



Efficacy of Intraoperative Neuromonitoring in Reoperation for Recurrent Thyroid Cancer Patients

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Background: The use of intraoperative neuromonitoring (IONM) in thyroid surgery to preserve recurrent laryngeal nerve (RLN) function has been widely accepted. We aimed to evaluate the usefulness of IONM in reoperation for recurrent thyroid cancer patients to help identify the RLN and prevent vocal cord palsy (VCP).

Methods: We analyzed 121 consecutive patients (with IONM group, 48 patients; without IONM group, 73 patients) who underwent reoperation for recurrent thyroid cancer after total thyroidectomy from January 2009 to March 2019 in our institution without VCP due to previous operations. Data including age, sex, number of previous operations, histologic subtype of the malignancy at the initial operation, operation time, RLNs at risk, difficulty of RLN identification, surgical procedure, VCP, and other postoperative complications were reviewed. Vocal cord movement evaluations were performed preoperatively and at 2 weeks postoperatively to evaluate RLN function. In patients with VCP, additional evaluations were performed. VCP exceeding 12 months after surgery was considered permanent VCP.

Results: VCP was observed in six (12.5%) and 16 (21.9%) patients with and without IONM (P=0.189). Transient and permanent VCP were found in three (6.3%) and three (6.3%) patients with IONM (P=0.098 and P=0.982, respectively) versus in 12 (16.4%) and four (5.5%) patients without IONM.

Conclusion: The incidence of transient VCP seems to be lower in reoperations with IONM; however, there was no statistical significances. Further study will be needed to ascertain the efficacy of IONM in reoperation for recurrent thyroid cancer patients.

Keywords: Reoperation; Vocal cord paralysis; Recurrent laryngeal nerve; Thyroid neoplasms; Recurrence

INTRODUCTION

Thyroid cancer is one of most common endocrine malignancies. Papillary thyroid carcinoma and follicular thyroid carcinoma account for over 90% of all thyroid cancers and have an excellent prognosis, and medullary thyroid carcinoma accounts for approximately 5% of all thyroid cancers [1]. The incidence of thyroid cancer has rapidly increased worldwide during the last

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three decades. Therefore, the number of thyroid cancer surgeries is also gradually increasing.

Vocal cord palsy (VCP) due to injury to recurrent laryngeal nerve (RLN) after thyroid cancer surgery is one of the most severe complications. Hoarseness and swallowing difficulties may occur due to unilateral VCP, and phonation disorders, stridor and respiratory failure may occur due to bilateral VCP [2,3]. According to reported data, the incidences of transient VCP and permanent VCP after thyroidectomy are 2% to 11% and 0.6% to 1.6%, respectively [4-6]. The use of intraoperative neuromonitoring (IONM) during thyroid surgery can help locate and easily expose the RLN [1]. Recently, nerve monitoring in thyroid cancer operations has been shown to help reduce the risk of RLN injury and is a widely accepted procedure in thyroid surgery [7,8]. However, there is a controversy for usefulness of IONM in thyroid surgery to reduce the incidence of RLN injury [9,10].

The risk of recurrent thyroid cancer ranges between 5% and 20% [11]. Usually, recurrence occurs within a few years after the initial operation either in the operation site or remnant thyroid [11]. In repeat thyroid surgery, operators, even skillful and experienced surgeons, have difficulty identifying the RLN because of anatomical changes and reparative fibrosis following the primary surgery [1,12]. According to a study by Barczynski et al. [13], the incidences of transient and permanent VCP in thyroid reoperation with IONM were 2.6% and 1.4%, respectively. In contrast, the incidence of transient and permanent VCP after repeat thyroid surgery without IONM was 6.3% and 2.4%, respectively [13].

However, there is little information focused on the usefulness of IONM in reoperation for recurrent thyroid cancer patients to prevent RLN injury. Previous studies compared transient and permanent VCP between groups with and without IONM to analyze the protective effect of IONM for VCP, but these studies included fewer than 50 cases of recurrent thyroid cancer [13, 14]. Salari et al. [15] analyzed surgical complications, including permanent VCP, in 181 patients who underwent reoperation with IONM for recurrent thyroid cancer, and they reported that permanent VCP was present in 13.8% of patients; however, they did not compare VCP with or without IONM.

The purpose of this study was to evaluate whether the use of IONM in reoperation for recurrent thyroid cancer patients can reduce the incidence of VCP following total thyroidectomy for thyroid cancer.

METHODS

Selection of patients and data collection

This retrospective cohort study was approved by the Institutional Review Board of Seoul National University Hospital (approval ID: H-2004-151-1118). Between January 2009 and March 2019, a total of 273 consecutive patients who underwent reoperation for recurrent thyroid cancer after total thyroidectomy in the Department of Surgery of Seoul National University Hospital (Seoul, Korea) were enrolled. Twenty-seven patients identified with VCP during the preoperative laryngoscopy examination were excluded. And 125 patients who underwent lateral neck dissection were also excluded. Finally, a total of 121 patients (34 male and 87 female; mean age, 49.3 ± 12.8 years) were included in the study to evaluate whether IONM could reduce RLN injury during reoperation for recurrent thyroid cancer. A total of 48 patients (11 men and 37 women; mean age, 47.0 ± 12.8 years) underwent reoperation with IONM, and 73 patients (23 male and 50 female; mean age, 50.8 ± 12.7 years) underwent reoperation without IONM. The data included age. sex, number of previous operations, histologic subtype of the malignancy at the initial operation, operation time, RLNs at risk, difficulty of RLN identification on operation records, surgical procedure, VCP, and other postoperative complications. The difficulty of RLN identification was divided into two categories (easy or difficult) based on the operation record.

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Surgical technique

Preoperative neck ultrasonography and contrast-enhanced neck computed tomography were routinely performed for all patients. Through these imaging studies, the extent and location of recurrent thyroid cancer and the anatomical relationship between recurrent cancer and the trachea, esophagus, and other important structures were evaluated.

All operations were performed under general anesthesia. A single low dose of short-acting muscle relaxant (rocuronium) was given to the patient upon anesthesia induction. Anesthesia was maintained with a continuous infusion of propofol and remifentanil. In the IONM group, no other muscle relaxants were used during the operation.

Reoperation was performed through a previous scar in patients who had undergone conventional open thyroidectomy. The lateral approach was routinely adopted for reoperation [15]. However, a central approach could also be applied if the recurrent thyroid cancer was located at the medial portion of the trachea. Because of the presence of adhesions and postoperative changes, special care was taken to prevent injury to important structures, including the RLN, parathyroid, trachea, esophagus, and blood vessels. In operations with IONM, RLN identification was facilitated with a nerve mapping technique using the IONM system in operations without IONM, the RLN was visually identified to be low in the neck. Once the RLN was visually identified, it was carefully dissected along its course upwards toward the larynx [13].

IONM technique

The NIM Response 2.0 or 3.0 system (Medtronic Xomed, Jacksonville, FL, USA) was used for IONM of the RLN. Patients were intubated with an electromyographic endotracheal tube (EMG tube; NIM Standard Reinforced EMG Endotracheal Tube) with two electrodes imbedded in the wall of the endotracheal tube. The correct positioning of the surface electrode was tested before and after positioning the patient's head on the operating table under direct laryngoscopy by an anesthesiologist. Two grounding wires were placed in the subcutaneous tissues of the substernal area. Motor nerves were stimulated using the probe with an electric current of 1.0 mA and a frequency of 30 Hz. If the signal was not identified, the electric current was increased up to 3.0 mA. Identification of the intact RLN was confirmed by visualized potentials on a nerve integrity monitor over a threshold set at 100 mV and an audible "beep" for each vocalis muscle contraction [16]. We applied IONM following international guidelines (L1, V1, R1, R2, V2, and L2) [7].

Perioperative management and follow-up

Indirect laryngoscopy or laryngeal ultrasonography was mandatory for all patients before and after the operation. In patients with VCP at 2 weeks postoperatively, additional evaluations were performed at 3, 6, and 12 months until vocal cord movement recovered. VCP lasting longer than 12 months after surgery was considered permanent VCP. Vocal cord movements were graded as I: normal movements, II: diminished movements, III: no mobility. Grade II, and III were regarded as VCP [17].

Other complications, such as hypocalcemia, wound complications, hematoma, and seroma, were evaluated at 2 weeks, 3, 6, and 12 months after the operation.

Statistical analysis

All statistical analyses were performed using SPSS version 25 software (IBM Co., Armonk, NY, USA). Data are presented as the mean \pm standard deviation (range). The statistical significance of categorical variables (sex, histologic subtype of the malignan-

cy at the initial operation, nerves at risk, RLNs at risk, difficulty of RLN identification, VCP, and other postoperative complications) was evaluated using the chi-square test, and Student's t test was used to compare continuous variables (age and operation time) between the two groups. A P value less than 0.05 was considered statistically significant.

RESULTS

The clinicopathological characteristics of the patients are summarized in (Table 1). There were no significant differences between the two groups regarding age, sex, number of previous operations, and histologic subtype of the malignancy at the initial operation.

The mean age was 49.3 years (range, 20 to 85; with IONM, 47.0 years vs. without IONM, 50.8 years). The mean reoperation time was 98.8 minutes (range, 25 to 275; with IONM, 100.4 minutes vs. without IONM, 97.8 minutes). The most common number of previous operations was 1. The highest number of

Table 1. Patient Characteristics				
Variable	Total (<i>n</i> =121)	IONM (-) (<i>n</i> =73)	IONM (+) (<i>n</i> =48)	P value
No. of patients	121	73 (60.3)	48 (39.7)	
Age, yr	49.3±12.8 (20-85)	50.8 ± 12.7 (21-85)	47.0±12.8 (20-78)	0.104
Sex				0.304
Male	34 (28.1)	23 (31.5)	11 (22.9)	
Female	87 (71.9)	50 (68.5)	37 (77.1)	
No. of previous operations				0.529
1	85 (70.2)	50 (68.5)	35 (72.9)	
2	25 (20.7)	17 (23.3)	8 (16.7)	
3	10 (8.3)	6 (8.2)	4 (8.3)	
4	1 (0.8)	0	1 (2.1)	
Histologic subtype of the malignancy at the initial operation				0.296
PTC	113 (93.4)	67 (91.8)	46 (95.8)	
FTC	2 (1.7)	2 (2.7)	0	
MTC	5 (4.1)	4 (5.5)	1 (2.1)	
PTC+FTC	1 (0.8)	0	1 (2.1)	

Values are expressed as number (%) or mean \pm standard deviation (range).

IONM, intraoperative neuromonitoring; PTC, papillary thyroid cancer; FTC, follicular thyroid cancer; MTC, medullary thyroid cancer.

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surgeries previously performed for thyroid cancer was 4. There were no significant differences in the histologic subtypes of the malignancies at the initial operation. The year-by-year use of IONM in recurrent thyroid cancer operation is summarized in (Fig. 1).

Table 2 shows the surgical outcomes of the reoperations for recurrent thyroid cancer patients. There were no significant differences in operation time, RLNs at risk, surgical procedures, or joint operation between the groups with and without IONM.

Regarding RLN identification, the group with IONM had a

higher proportion of easy identifications (85.4%) than the group without IONM (72.6%); however, there was no significant difference (P=0.098). The incidence of other complications, including wound problems, and postoperative bleeding were not different between the two groups (P=0.333). In the group with IONM, three cases (6.3%; one mediastinal lymph node dissection, one partial resection of clavicle by thoracic surgery, and one wound revision by plastic surgery) of joint operations were performed, and in the group without IONM, three cases (4.1%; two mediastinal lymph node dissections, and one partial resec-



Fig. 1. Yearly distribution of recurrent thyroid cancer operations with regard to the use of intraoperative neuromonitoring (IONM) among patients treated in 2009 to 2019 (with IONM [n=48], without IONM [n=73]).

Variable	Total (<i>n</i> =121)	IONM (–) (<i>n</i> =73)	IONM (+) (<i>n</i> =48)	P value
Operation time, min	98.8±47.2 (25–275)	97.8±45.0 (29–275)	100.4±50.7 (25-263)	0.766
Recurrent laryngeal nerves at risk				0.274
1	109 (90.1)	64 (87.7)	45 (93.8)	
2	12 (9.9)	9 (12.3)	3 (6.2)	
Difficulty of RLN identification				0.098
Easy	94 (77.7)	53 (72.6)	41 (85.4)	
Difficult	27 (22.3)	20 (27.4)	7 (14.6)	
Surgical procedure				0.189
Operation site excision	13 (10.7)	8 (11.0)	5 (10.4)	
Central node dissection	21 (17.4)	10 (13.7)	11 (22.9)	
Central and lateral node dissection	87 (71.9)	55 (75.3)	32 (66.7)	
Postoperative hypocalcemia	4 (3.3)	3 (4.1)	1 (2.9)	0.542
Other complications				0.333
Wound problem	1 (0.8)	0	1 (2.9)	
Postoperative bleeding	1 (0.8)	0	1 (2.9)	
Joint operation	6 (5.0)	3 (4.1)	3 (6.3)	0.596

Values are expressed as mean±standard deviation (range) or number (%). IONM, intraoperative neuromonitoring; RLN, recurrent laryngeal nerve.

Vocal cord palsy	IONM (–) (<i>n</i> =73)	IONM (+) (<i>n</i> =48)	P value	
Transient	12 (16.4)	3 (6.3)	0.098	
Permanent	4 (5.5)	3 (6.3)	0.982	
Total	16 (21.9)	6 (12.5)	0.189	

tion of sternum by thoracic surgery) of joint operations were performed.

Table 3 shows the incidence of VCP after reoperation in recurrent thyroid cancer patients. VCP was observed in 12.5% (6/48) of patients with IONM and 21.9% (16/73) of patients without IONM (P=0.189). Transient and permanent VCP were present in 6.3% (3/48) and 6.3% (3/48) of patients with IONM versus in 16.4% (12/73) and 5.5% (4/73) of patients without IONM. The incidence of transient was lower in reoperations with IONM, however, there was no statistical significances.

We also analyzed the VCP rate according to RLNs at risk. A total of 133 nerves at risk were present during reoperation, including 51 nerves at risk in the group with IONM and 82 nerves at risk in the group without IONM. The number of RLNs at risk was defined as one in unilateral operations, and two in bilateral operations. There was no statistically significant differences in the incidence of VCP between the groups with IONM and without IONM (P=0.274).

Table 4 shows the incidence of VCP in patients according to the surgical extents with or without IONM. In operation site excision or central dissection only group, and central and lateral dissection group, there was no significant differences between the group with IONM and the group without IONM.

DISCUSSION

To the best of our knowledge, this is the largest study to date to compare VCP in patients undergoing reoperation with and without IONM for recurrent thyroid cancer following total thyroidectomy for thyroid cancer. In the present study, we could not find usefulness of IONM to reduce transient, and permanent VCP in reoperation for a previously dissected area.

The overall prognosis of differentiated thyroid cancer patients is favorable, but 5% to 20% of differentiated thyroid cancer patients have locoregional recurrence [11]. For most locoregional recurrences, surgery is the best treatment. However, even for
 Table 4. Incidence of Vocal Cord Palsy According to Surgical

 Procedures

Operation extent	Vocal cord palsy	IONM (-)	IONM (+)	P value
Operation site	Transient	3/18 (16.7)	0/16(0)	0.078
excision or central	Permanent	2/18 (11.1)	1/16 (6.3)	0.509
dissection only	Total	5/18 (27.8)	1/16 (6.3)	0.101
(<i>n</i> =34)				
Central dissection	Transient	9/55 (16.4)	3/32 (9.4)	0.385
and lateral	Permanent	2/55 (3.6)	2/32 (6.3)	0.632
dissection $(n=87)$	Total	11/55 (20)	5/32 (15.6)	0.612
Values are expressed as number (%). ONM. intraoperative neuromonitoring.				

experienced surgeons, it is more challenging to find and visualize the RLN in reoperation for recurrent thyroid cancer than in the primary operation because of scarring and nerve entrapment due to fibrotic tissues, which significantly distort the normal anatomic relationship [15,18,19].

Therefore, surgeons have tried to overcome these difficulties in RLN identification and preservation in repeat thyroid surgery using IONM. However, the protective effect of IONM on VCP in reoperation for thyroid cancer is still controversial. Alesina et al. [14] reported that IONM does not seem to reduce the incidence of transient VCP or permanent VCP in reoperation of a previously dissected site. Barczynski et al. [13] reported that the incidences of transient VCP significantly reduced in the IONM group; however, there were no significant differences of incidence of permanent VCP compared with the incidences in the without IONM group. Our study showed that the incidence of transient, and permanent VCP after surgery was not reduced when IONM is applied.

Although IONM had no significant positive effect on VCP in reoperations focused on the primary operation site and central dissection only, in the easy RLN identification group, there were no cases of VCP in the group with IONM and three cases of transient VCP and one case of permanent VCP in the group without IONM (P=0.032). However, in the difficult RLN identification group, there was one case of permanent VCP in the group with IONM and one case of permanent VCP in the group without IONM (P=0.248). IONM could not reduce the rate of VCP for either dissection around scar tissue adhesions to RLNs or surgery for tumor invasion because even though IONM might be helpful in the identification of RLNs, preservation of intact RLN function was difficult. However, IONM might re-

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duce accidental nerve injuries by facilitating nerve visualization in the scar tissue in the easy RLN identification group. We collected the information for difficulty of RLN identification (easy/ difficult) based on the structured operation records, but, that was determined by subjective judgement by each operator. Therefore, it is necessary to establish criteria for judgment on the difficulty of RLN identification, such as time for RLN identification, and severity of adhesion.

Although there are previous studies that have compared the incidence of VCP in reoperation with and without IONM, these previous studies included less than 50 cases of recurrent thyroid cancer [13,14]. Our study included 121 recurrent thyroid cancer patients who underwent reoperation to treat locoregional recurrence following total thyroidectomy, and also analyzed the incidence of VCP in patients according to the RLNs at risk, and surgical procedures with or without IONM.

In the present study, all operations were performed by five surgeons. Three surgeons performed 91.7% (111/121) of reoperations. There was no statistical significance of the incidence of transient, and permanent VCP between the groups with IONM and without IONM groups with respect to surgeons.

The present study has some limitations. Our study was a retrospective study, and a specific indication of the use of IONM was not known during the study period. Therefore, it may be necessary to perform further studies, such as randomized controlled trials, to determine whether IONM can provide benefits to preventing VCP in reoperation for recurrent thyroid cancer. In addition, it can be also assumed that the size of recurrent thyroid cancer may have a significant impact on VCP. However, only a few cases clearly described the size of recurrent thyroid cancer in operation records and pathological reports. Further studies will be needed to analyze VCP with respect to the size of recurrent tumor. However, regarding the clinical and pathologic features, there were no significant differences between the groups with and without IONM regarding age, sex, number of previous operations, or histologic subtype of the malignancy at the initial operation, and we recruited consecutive patients who underwent total thyroidectomy for thyroid cancer to reduce the bias in surgical extent of the previous operations.

Although there are limitations, the present study provides useful information for surgeons, and patients to develop a plan for reoperation to treat recurrent thyroid cancers. The present study is the first to analyze the VCP rate focused on recurrent thyroid cancer patients who had underwent reoperation for a previously dissected area.

In conclusion, thyroid cancer reoperations have a higher risk

of VCP because of the history of previous operations, changes in the anatomy of important structures and existing scar tissue. The incidence of transient RLN injury tended to be lower in reoperation for a previously dissected area in recurrent thyroid cancer patients; however, there was no statistical significances. Further study will be needed to ascertain the efficacy of IONM in reoperation for recurrent thyroid cancer patients.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conception or design: J.K., S.K. Acquisition, analysis, or interpretation of data: J.K., S.K. Drafting the work or revising: J.K., S.K., Z.X., J.K., J.A., H.W.Y., Y.J.C., J.Y.C., K.E.L. Final approval of the manuscript: J.K., S.K.

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