without dissecting the carotid sheath to expose the VN) was stimulated with a 5-10 mA stimulus current before and after RLN dissection, and $V_1$ and $V_2$ signals were obtained. At the first identification, the RLN was stimulated with 3-5 mA, and the R1 signal was obtained. After complete RLN dissection, the exposed RLN was stimulated at the most proximal and distal ends near the laryngeal entry point, and $R_{2p}$ and $R_{2d}$ signals were obtained. The largest amplitudes of these five EMG signals ($V_1$-$R_1$-$R_{2p}$-$R_{2d}$-$V_2$) were registered in all cases.

The EMG amplitude was monitored for changes during the phase of medial thyroid traction and RLN dissection. An EMG amplitude decrease >50% of the $R_1$ signal was defined as a significant EMG amplitude decrease. When a significant EMG amplitude decrease was detected, the surgical maneuver was immediately stopped, and the mechanism (traction injury, thermal injury, and dissection trauma) of nerve injury was immediately determined and recovery of EMG amplitudes was closely monitored. Nerve dissection was restarted with gentle thyroid traction after the EMG amplitude recovered and reached a stable amplitude. A stable amplitude is defined as less than 10% amplitude change in one minute. Secondary significant EMG amplitude decreases can be observed and recorded in some nerves. After finishing RLN dissection, the amplitudes of $R_{2p}$ and $R_{2d}$ signals were compared. If the $R_{2p}/R_{2d}$ ratio reduction was over 10%, the whole exposed RLN was mapped to identify the injured point with 1 mA. The difference in the $R_{2p}$ and $R_{2d}$ signals within ±10% is regarded as the normal variation in the monitoring system. Before closing the wound, we repeated the same procedure to confirm and record the final data.

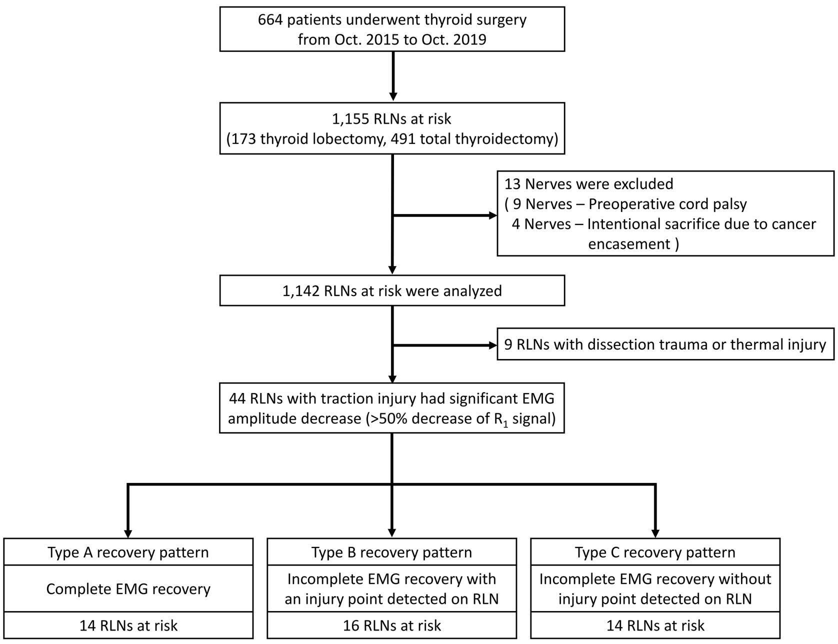



FIGURE 1
Flowchart of the procedure for the inclusion and exclusion of patients and the patterns, definitions, and patient distribution summarized from this study. RLN= Recurrent laryngeal nerve.


FIGURE 2
The novel intermittent intraoperative neuromonitoring method in this study. Medtronic two paired subdermal electrodes were inserted into the subperichondrium of the middle thyroid lamina for the EMG recording **(A)**. A Medtronic stimulation wire was connected to the conventional dissecting forceps **(B)**, and it became a stimulating dissecting instrument **(C)**.

LOS was defined as the absence of EMG signals (amplitude less than 100 μV) after nerve stimulation. Type 1 LOS was defined as a localized injury point detected on the RLN, and Type 2 LOS was defined as no injury point on the whole exposed RLN. All patients received pre- and postoperative video recordings of VC function. Symmetric VC mobility was regarded as a normal VC function. Weak VC mobility was defined as asymmetric VC movement (VC still moved and was approximated well). VC palsy was defined as fixation of VC mobility. When VC palsy was found, VC function was examined every 2 weeks initially and every 4 weeks after that until complete recovery was achieved. VC palsy was considered permanent if it persisted for more than 6 months postoperatively.

The study was approved by the Institutional Review Board (IRB) of Kaohsiung Medical University Hospital (KMUHIRB-E (I)-20210358).

## Results

Forty-four of 1142 nerves (3.9%) exhibited a significant EMG amplitude decrease (>50% decrease in $R_1$ signal) during RLN dissection, and all (100%) showed gradual progressive amplitude recovery within a few minutes after releasing thyroid traction (Figure 3). Ten nerves recovered from LOS, and another 34 nerves recovered from a 51-90% amplitude decrease.

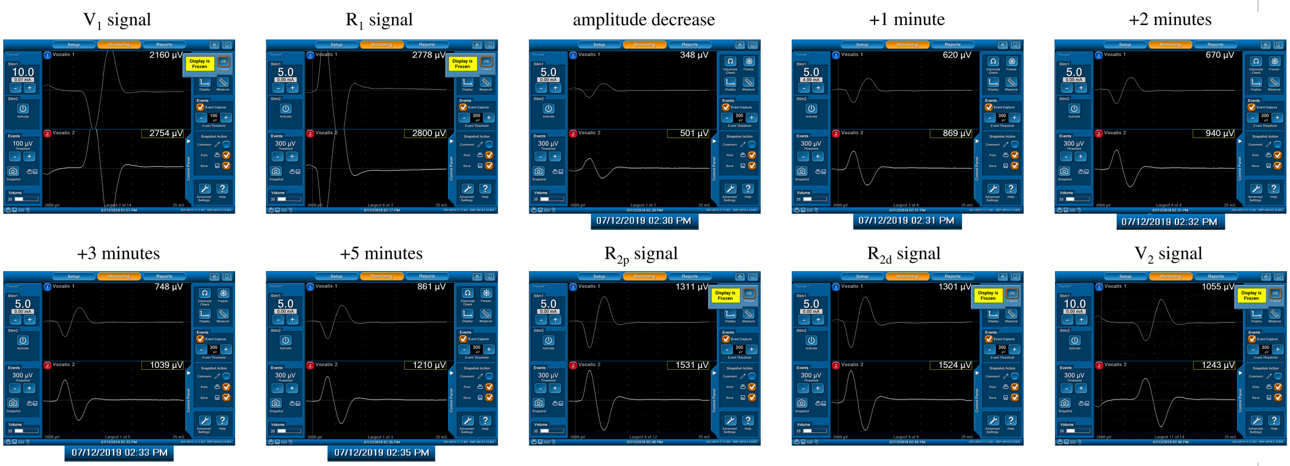



FIGURE 3
A significant amplitude decrease (channel 2) from 2800 μV (R1 signal) to 501 μV was detected. The actual operation time of the neuromonitoring screenshots is magnified and displayed below, according to amplitude decrease, +1, +2, +3, +5 minutes after amplitude decrease, respectively. Gradual and progressive amplitude recovery was found within a few minutes after releasing thyroid traction. The amplitudes between the $R_{2p}$ and $R_{2d}$ signals showed no difference, but there was a 66% amplitude decrease between the $R_{2p}$ and $R_1$ signals. This is a case of a Type C recovery pattern after traction injury.

After restarting the surgical maneuver, a secondary significant EMG amplitude decrease occurred in 6 (13.6%) of 44 nerves. A substantial $R_{2p}/R_{2d}$ ratio reduction (81% and 92%) in 2 nerves and unrecovered LOS in 4 nerves occurred due to inevitable repeated traction, and all 6 nerves developed temporary VC palsy.

Three types of EMG recovery patterns were summarized. Type A recovery pattern showed complete EMG amplitude recovery in 14 (32%) nerves; Type B showed incomplete recovery with an injury point detected on the RLN in 16 (36%) nerves. Type C showed incomplete recovery without an injury point detected in 14 (32%) nerves (Figure 1). Regarding Type A recovery pattern, 2 of 14 nerves had LOS during the surgical maneuver. No (0%) patient had postoperative weak or fixed VC mobility (Table 1). Of the nerves with the Type B recovery pattern, 6 of 16 nerves had LOS during the surgical maneuver. Seven (44%) patients had abnormal postoperative VC mobility, including 2 patients had weak VC mobility and 5 patients had fixed VC mobility. All 16 nerve injury points were located in the upper portion of exposed RLN (at the region of Berry's ligament or near the laryngeal entry point) (Table 2). Of the nerves with Type C recovery pattern, 2 of 14 nerves had LOS during the surgical maneuver. Two (14%) patients had abnormal postoperative VC mobility, including one patient had weak VC mobility, and one patient had fixed VC mobility (Table 3).

In this study, a substantial EMG amplitude decrease was also found in 9 nerves caused by dissection trauma or thermal injury but without showing the feature of progressive recovery. Complete LOS was found in 5 nerves, and incomplete LOS was found in 4 nerves. Temporary VC palsy occurred in 7 nerves, and permanent VC palsy occurred in 2 nerve with thermal injury.

## Discussion

RLN traction injury frequently occurs at the region of Berry's ligament since the anatomical relationship between RLN, Berry's ligament and surrounding vessels is highly variable (21–24) The RLN is located not only posterolateral to Berry's ligament but also posteromedial to it, and the anterior motor branch of the RLN may penetrate the ligament. Additionally, blood vessels often intertwine with the RLN at the region of Berry's ligament. The RLN can be overstretched during medial thyroid traction by Berry's ligament or an intertwined vessel (Figures 4A–C).

When applying C-IONM in thyroid surgery, a progressive decrease in EMG amplitude is the characteristic feature of traction distress on the RLN (11–14). Prolonged traction may result in unrecovered LOS and postoperative VC palsy. Therefore, the weakness of conventional I-IONM compared to C-IONM is that early detection of imminent RLN injury and relief of traction distress are less effective to avoid signals deteriorating to an unrecoverable level (13). In this study, SDI was used for nerve stimulation and tissue dissection. It is a simple and effective way to real-time monitor nerve function during the highest risk phase for RLN injury (25, 26). In our experience, SDI is not inferior to C-IONM in early detection of nerve injury, furthermore, C-IONM cannot replace I-IONM in locating the nerve injury point. Additionally, we chose the trans-thyroid cartilage recording method for EMG signal recording. It

TABLE 1 Type A EMG recovery pattern (complete EMG recovery).

| No. | $V_1$ (μV) | $R_1$ (μV) | $R_{2p}$ (μV) | $R_{2d}$ (μV) | $V_2$ (μV) | $R_{2p}/R_{2d}$ reduction# | Amplitude decrease (μV) + | Amplitude decrease ratio (%)* | VC mobility |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 2532 | 3415 | 3276 | 3438 | 2322 | nil | 1565 | 54% | sym |
| 2 | 1485 | 1944 | 1899 | 1944 | 1480 | nil | 535 | 72% | sym |
| 3 | 1495 | 1661 | 1671 | 1681 | 1533 | nil | 276 | 83% | sym |
| 4 | 1731 | 2159 | 2135 | 2131 | 1618 | nil | 559 | 74% | sym |
| 5 | 853 | 1295 | 1177 | 1277 | 879 | nil | 353 | 73% | sym |
| 6 | 1825 | 2490 | 2508 | 2525 | 1983 | nil | 452 | 82% | sym |
| 7 | 785 | 772 | 833 | 881 | 767 | nil | 306 | 60% | sym |
| 8 | 1397 | 1709 | 1652 | 1632 | 1240 | nil | 565 | 67% | sym |
| 9 | 1875 | 1904 | 1988 | 2072 | 1711 | nil | 940 | 51% | sym |
| 10 | 1223 | 1948 | 1859 | 1925 | 1334 | nil | 650 | 67% | sym |
| 11 | 2624 | 3684 | 4229 | 4168 | 3024 | nil | 1565 | 58% | sym |
| 12 | 2203 | 3350 | 3239 | 3345 | 2533 | nil | 819 | 63% | sym |
| 13 | 1472 | 1805 | 1734 | 1751 | 1395 | nil | LOS | ≒100% | sym |
| 14 | 1508 | 1880 | 1819 | 1801 | 1400 | nil | LOS | ≒100% | sym |

# the difference of EMG signal between $R_{2p}$ and $R_{2d}$ within ±10% is regarded as a normal variation of the monitoring system.
+ the decreased EMG signal detected during the surgical maneuver.
* the decrease ratio between the decreased EMG amplitude and $R_1$ signal.
EMG, electromyography; VC, vocal cord; sym, symmetric.

TABLE 2 Type B EMG recovery pattern (incomplete EMG recovery with an injury point detected on RLN).

| No. | $V_1$ (μV) | $R_1$ (μV) | $R_{2p}$ (μV) | $R_{2d}$ (μV) | $V_2$ (μV) | $R_{2p}/R_{2d}$ reduction# | Amplitude decrease (μV) + | Amplitude decrease ratio (%)* | VC mobility |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 2862 | 2993 | LOS | 3279 | LOS | ≒100% | LOS | ≒100% | fixed |
| 2 | 1391 | 1581 | LOS | 1242 | LOS | ≒100% | LOS | ≒100% | fixed |
| 3 | 2430 | 2882 | LOS | 2976 | LOS | ≒100% | 825 | 71% | fixed |
| 4 | 3598 | 3752 | 1337 | 2806 | 1068 | 52% | LOS | ≒100% | sym |
| 5 | 2235 | 3695 | 1480 | 3855 | 1072 | 62% | LOS | ≒100% | weak |
| 6 | 1261 | 2222 | 512 | 1214 | 358 | 58% | LOS | ≒100% | weak |
| 7 | 1152 | 1289 | 145 | 755 | 138 | 81% | LOS | ≒100% | fixed |
| 8 | 2896 | 3773 | 323 | 3822 | 290 | 92% | 1350 | 64% | fixed |
| 9 | 1153 | 1278 | 364 | 1480 | 244 | 66% | 429 | 66% | sym |
| 10 | 2131 | 3278 | 1839 | 3307 | 1597 | 44% | 1317 | 60% | sym |
| 11 | 1213 | 1591 | 999 | 1274 | 893 | 22% | 153 | 90% | sym |
| 12 | 2716 | 3217 | 3075 | 2259 | 2096 | 36% | 1323 | 59% | sym |
| 13 | 2183 | 1913 | 1435 | 2054 | 811 | 30% | 482 | 75% | sym |
| 14 | 1957 | 2354 | 954 | 2325 | 801 | 59% | 440 | 81% | sym |
| 15 | 1289 | 1389 | 1182 | 1619 | 1101 | 28% | 453 | 67% | sym |
| 16 | 949 | 1017 | 708 | 1431 | 655 | 51% | 305 | 70% | sym |

The descriptions of #, +, *, and abbreviations are the same as those in Table 1.

provides high initial EMG amplitudes during VN and RLN stimulation, and the amplitudes remain stable during the entire course of the operation (27–29). This technique solves the major limitation of the EMG tube recording method. A significant EMG amplitude decrease can also occur due to EMG tube displacement during surgical manipulation of the thyroid lobe or trachea. Using an EMG tube for signal recording make it difficult to tell an actual EMG amplitude decrease from a false one. In this study, applying these two novel IONM techniques, we detected 44 nerves with a significant EMG amplitude decrease during RLN dissection and gradual progressive amplitude recovery after releasing thyroid traction. The EMG signal recovers from LOS in 10 nerves and a 51-90% amplitude decrease in 34 nerves. The results suggest a high chance of signal recovery after a substantial amplitude decrease, even after LOS, if traction strain on the RLN was relieved in time. In cases with large tumors or complicated anatomical relationships between the RLN and Berry's ligament, a secondary EMG amplitude

TABLE 3 Type C EMG recovery pattern (incomplete EMG recovery without injury point detected on RLN).

| No. | $V_1$ (μV) | $R_1$ (μV) | $R_{2p}$ (μV) | $R_{2d}$ (μV) | $V_2$ (μV) | $R_{2p}/R_{2d}$ reduction# | Amplitude decrease (μV) + | Amplitude decrease ratio (%)* | VC mobility |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1716 | 2585 | LOS | LOS | LOS | nil | 702 | (73%) | fixed |
| 2 | 1251 | 1515 | 509 | 462 | 346 | nil- | LOS | ≒100% | weak |
| 3 | 1493 | 2331 | 1535 | 1516 | 912 | nil | LOS | ≒100% | sym |
| 4 | 2845 | 3020 | 1553 | 1622 | 1628 | nil | 532 | 82% | sym |
| 5 | 814 | 1422 | 852 | 872 | 414 | nil | 350 | 75% | sym |
| 6 | 1014 | 1141 | 816 | 826 | 816 | nil | 406 | 64% | sym |
| 7 | 2754 | 2800 | 1531 | 1524 | 1243 | nil | 501 | 82% | sym |
| 8 | 511 | 784 | 346 | 362 | 254 | nil | 152 | 81% | sym |
| 9 | 2490 | 2606 | 2260 | 2326 | 2166 | nil | 1135 | 56% | sym |
| 10 | 1758 | 3221 | 2834 | 2807 | 2060 | nil | 1434 | 55% | sym |
| 11 | 1675 | 2711 | 1907 | 2000 | 1528 | nil | 612 | 77% | sym |
| 12 | 1905 | 3005 | 2586 | 2491 | 1837 | nil | 1350 | 55% | sym |
| 13 | 2931 | 3385 | 2720 | 2626 | 2071 | nil | 1125 | 67% | sym |
| 14 | 1715 | 2686 | 2226 | 2233 | 1510 | nil | 1154 | 57% | sym |

The descriptions of #, +, *, and abbreviations are the same as those in Table 1.

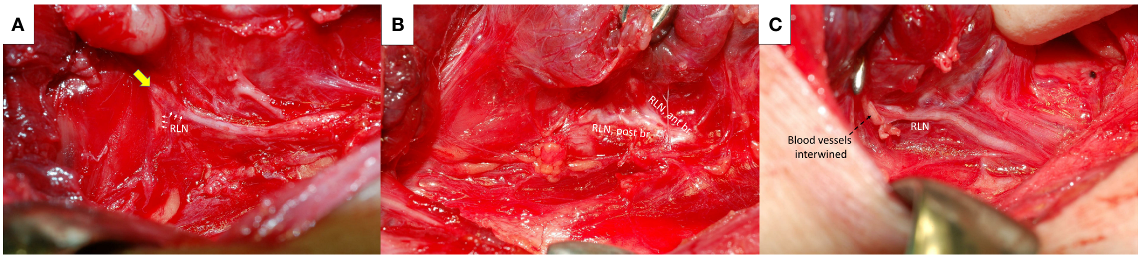



FIGURE 4
Recurrent laryngeal nerve (RLN) and Berry's ligament. The RLN (white arrows) was severely stretched upward at the region of Berry's ligament (yellow arrow) **(A)**. The anterior motor branch of the RLN penetrates Berry's ligament **(B)**. A surrounding blood vessel intertwined (black dotted arrows) with the RLN at the region of Berry's ligament **(C)**. ant br., anterior branch; post br., posterior branch.

decrease still occurred after restarting the surgical maneuver with gentle thyroid traction and careful nerve dissection due to unavoidable repeated traction. A persistent substantial amplitude decrease was found in 6 nerves after finishing RLN dissection (2 nerves with 81% and 92% $R_{2p}/R_{2d}$ ratio reduction; 4 nerves with unrecovered LOS). All 6 nerves developed temporary VC palsy. The results indicate that the RLN is highly vulnerable to repetitive stretching.

From the results of the five EMG signals ($V_1$-$R_1$-$R_{2p}$-$R_{2d}$-$V_2$) obtained from VN and RLN stimulation in this study, we found 3 types of EMG recovery patterns. Type A recovery showed complete EMG amplitude recovery, and the amplitudes of the $R_{2p}$, $R_{2d}$ and $R_1$ signals were similar (Table 1). Type B recovery showed incomplete EMG recovery when comparing $R_{2p}$ with $R_1$ signals, and it was combined with an injury point on the RLN and a significant reduction in the $R_{2p}/R_{2d}$ ratio (Table 2). Type C recovery showed incomplete EMG recovery, but without an injury point detected on the RLN (Table 3). In Type C recovery pattern, we can see that the amplitudes of the $R_{2p}$ and $R_{2d}$ signals are similar, but the amplitudes show a significant decrease compared with the $R_1$ signal (Figure 3). Case No. 2 in Table 3 did not show a reduction of the $R_{2p}/R_{2d}$ ratio. Still, it had a 66% amplitude decrease compared to the $R_{2p}$ and $R_1$ signals (509 vs. 1515 μV), and this case developed weak VC mobility postoperatively. This kind of nerve injury was unrecognized when using the EMG tube recording method since the amplitude change would be mistaken for EMG tube displacement. Overall, different recovery patterns have different vocal cord function outcomes, to elucidate the recovery patterns can assist surgeons in the intraoperative decision making and postoperative management (i.e. speech therapy and injection laryngoplasty).

Regarding LOS after traction injury, Chiang (7) reported that nerve injuries caused by overstretching of Berry's ligament could be divided into type 1 and type 2 stretch injuries. A type 1 stretch injury was caused by direct distress on the nerve and featured an injury point on the nerve. A type 2 stretch injury could be caused by pulling down the distal part of the RLN when the RLN was stretched excessively at the region of Berry's ligament, and the nerve might be injured at a higher position above the laryngeal entry point. From the evidence of type B and type C EMG recovery patterns, we find that type 1 or type 2 nerve injury occurs not only in LOS (7, 9, 30) but also in incomplete LOS. In this study, there were 3 nerves with type 1 LOS and 1 nerve with type 2 LOS. In addition, there were 13 nerves with a type 1 incomplete LOS with a weak point of nerve conduction detected on the RLN (case No. 4-16 in Table 2) and 13 nerves with a type 2 incomplete LOS with no weak point detected (case No. 2-14 in Table 3).

In our clinical experience, some patients with very late recovery of muscle tone under neuromuscular blockade agent and the accuracy of the amplitudes of V1 and R1 may be questionable. In this study, the time from the administration of rocuronium (0.3 mg/kg), neck positioning, skin preparation to skin incision is around 20 minutes. And the time from skin incision, skin flap elevation, pyramidal dissection, superior thyroid pole dissection to V1 and R1 signals takes another 30 minutes, which is even longer. From the results of our patients without nerve injury, the data of V1-R1-R2p-R2d-V2 showed stable. It indicates that neuromuscular blockade has been almost completely recovered through 50 minutes. Therefore, the use of R1 signal as basic reference baseline should be reliable, although more studies are necessary to prove it.

Several limitations of this study were noted. First, this was an observational study and lacked a control group. Second, the comparisons between conventional I-IONM, SDI, and C-IONM were not studied. Furthermore, the combined SDI and C-IONM technique is an optimal procedure (least missed EMG changes) with distinct advantages that merit evaluation by a specific design study. Third, the recovery time might differ between type A, B, and C EMG recovery patterns in this study. When the nerve recovers quickly, the surgeon tends to wait and observe until the signal reaches a stable amplitude; when the nerve recovers slowly, the surgeon tends to perform surgical dissection of the contralateral or other regions first. Therefore, no exact recovery time can be provided in the current study, but a gentle thyroid traction and nerve dissection is strongly recommended after adverse EMG event. Fourth, the patient number of each recovery type is relatively small; however, the characteristics of each recovery type can be clearly shown in this study. Further large-scale studies in multiple centers are helpful for the analysis of the clinical presentation in the different recovery types.

## Conclusion

A significant EMG amplitude decrease and progressive recovery after releasing thyroid traction is the characteristic feature of traction strain on the RLN during thyroid surgery. In this study, early detection and release of thyroid traction results in intraoperative EMG recovery and helps to avoid a signal deterioration to an unrecoverable LOS. Gentle traction of the thyroid lobe is recommended during the entire course of the operation, and frequent stimulation of the RLN is necessary for the early detection of EMG amplitude changes, particularly when using a stimulating probe for nerve stimulation. Overall, different recovery patterns result in different vocal cord function outcomes which elucidate that the recovery patterns can assist surgeons in the intraoperative decision making and postoperative management.

## Data availability statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding authors.

## Ethics statement

Ethical approval of this study was obtained from the Kaohsiung Medical University Hospital Institutional Review Board (KMUHIRB-E(I)-20210358). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## Author contributions

Supervision – T-ZH, W-HY, C-WW, GD, and F-YC; Materials – C-FL, T-ZH, Y-CS, T-YH, and F-YC; Data Collection and Processing – K-LC, ChihCW, ChieCW , and Y-CS; Analysis and Interpretation – K-LC, C-FL, W-HVY, T-YH, and F-YC; Literature Search – K-LC, ChihCW, ChieCW , T-YH, and F-YC; Writing Manuscript – All authors. All authors have read and agreed to the published version of the manuscript.

## Funding

This study was supported by grants from Kaohsiung Medical University Hospital, Kaohsiung Medical University (KMUH110-0R51), and Ministry of Science and Technology (MOST 110-2314-B-037-104-MY2, MOST 110-2314-B-037-120, MOST 111-2628-B-037-007), Taiwan.

## Acknowledgments

The authors would like to thank all the patients included in this study.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

## References

1. Karlan MS, Catz B, Dunkelman D, Uyeda RY, Gleischman S. A safe technique for thyroidectomy with complete nerve dissection and parathyroid preservation. *Head Neck Surg* (1984) 6(6):1014–9. doi: 10.1002/hed.2890060606

2. Jatzko GR, Lisborg PH, Müller M, Wette VM. Recurrent nerve palsy after thyroid operations–principal nerve identification and a literature review. *Surgery* (1994) 115(2):139–44.

3. Steurer M, Passler C, Denk DM, Schneider B, Niederle B, Bigenzahn W. Advantages of recurrent laryngeal nerve identification in thyroidectomy and parathyroidectomy and the importance of preoperative and postoperative laryngoscopic examination in more than 1000 nerves at risk. *Laryngosc* (2002) 112(1):124–33. doi: 10.1097/00005537-200201000-00022

4. Chiang F-Y, Wang L-F, Huang Y-F, Lee K-W, Kuo W-R. Recurrent laryngeal nerve palsy after thyroidectomy with routine identification of the recurrent laryngeal nerve. *Surgery* (2005) 137(3):342–7. doi: 10.1016/j.surg.2004.09.008

5. Snyder SK, Lairmore TC, Hendricks JC, Roberts JW. Elucidating mechanisms of recurrent laryngeal nerve injury during thyroidectomy and parathyroidectomy. *J Am Coll Surg* (2008) 206(1):123–30. doi: 10.1016/j.jamcollsurg.2007.07.017

6. Dionigi G, Wu C-W, Kim HY, Rausei S, Boni L, Chiang F-Y. Severity of recurrent laryngeal nerve injuries in thyroid surgery. *World J Surg* (2016) 40 (6):1373–81. doi: 10.1007/s00268-016-3415-3

7. Chiang F-Y, Lu I-C, Kuo W-R, Lee K-W, Chang N-C, Wu C-W. The mechanism of recurrent laryngeal nerve injury during thyroid surgery—the application of intraoperative neuromonitoring. *Surgery* (2008) 143(6):743–9. doi: 10.1016/j.surg.2008.02.006

8. Liu M-Y, Chang C-P, Hung C-L, Hung C-J, Huang S-M. Traction injury of recurrent laryngeal nerve during thyroidectomy. *World J Surg* (2020) 44(2):402–7. doi: 10.1007/s00268-019-05178-6

9. Wu C-W, Hao M, Tian M, Dionigi G, Tufano RP, Kim HY, et al. Recurrent laryngeal nerve injury with incomplete loss of electromyography signal during monitored thyroidectomy—evaluation and outcome. *Langenb Arch Surg* (2017) 402(4):691–9. doi: 10.1007/s00423-016-1381-8

10. Liu N, Chen B, Li L, Zeng Q, Sheng L, Zhang B, et al. Mechanisms of recurrent laryngeal nerve injury near the nerve entry point during thyroid surgery: A retrospective cohort study. *Int J Surg* (2020) 83:125–30. doi: 10.1016/j.ijsu.2020.08.058

11. Wu C-W, Dionigi G, Sun H, Liu X, Kim HY, Hsiao P-J, et al. Intraoperative neuromonitoring for the early detection and prevention of rln traction injury in thyroid surgery: A porcine model. *Surgery* (2014) 155(2):329–39. doi: 10.1016/j.surg.2013.08.015

12. Brauckhoff K, Aas T, Biermann M, Husby P. EMG changes during continuous intraoperative neuromonitoring with sustained recurrent laryngeal nerve traction in a porcine model. *Langenb Arch Surg* (2017) 402(4):675–81. doi: 10.1007/s00423-016-1419-y

13. Schneider R, Randolph GW, Sekulla C, Phelan E, Thanh PN, Bucher M, et al. Continuous intraoperative vagus nerve stimulation for identification of imminent recurrent laryngeal nerve injury. *Head Neck* (2013) 35(11):1591–8. doi: 10.1002/hed.23187

14. Schneider R, Bures C, Lorenz K, Dralle H, Freissmuth M, Hermann M. Evolution of nerve injury with unexpected emg signal recovery in thyroid surgery using continuous intraoperative neuromonitoring. *World J Surg* (2013) 37(2):364–8. doi: 10.1007/s00268-012-1853-0

15. Ku D, Hui M, Cheung P, Chow O, Smith M, Riffat F, et al. Meta-analysis on continuous nerve monitoring in thyroidectomies. *Head Neck* (2021) 43(12):3966–78. doi: 10.1002/hed.26828

16. Kandil E, Mohsin K, Murcy MA, Randolph GW. Continuous vagal monitoring value in prevention of vocal cord paralysis following thyroid surgery. *Laryngosc* (2018) 128(10):2429–32. doi: 10.1002/lary.27144

17. Schneider R, Randolph GW, Barczynski M, Dionigi G, Wu C-W, Chiang F-Y, et al. Continuous intraoperative neural monitoring of the recurrent nerves in thyroid surgery: A quantum leap in technology. *Gland Surg* (2016) 5(6):607. doi: 10.21037/gs.2016.11.10

18. Barber SR, Liddy W, Kyriazidis N, Cinquepalmi M, Lin BM, Modi R, et al. Changes in electromyographic amplitudes but not latencies occur with endotracheal tube malpositioning during intraoperative monitoring for thyroid surgery: Implications for guidelines. *Laryngosc* (2017) 127(9):2182–8. doi: 10.1002/lary.26392

19. Zhang D, Wu C-W, Wang T, Zhao Y, Kim HY, Pino A, et al. Drawbacks of neural monitoring troubleshooting algorithms in transoral endoscopic thyroidectomy. *Langenb Arch Surg* (2021) 406(7):2433–40. doi: 10.1007/s00423-021-02217-6

20. Chiang F-Y, Lee K-W, Chen H-C, Chen H-Y, Lu I-C, Kuo W-R, et al. Standardization of intraoperative neuromonitoring of recurrent laryngeal nerve in thyroid operation. *World J Surg* (2010) 34(2):223–9. doi: 10.1007/s00268-009-0316-8

21. Yalçın B, Ozan H. Detailed investigation of the relationship between the inferior laryngeal nerve including laryngeal branches and ligament of berry. *J Am Coll Surg* (2006) 202(2):291–6. doi: 10.1016/j.jamcollsurg.2005.09.025

22. Yalcxin B. Anatomic configurations of the recurrent laryngeal nerve and inferior thyroid artery. *Surgery* (2006) 139(2):181–7. doi: 10.1016/j.surg.2005.06.035

23. John A, Etienne D, Klaassen Z, Shoja MM, Tubbs RS, Loukas M. Variations in the locations of the recurrent laryngeal nerve in relation to the ligament of berry. *Am Surg* (2012) 78(9):947–51. doi: 10.1177/000313481207800933

24. Chiang F-Y, Lu I-C, Chen H-C, Chen H-Y, Tsai C-J, Hsiao P-J, et al. Anatomical variations of recurrent laryngeal nerve during thyroid surgery: How to identify and handle the variations with intraoperative neuromonitoring. *Kaohsiung J Med Sci* (2010) 26(11):575–83. doi: 10.1016/S1607-551X(10)70089-9

25. Chiang FY, Lu IC, Chang PY, Sun H, Wang P, Lu XB, et al. Stimulating dissecting instruments during neuromonitoring of rln in thyroid surgery. *Laryngosc* (2015) 125(12):2832–7. doi: 10.1002/lary.25251

26. Sung E-S, Lee J-C, Shin S-C, Choi S-W, Jung D-W, Lee B-J. Development of a novel detachable magnetic nerve stimulator for intraoperative neuromonitoring. *World J Surg* (2018) 42(1):137–42. doi: 10.1007/s00268-017-4159-4

27. Chiang F-Y, Wu C-W, Chang P-Y, Wu S-H, Chen H-Y, Lin Y-C, et al. Trans-thyroid cartilage recording for neural monitoring of the recurrent laryngeal nerve in thyroid surgery. *Laryngosc* (2020) 130(4):E280–E3. doi: 10.1002/lary.28049

28. Liddy W, Lawson BR, Barber SR, Kamani D, Shama M, Soylu S, et al. Anterior laryngeal electrodes for recurrent laryngeal nerve monitoring during thyroid and parathyroid surgery: New expanded options for neural monitoring. *Laryngosc* (2018) 128(12):2910–5. doi: 10.1002/lary.27362

29. Chiang FY, Lu IC, Chang PY, Dionigi G, Randolph GW, Sun H, et al. Comparison of EMG signals recorded by surface electrodes on endotracheal tube and thyroid cartilage during monitored thyroidectomy. *Kaohsiung J Med Sci* (2017) 33(10):503–9. doi: 10.1016/j.kjms.2017.06.014

30. Wu C-W, Wang M-H, Chen C-C, Chen H-C, Chen H-Y, Yu J-Y, et al. Loss of signal in recurrent nerve neuromonitoring: Causes and management. *Gland Surg* (2015) 4(1):19. doi: 10.3978/j.issn.2227-684X.2014.12.03