Risk Factors for Thyroid Surgery–Related Unilateral Vocal Fold Paralysis

Hung-Chun Chen, MD ©; Yu-Cheng Pei, MD, PhD; Tuan-Jen Fang, MD

The prevalence of UVFP is thus increasing with the increasing frequency of surgeries for various diseases.2–5 Although previous studies have shown recent increases in the proportion of iatrogenic UVFP induced by surgeries such as cardiac, carotid, esophageal, and pulmonary surgeries, thyroid surgery remains the major cause of UVFP.2,4 The incidence of vocal fold paralysis caused by thyroid surgery is reported to be 1.5% to 5.3%, among whom 15% to 17% of cases will have permanent vocal fold palsy.6–10

Laryngeal electromyography (LEMG) is the gold standard for identifying the lesioned nerve in patients with UVFP, providing diagnostic, functional, and prognostic information.11–15 Quantitative LEMG has been proposed to evaluate the severity of denervation further, by analyzing the frequency of turns that reflect the remaining muscle recruitment.16 Simultaneous external branch superior laryngeal nerve (EBSLN) injury can also be revealed by LEMG evaluation of cricothyroid (CT) muscle.

Thyroid surgery–related UVFP has a distinct clinical presentation, including greater involvement of the EBSLN, compared with UVFP caused by other surgeries.17,18 However, thyroid surgery comprises a wide spectrum of diagnoses from benign to malignant lesions, and the types of surgery range from minimally invasive to radical procedures, such as total thyroidectomy with neck dissection (TTND). The incidence of UVFP may be different among the procedures but has not been concluded. Results from Ahn et al. showed that the UVFP rate is

INTRODUCTION

Unilateral vocal fold paralysis (UVFP) causes glottic insufficiency, resulting in a breathy voice, voice fatigue, and aspiration, further limiting the patient’s quality of life.1 Surgical injury is the most common cause of UVFP.2

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From the Department of Otolaryngology-Head and Neck Surgery (H.-C.C., Y.-C.P.); Center of Vascularized Tissue Allograft (Y.-C.P.), Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan; the Healthy Aging Research Center (Y.-C.P.); and the School of Medicine (Y.-C.P., T.-J.F.), Chang Gung University, Taoyuan, Taiwan.

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H.-C. C. and Y.-C.P. contributed equally to this study.

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Send correspondence to Tuan-Jen Fang, MD, Chang Gung Memorial Hospital, No. 5 Fushing Street, Taoyuan 333, Taiwan. E-mail: fang3109@cgmh.org.tw

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higher in specific thyroidectomy with neck dissection but not noted in Sancho’s report.19,20 The combining of EBSLN has also not been reported in the above two reports due to lack of LEMG confirmation.

Novel intraoperative nerve monitoring (IONM) for laryngeal nerves is being developed and may reduce the risk of UVFP following thyroid surgery.21,22 Regularly performing IONM during thyroid surgery was suggested, but its cost-effectiveness remains unclear.23 A more effective application of IONM is reasonable in patients with higher risks.24 To this end, this study aimed to identify the risk factors for thyroid surgery–related UVFP by analyzing patient demographics, comorbidities, diagnosis, and surgery type. We also used comprehensive assessments, including quantitative LEMG and quality of life assessments, to characterize the disease presentations in these patients.

MATERIALS AND METHODS

Human Subjects

This study included two subject populations: patients who received thyroid-related surgery from April 2011 to February 2016 in a medical center in Taiwan and were reviewed retrospectively by searching the Health Insurance Surgical Orders and by chart review; and patients with symptoms or signs of vocal fold palsy who presented after thyroid surgery and were referred to the otolaryngology outpatient clinic for further evaluation. Written informed consent was obtained from each participant in the second population before examination. UVFP and bilateral vocal fold paralysis (BVFP) were confirmed by transnasal laryngoscopy, and UVFP was further confirmed by videolaryngostroboscopy and needle LEMG. The two patient populations were combined for analysis. Patients were excluded if they had an uncertain diagnosis or follow-up, were younger than 20 years, or had BVFP. All aspects of the study were approved by the Human Studies Research Committee of Chang Gung Medical Foundation.

Procedures

Patients with thyroid surgery–related UVFP underwent assessments including LEMG with quantitative analysis, videolaryngostroboscopy, the Voice Outcome Survey (VOS) questionnaire for voice-related quality of life, and the Short Form-36 (SF-36) Health Survey quality-of-life questionnaire. These assessments were performed within 2 weeks of the day of LEMG assessment.

LEMG Examination

The standard protocol for needle LEMG was performed by a board-certified otolaryngologist (T.-J.F.) and a physiatrist (Y.-C.P.). The diagnosis of denervation changes of the recurrent laryngeal nerve (RLN) or concomitant EBSLN was based on abnormal findings in the thyroarytenoid-lateral cricoarytenoid (TA/LCA) and CT muscles, respectively. Patients rested on an operating table with the neck extended and head supported by the adjustable head rest. The LEMG needle-insertion site was injected subcutaneously with 0.3 to 0.5 mL of 2% lidocaine before the examination. LEMG was performed using a concentric needle electrode with a surface-ground electrode adhered to the forehead. For the TA/LCA muscle complex, the electrode was inserted through the cricothyroid membrane at an angle 15° superiorly and 30° laterally and off-midline. The patient was asked to produce three series of /i/ sounds at three different intensities (low, moderate, and as high as possible), with each sound lasting at least 400 ms and each inter-/i/ interval lasting approximately 200 ms. For the CT muscle, the electrode was angled 50° laterally and inserted about 5 mm lateral to the midline at the level of the center of the cricothyroid membrane. The patient was asked to produce three upward glissando /i/ sounds at conversational loudness, with each inter-/i/ interval lasting about 3 sec. Raw LEMG traces were recorded for offline quantitative analysis with sweep speeds of 10 ms per division and a gain of 200 μV per division.

Spontaneous activity and insertional activity were evaluated first. Recruitment analysis and semiquantitative motor-unit analysis were then performed, specifically when the rise time of a motor unit action potential was <0.6 ms, indicating a close proximity to the recorded motor unit. A Nicolet Viking Select (Cardinal Health, Dublin, OH) was used with a band-pass filter set between 20 and 10 kHz. An abnormal LEMG was defined as the occurrence of spontaneous activities (such as positive sharp wave, fibrillation, or complex repetitive discharge), >30% polyphasia, or decreased interference pattern (reduced, discrete, or no interference pattern).

Quantitative LEMG Analysis

We designed a MATLAB (MathWorks, Natick, MA)-based program to analyze the raw LEMG data. The raw LEMG waveforms were initially binned into nonoverlapping epochs. The epoch duration for the TA/LCA was 200 ms. The timing of each turn and its amplitude were localized using an automatic algorithm. Specifically, a turn was defined by a change in polarity with an amplitude ≥100 μV before and after the change, to exclude noise-related peaks. Turn frequency was computed for each epoch as the number of turns divided by the epoch duration. For each muscle, the turn frequencies for the epochs were averaged with turn frequencies that ranked among the top three epochs, to yield the peak turn frequency.

Statistical Analysis

Differences between groups were compared using Student t tests for continuous data and χ2 or Fisher exact tests for nominal data (such as sex, preoperative diagnosis of thyroid lesion, comorbidity, and type of surgery). All variables that were significant in univariate analyses were further analyzed by using a stepwise multivariate logistic regression model to estimate odds ratios and 95% confidence intervals. The level of significance was defined as P < .05.

RESULTS

This study reviewed patients who received thyroid-related surgeries. None received IONM during the thyroid surgeries. The procedures were performed by general surgeons. A total of 3,527 patients receiving thyroid surgery were reviewed, among whom 704 patients were excluded because of uncertain diagnosis or follow-up (n = 689) or because they were under 20 years old (n = 15) (Fig. 1).

Sixty patients (12 males and 48 females) were noted to suffer UVFP, and eight developed BVFP, yielding overall UVFP and BVFP incidences of 2.1% and 0.3%, respectively (Fig. 2). Due to the limited sample size, the eight
patients with BVFP were analyzed by case characteristics and were not included in the statistical analysis.

**Demographics**

Regarding the surgery type, 1,273 patients underwent lobectomy (LB), 158 TTND, 982 total thyroidectomy (TT), 57 unilateral subtotal thyroidectomy (UST), and 345 bilateral subtotal thyroidectomy (BST). Patients with UVFP (UVFP group) were older than those without UVFP (no-UVFP group) (57.0 ± 13.3 vs. 50.9 ± 13.9; \( P < .001 \)). The UVFP group had a higher proportion of patients with thyroid malignancy (benign/malignant: 35/25) than the no-UVFP group (benign/malignant: 2011/744) (\( P = .02 \)). Patients in the UVFP group were also more likely to have hypertension (6/60, 10.0% vs. 105/2,755, 3.8%; \( P = .03 \)) compared with the no-UVFP group (Table I).

According to the different types of surgery, UVFP developed in 18 with LB (1.4%), 10 patients with TTND (6.3%), 25 with TT (2.5%), 0 with UST (0%), and seven with BST (2.0%) (Fig. 3A), with the highest incidence in the TTND group and the lowest in the UST group. Among the patients undergoing TTND (n = 10), five underwent central neck dissection, four central with lateral neck dissection, and one lateral neck dissection. By multivariate logistic regression analysis, the risk of UVFP was higher in patients over 60 years old (odds ratio, 1.89; 95% confidence interval, 1.01-3.26; \( P = .01 \)) and highest in patients undergoing TTND (odds ratio, 3.47; 95% confidence interval, 1.42-8.44; \( P = .006 \)).

**UVFP in Patients With Thyroid Malignancies**

Among 769 patients with thyroid malignancies, 143 underwent TTND and 626 underwent thyroidectomy without neck dissection. The incidence of UVFP was significantly higher in patients receiving concurrent neck dissection than in those without (13/143, 9.1% vs. 27/626, 4.3%; \( P = .03 \)).

**Patients With and Without EBSLN Involvement**

All of the 2,815 patients were further divided into two groups according to the presence of UVFP combining EBSLN injury revealed by LEMG (Table II). Patients with EBSLN injury included a higher proportion of patients with thyroid malignancies (benign/malignant: 9/10) than the no-EBSLN injury group (benign/malignant: 2037/759) (\( P = .02 \)). They were
also more likely to have diabetes mellitus (DM) (3/19, 15.8% vs. 43/2796, 1.5%; \( P = .003 \)). The incidences of EBSLN involvement among patients with UVFP differed among surgery types, being highest in the TTND group (5/158, 3.2%) and lowest in the UST group (0/57, 0%) (Fig. 3B). By multivariate logistic regression analysis, the risk of UVFP combining EBSLN injury was higher in patients with DM (odds ratio, 14.19; 95% confidence interval, 3.80-52.94; \( P < .001 \)) and highest in patients undergoing TTND (odds ratio, 6.77; 95% confidence interval, 1.51-30.29; \( P = .007 \)).

UVFP Patients With and Without EBSLN Involvement

The 60 patients with UVFP were divided into two subgroups according to the LEMG findings: patients with only RLN and those with RLN + EBSLN injuries (Table III). Nineteen of the 60 UVFP patients (31.7%) had concomitant EBSLN injury. Most of the EBSLN injuries (n = 16, 84.2%) were at the same side as RLN injury, whereas one (5.3%) was on the contralateral side and the other two (10.5%) on both sides. There was no difference between the RLN and RLN + EBSLN groups in terms of sex, age, or the side of UVFP.

Quantitative LEMG

Quantitative recruitment analysis revealed no difference in turn frequency or turn ratio of the lesioned TA/LCA muscle complex between patients with RLN and those with RLN + EBSLN injuries, indicating an equal level of RLN denervation. The turn frequency of the CT muscle on the lesioned side was significantly lower in the RLN + EBSLN group compared with the RLN group.
### TABLE I.
Demographics of Patients Undergoing Thyroid Surgery

|                         | No-UVFP Group | UVFP Group | \( P \) Value |
|-------------------------|---------------|------------|-------------|
| **No. of cases**        | 2,755 (97.9)  | 60 (2.1)   | 1.00        |
| **Sex (male/female)**   | 561/2,194     | 12/48      | <.001*      |
| **Age, yr**             | 50.9 ± 13.9   | 57.0 ± 13.3| <.001*      |
| **Malignancy status (benign/malignant)** | 2,011/744 | 35/25 | .02†       |
| **Comorbidity**         |               |            |             |
| Hypertension (yes/no)   | 105/2,650     | 6/54       | .03†        |
| Diabetes mellitus (yes/no) | 43/2,712 | 3/57   | .07         |
| Heart disease (yes/no)  | 10/2,745      | 1/59       | .21         |
| Stroke (yes/no)         | 7/2,748       | 0/60       | 1.00        |
| **Type of surgery**     |               |            | <.001*      |
| LB                      | 1,255 (45.6)  | 18 (30.0)  |             |
| TTND                    | 148 (5.4)     | 10 (16.7)  |             |
| TT                      | 957 (34.7)    | 25 (41.7)  |             |
| UST                     | 57 (2.1)      | 0 (0)      |             |
| BST                     | 338 (12.3)    | 7 (11.7)   |             |
| **Preoperative diagnosis** |         |            |             |
| Benign neoplasm         | 466 (16.9)    | 13 (21.7)  |             |
| Nontoxic uniodular goiter| 317 (11.5)   | 1 (1.7)    |             |
| Nontoxic multinodular goiter | 497 (18.0) | 7 (11.7)  |             |
| Nontoxic diffuse goiter  | 14 (0.5)      | 0 (0)      |             |
| Toxic nodular goiter    | 6 (0.2)       | 0 (0)      |             |
| Toxic multinodular goiter| 41 (1.5)     | 1 (1.7)    |             |
| Toxic diffuse goiter     | 637 (23.1)    | 12 (20.0)  |             |
| Thyrotoxicosis          | 30 (1.1)      | 2 (3.3)    |             |
| Thyroiditis             | 2 (0.1)       | 0 (0)      |             |
| Malignant neoplasm      | 745 (27.0)    | 24 (40.0)  |             |

Data are presented as mean ± standard deviation or as the number (percentage) of patients.

*\( P < .001. \)

†\( P < .05. \)

BST = bilateral subtotal thyroidectomy; LB = lobectomy; TT = total thyroidectomy without neck dissection; TTND = total thyroidectomy with neck dissection; UST = unilateral subtotal thyroidectomy; UVFP = unilateral vocal fold paralysis.

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**A. UVFP incidence**

**B. EBSLN injury incidence**

Fig. 3. Comparison of incidence across surgery types. (A) The incidence of UVFP is significantly higher in the TTND group. (B) The incidence of concomitant EBSLN injury is the highest in the TTND group. *\( P < .05. \) **\( P < .001. \) BST = bilateral subtotal thyroidectomy; EBSLN = external branch of superior laryngeal nerve; LB = lobectomy; TT = total thyroidectomy without neck dissection; TTND = total thyroidectomy with neck dissection; UST = unilateral subtotal thyroidectomy; UVFP = unilateral vocal fold paralysis. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]
There was no difference in VOS score (31.1 ± 16.7 vs. 29.0 ± 16.8; P = .64) between the RLN and RLN + EBSLN groups. There were also no differences between the two groups in any quality-of-life domains measured by the SF-36, including general health perceptions (P = .08), vitality (P = .462), physical functioning (P = .40), bodily pain (P = .63), physical role functioning (P = .79), emotional role functioning (P = .60), social functioning (P = .25), and mental health (P = .39).

**BVFP Characteristics**

Eight of the 68 patients with vocal fold paralysis had BVFP. One of these patients had no dyspnea, whereas the rest had dyspnea of differing severities. Four of these received elective tracheostomy, and three received intralaryngeal botulinum toxin type A (BTX-A; Allergan, County Mayo, Ireland) injections (Table IV).

**DISCUSSION**

Thyroid diseases, including benign and malignant lesions, are common clinical problems, and the incidence of thyroid cancer has increased about twofold over the past 15 years. The 2015 American Thyroid Association (ATA) guidelines suggest that surgical therapy should be considered for malignancies and growing benign nodules with compressive or structural symptoms, though the extent of surgery for differentiated thyroid cancer depends on the tumor stage, cell types, and presenting function of the larynx. Notably, however, thyroid surgery remains the leading cause of UVFP, and it is therefore necessary to identify the risk factors related to UVFP in patients undergoing thyroidectomy.
The present study revealed that the incidence of thyroid surgery–related UVFP was higher in older patients, and patients with DM had higher risk for UVFP combining EBSLN injury. Among the different types of surgery, TTND was associated with the highest incidences of both UVFP and EBSLN injury. These results will provide useful information for patient consultations before surgery. Aging increases the risk of malignancy and also of UVFP, according to our results. However, the decade-specific disease progression rate

### TABLE III.
Demographics, Laryngeal Muscle Recruitment, and Quality of Life in Patients With Thyroid Surgery–Related Unilateral Vocal Fold Paralysis

|                          | RLN Group | RLN + EBSLN Group | P Value |
|--------------------------|-----------|-------------------|--------|
| No. of cases             | 41 (68.3) | 19 (31.7)         |        |
| Sex (male/female)        | 6/35      | 6/13              | .17    |
| Age, yr                  | 53.0 ± 13.5 | 55.2 ± 14.2      | .57    |
| Side of UVFP (left/right)| 19/22     | 11/8              | .58    |
| Preoperative diagnosis (benign/malignant) | 26/15 | 14/5              | .56    |

#### Recruitment analysis

- Lesioned TA/LCA (turn/s): 306.0 ± 255.1 vs 217.9 ± 203.8, P = .19
- Normal TA/LCA (turn/s): 890.2 ± 287.6 vs 872.5 ± 339.7, P = .84
- Turn ratio of TA/LCA: 0.35 ± 0.29 vs 0.32 ± 0.33, P = .66
- Lesion side of CT (turn/s): 753.7 ± 244.7 vs 326.6 ± 221.3, P < .001
- Normal side of CT (turn/s): 846.7 ± 327.0 vs 664.6 ± 412.7, P = .07
- Turn ratio of CT: 1.01 ± 0.48 vs 0.61 ± 0.58, P = .006

#### SF-36

- Vitality: 53.3 ± 16.1 vs 49.7 ± 18.8, P = .46
- Physical functioning: 77.9 ± 19.5 vs 82.1 ± 14.2, P = .40
- Bodily pain: 79.3 ± 19.1 vs 76.5 ± 22.4, P = .63
- General health perceptions: 53.8 ± 19.8 vs 44.0 ± 18.9, P = .08
- Physical role functioning: 41.3 ± 46.9 vs 44.7 ± 49.0, P = .79
- Emotional role functioning: 54.1 ± 46.4 vs 47.3 ± 44.9, P = .60
- Social functioning: 57.7 ± 26.3 vs 49.5 ± 23.5, P = .25
- Mental health: 63.0 ± 17.9 vs 58.7 ± 17.4, P = .39

Data are presented as mean ± standard deviation or as the number (percentage) of patients.

*P < .001.

†P < .01.

CT = cricothyroid muscle; EBSLN = external branch of superior laryngeal nerve; RLN = recurrent laryngeal nerve; SF-36 = Short Form-36 Health Survey; TA/LCA = thyroarytenoid/lateral cricoarytenoid muscle complex; UVFP = unilateral vocal fold paralysis; VOS = Voice Outcome Survey.

### TABLE IV.
Summary of Eight Patients With Thyroid Surgery–Related Bilateral Vocal Fold Paralysis

| Sex | Age (Years) | Diagnosis                                      | Surgery Type | Surgery Duration (Minutes) | Symptoms and Signs                      | Intervention        | Time to Intervention (Days) |
|-----|-------------|------------------------------------------------|--------------|---------------------------|----------------------------------------|---------------------|----------------------------|
| Female | 45       | Follicular adenoma and parathyroid gland hyperplasia | LB          | 234                     | Dyspnea, choking                       | Tracheostomy       | 66                         |
| Female | 51       | Recurrent PTC with neck metastasis              | LB          | 219                     | Dyspnea                               | Tracheostomy       | 69                         |
| Female | 54       | Nodular hyperplasia                             | LB          | 144                     | Dyspnea                               | Tracheostomy       | 6                          |
| Female | 40       | PTC, follicular variant, and nodular hyperplasia | TT          | 310                     | Dyspnea                               | Tracheostomy       | 28                         |
| Female | 41       | PTC, follicular variant and nodular hyperplasia  | TT          | 237                     | Dyspnea                               | BTX-A injection    | 56                         |
| Female | 54       | Nodular hyperplasia                             | TT          | 212                     | Exertional dyspnea, falsetto           | BTX-A injection    | 638                        |
| Female | 78       | PTC, pT3N1b                                      | TTND        | 211                     | Exertional dyspnea, choking            | BTX-A injection    | 348                        |
| Female | 43       | Diffuse hyperplasia with nodular formations     | TT          | 152                     | Dysphonia, choking                     | Observation        | —                          |

BTX-A = botulinum toxin type A; LB = lobectomy; PTC = papillary thyroid carcinoma; TT = total thyroidectomy; TTND = total thyroidectomy with neck dissection.
declines with age in patients with thyroid microcarcinoma. In light of the increased risk of surgical complications, we agree with Miyauchi in recommending active surveillance rather than aggressive surgery in elderly patients.

The role of neck dissection in thyroid malignancies remains arguable. In a cohort of 155 patients with papillary thyroid cancer, no significant difference in the incidences of vocal fold paralysis between TTND and TT were reported. However, Ahn et al. reported that, in the case of cN0 neck, TTND resulted in a significantly higher rate of vocal fold paralysis than only TT, and they suggested that TTND should be reserved for patients with local or neck recurrences. Similar to the results from Ahn et al., the present study showed that TTND was associated with a significantly higher risk of UVFP compared with surgery without neck dissections in patients with thyroid malignancies. However, for the oncologic control, the current ATA guidelines suggest TTND for clinically involved neck metastasis and for advanced primary tumors (T3, T4), with or without neck metastasis. Given the success of early temporary injection for UVFP, we suggest that radical surgical treatment should still be considered in patients with high-risk primary thyroid cancers, despite the risk of surgery-related UVFP. However, it is essential to emphasize the risks prior to surgery and try to preserve nerve function without impacting on the oncologic outcomes in those requiring surgery to manage thyroid cancer.

IONM is helpful in detecting laryngeal nerve during operation, but the benefit of reducing UVFP or the cost-effectiveness of routine use of IONM remains controversial. Visual identification was reported to be more cost-effective than IONM for identifying the RLN during thyroidectomy, whereas Al-Qurayshi et al. claimed the use of IONM has an economic advantage in cases receiving bilateral thyroid surgery as a result of the avoidance of bilateral nerve injury through surgical staging. The present study revealed that patients with thyroid malignancies who underwent TTND were at higher risk of postoperative UVFP, implying that IONM might be beneficial in this patient population. In addition, given a higher risk of UVFP, IONM might also be considered for older patients and those with DM scheduled for thyroidectomy.

Approximately one-third of patients in the current study who developed thyroid surgery–related UVFP had concomitant EBSLN injury. The risk of EBSLN injury induced by thyroid surgery has gained increasing attention, and the ATA recommends careful dissection of the superior pole of the thyroid gland to preserve the EBSLN. Jansson et al. found that nine of 20 patients undergoing thyroid surgery had superior laryngeal nerve (SLN) injury postoperatively, of whom three patients had partial SLN lesions before surgery, whereas Teitelbaum and Wenig found that one of 20 patients undergoing thyroid surgery had SLN injury. However, these studies did not consider the type of thyroid surgery or which patient groups were more likely to have EBSLN injury. In contrast, our study revealed that patients with DM were at particularly high risk. Furthermore, patients who underwent more radical procedures were at greater risk of EBSLN injury. These results highlight the need to consider the possible complications before carrying out thyroid surgeries.

The number of UVFP cases may be overestimated because some patients may have malignancy-related UVFP before surgery, which remained undiagnosed because of their silent clinical presentation. Patients with papillary thyroid cancer were reported to have a 50% chance to having RLN paralysis before surgery, though only 64% of them had dysphonia. A previous study showed that 1.3% of 1,923 patients who received thyroid surgery had preoperative vocal fold paralysis, and 76% of these were later proven to have malignancies. Preoperative assessment of vocal fold paralysis should thus be carried out in patients undergoing thyroid surgery, especially for thyroid malignancies.

This study had several potential limitations. First, retrospective data may have been missing, and the Health Insurance Surgical Orders may have been imprecise. Second, the surgeries were not all performed by the same surgeon, which may have resulted in variations in the incidences of nerve injuries. Third, the incidence of postoperative UVFP may have been overestimated because preoperative UVFP was not assessed routinely and may therefore have been underestimated in patients without notable symptoms or signs. It is therefore necessary to conduct a prospective cohort study including regular pre- and postoperative assessments to verify the incidence of thyroid surgery–related nerve injuries.

CONCLUSION

Patients receiving TTND are at the highest risk of both UVFP and concomitant EBSLN injury. Older patients are at increased risk of developing postoperative UVFP, whereas patients with DM are more likely to have EBSLN injury. The results have implications for necessary intraoperative nerve monitoring in such high-risk groups.

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