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HEAD AND NECK

# Risk factors predisposing for recurrent laryngeal nerve palsy following thyroid malignancy surgery: experience from a tertiary oncology centre

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## Abstract

**Background** Postoperative recurrent laryngeal nerve (RLN) palsy is one of the major morbidities encountered after thyroid surgery. The risk further increases when surgery is performed for thyroid malignancies.

**Methodology** A retrospective study of patients who underwent hemi, total or completion thyroidectomy at our institute between June 2017 to May 2019 were analyzed. We assessed factors that predisposed to the development of RLN palsy.

**Results** The study comprised of 228 patients. A total of 400 nerves were at risk. The RLN palsy rate was 6.8% ($n=27$). On univariate and multivariate analysis, the risk of RLN palsy was seen most with pT4a tumor (OR = 8.5), gross extra-thyroidal extension (ETE) (OR = 3.5) and tracheo-esophageal groove (TEG) (OR = 2.8) involvement, followed by aggressive histopathology, and central compartment node positivity.

**Conclusion** pT4a tumors, gross ETE, and TEG involvement were the leading causes predisposing for the development of RLN palsy in our series.

**Keywords** Recurrent laryngeal nerve · Papillary thyroid carcinoma · Thyroidectomy · Central compartment dissection · Extra thyroidal extension · Tracheo-esophageal groove

## Introduction

Post-operative recurrent laryngeal nerve (RLN) palsy remains one of the major morbidities following surgery for thyroid [1]. The incidence of RLN palsy has been reported to be 1.3–20% [2–4]. This risk further increases when the surgery is performed for thyroid malignancies [5–7].

Regular routine visual identification of the RLN during thyroid surgery by diligent dissection is one of the best methods to circumvent any trauma to the nerve and prevent RLN palsy [8]. Unanticipated RLN palsy can still occur despite an anatomically intact nerve [8]. It is important to know the factors that could predispose to such RLN palsy despite all precautions and standard surgical techniques. Intra-operative nerve monitoring (IONM) is a relatively newer method, which is purported to decrease the incidence of RLN palsy as compared to visual identification exclusively [9]. There is a lack of compelling evidence for its regular use in all thyroid surgeries [10]. The present study was undertaken to evaluate the risk factors predisposing for the development of RLN palsy following surgery for thyroid malignancy.

## Methodology

This retrospective study was done on a prospectively collected data of patients who underwent thyroid surgery for malignancy with or without IONM in a single unit of a tertiary head neck cancer center between 1st June 2017 to 31st May 2019. The aim of our study was to identify risk factors predisposing to the development of RLN palsy. All clinical, radiological, and histopathology details were retrieved from the electronic medical records and the departmental

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database. As per our institute policy, all patients would undergo an examination of the vocal cord status with 90° Hopkins rigid endoscope and/or fiber optic laryngoscopy examination preoperatively and postoperatively (before discharge). As the patient follow-up for a significant proportion of patients in the cohort was for less than one year, the results related to permanent RLN palsy have not been reported in the present study. However, there is a study published from our institute regarding the permanent RLN palsy previously [11].

The statistical analysis was performed using SPSS version 24 (IBM Corp, Armonk, USA). The occurrence of palsy in the immediate postoperative period (day 1 to day 7) was defined as the event. Based on the available evidence in the literature and our experience, multiple factors like pathological T stage (pT1–4), extra-thyroidal extension (ETE), tracheo-esophageal groove (TEG) involvement, aggressive histopathology, and central compartment lymph nodes (CCLN) positivity were considered for analysis among others. Univariate analysis was done using the Chi-square test to check for the associations of these factors on the event. Multivariate analysis was done subsequently using Binomial logistic regression (forward stepwise selection). A $p$ value of $<0.05$ was considered significant. The risk preference for each factor was generated. The sensitive risk factors were measured with the odds ratio.

## Results (Table 2)

A total of 255 patients underwent thyroid surgeries at our unit of a tertiary head neck cancer center during this period. All cases in which the final histopathology was benign were excluded. A total of 228 patients satisfied the eligibility criteria and were included in the study. The details of the surgical procedures are given in Table 1. Based on the procedure performed on each patient, two RLN were at risk (NAR) with total thyroidectomy, while a unilateral procedure put one NAR. Accordingly, 406 nerves were at risk of developing RLN palsy. Nerves with preoperative vocal cord palsies, as well as those in whom the nerve was sacrificed due to involvement by disease during the surgery were excluded ($n=6$), thereby bringing down the total NAR in the study to 400.

At our institute, we have recently, since June 2017, started using IONM in selected cases of thyroid surgeries. Since then we have used IONM in 84 patients (150 NAR, 37.5%) (Table 2) in addition to the standard RLN visualization. In 144 patients (250 NAR, 63.2%) only standard RLN visualization was used. The decision to use IONM was taken on a case to case basis by the operating surgeon based on one or more of the following factors: second surgery, ETE on imaging, TEG involvement on imaging, advanced T stage

**Table 1** Surgery details

| | |
|---|---|
| Primary surgery | |
| Hemi thyroidectomy | 27 (NAR 27) |
| Total thyroidectomy | 133 (NAR 266) |
| Completion thyroidectomy | 68 (NAR 107) |
| Central compartment (CC) | |
| Bilateral CC procedures | 124 (NAR 242) |
| Unilateral CC procedures | 43 (NAR 69) |
| No CC procedure | 61 (NAR 89) |
| Lateral neck | |
| Bilateral procedures | 118 |
| Unilateral procedures | 65 |
| No lateral neck procedure | 72 |

and when CC lymph nodes were expected to be positive or as seen in imaging (CECT).

The overall postoperative RLN palsy rate was 6.8% ($n=27$) in our series. Out of these, in five of the cases, the disease was shaved off the nerve. None of the patients developed bilateral vocal cord palsies. Tumors were staged in accordance with the 8th edition of the American Joint Committee on Cancer (AJCC) staging system (Table 3) [12]. The majority of the thyroid malignancies that we performed surgery for were T2 and above (Table 3).

The median age of the patients was 40 years (range 12–80 years) (Table 2). Age overall had no influence on the RLN palsy rates. The majority of our patients were females ($n=143$, NAR = 250, 62.5%). The palsy rates were higher in males compared to females ($p=0.016$). However, this association was not significant in the multivariate analysis. Only 28% ($n=71$) of the patients had some form of co-morbidities. Diabetes mellitus and hypertension were the most common associated co-morbidities either alone or in combination. The presence of co-morbidities did not have any influence on the NAR to develop RLN palsy ($p=0.977$). Most of our patients were treatment naïve ($n=171$, NAR = 265, 67%). The palsy rates in our series were 7.9% and 4.4% for treatment naïve and second surgery patients respectively with no statistically significant difference between the two groups ($p=0.190$). The largest distribution of RLN palsies among T staging (as per AJCC 2018) belonged to the pT4 stage (Table 2). The nerve was sacrificed in four pT4 cases due to involvement by disease. The RLN palsy was seen in 11 out of 41 NAR in pT4 tumors (26.8% palsy rate). On multivariate analysis, the pT4 stage had the maximum influence on the possibility of the development of RLN palsy postoperatively ($p<0.001$, OR = 8.5 (95% CI 3.6–10.1)]. Among the patients observed to have gross ETE during surgery (NAR = 70), 14 (20%) developed postoperative RLN palsy ($p=0.001$). The majority of gross ETE was found in pT4 stage lesions ($n=30/70$).

**Table 2** Patient demographics, clinical, and histopathology details (for nerves at risk-NAR)

| Variables | Numbers (%) | RLN palsy present (%) | RLN palsy absent (%) | *p* value (univariate) | *p* value (multivariate with odds ratio, 95 confidence interval) |
|---|---|---|---|---|---|
| Age (years) | | | | | – |
| ≤55 | 340 (85) | 24 (7.1) | 316 (92.9) | 0.558 | |
| >55 | 60 (15) | 3 (5) | 65 (95) | | |
| Gender | | | | | – |
| Male | 150 (37.5) | 16 (10.7) | 134 (89.3) | 0.016 | |
| Female | 250 (62.5) | 11 (4.4) | 239 (95.6) | | |
| Co-morbidities | | | | | – |
| Yes | 107 (26.8) | 7 (6.5) | 100 (93.5) | 0.920 | |
| No | 293 (73.3) | 20 (6.8) | 273 (93.2) | | |
| pT-stage | | | | | <0.001 [8.5 (3.6–10.1)] |
| <T4 | 359 (89.8) | 16 (4.5) | 343 (95.5) | <0.001 | |
| T4 | 41 (10.3) | 11 (26.8) | 30 (73.2) | | |
| Case type | | | | | – |
| Treatment naïve | 265 (66.3) | 21 (7.9) | 244 (92.1) | 0.190 | |
| Previous surgery | 135 (33.8) | 6 (4.4) | 129 (95.6) | | |
| Tracheo-esophageal groove involvement | | | | | 0.05 [2.8 (1.0–8.1)] |
| Yes | 31 (7.8) | 8 (25.8) | 23 (74.2) | <0.001 | |
| No | 369 (92.3) | 19 (5.1) | 350 (94.9) | | |
| pCCLN status | | | | | – |
| N0 | 287 (71.8) | 14 (4.9) | 273 (95.1) | 0.017 | |
| N+ | 113 (28.2) | 13 (11.5) | 100 (88.5) | | |
| Aggressive histopathology type | | | | | – |
| Yes | 59 (14.8) | 8 (13.6) | 51 (86.4) | 0.024 | |
| No | 341 (85.3) | 19 (5.6) | 322 (94.4) | | |
| Gross extrathyroidal extension | | | | | 0.014 [3.5 (1.3–11.2)] |
| Yes | 70 (17.5) | 14 (20) | 56 (80) | <0.001 | |
| No | 330 (82.5) | 13 (3.9) | 317 (96.1) | | |
| IONM used | | | | | – |
| Yes | 150 (37.5) | 17 (11.3) | 133 (88.7) | 0.005 | |
| No | 250 (62.5) | 10 (4.0) | 240 (96) | | |

**Table 3** Distribution of tumor staging in accordance with the American Joint Committee on Cancer (AJCC) staging system, 8th edition

| | pN0 | pN1a | pN1b | pNx |
|---|---|---|---|---|
| pT1 | 17 | 2 | 24 | 0 |
| pT2 | 27 | 3 | 28 | 0 |
| pT3 | 17 | 0 | 16 | 0 |
| pT4 | 5 | 1 | 20 | 0 |
| pTx | 20 | 0 | 38 | 10 |

Tracheo-esophageal grove (TEG) involvement was noticed in 16 patients. In terms of the NAR, 31 nerves were at risk in view of TEG involvement. The definition of TEG involvement was based on preoperative findings on imaging (CECT) such as an ill-defined fat plane with the esophageal wall. Intraoperative finding such as an unclear plane in the TEG or its involvement with the disease was also considered as TEG involvement. TEG involvement ($n=31$) was associated with RLN palsy in eight (25.8%) cases ($p=0.001$).

Histopathological distribution of patients included 182 patients (79.8%) with non-aggressive papillary thyroid carcinoma, 9 (3.9%) patients with aggressive papillary thyroid carcinoma (variants included tall, columnar, solid, insular and diffuse sclerosing), 11 (4.8%) patients with follicular thyroid carcinoma, 9 (3.9%) patients with poorly differentiated thyroid carcinoma, 14 (6.1%) patients with medullary thyroid carcinoma, 2 (0.9%) patients with hurthle cell carcinoma and 1 (0.4%) patient with anaplastic carcinoma. Among these cases, those with aggressive histopathology (aggressive papillary thyroid carcinoma, poorly differentiated thyroid carcinoma, medullary thyroid carcinoma, anaplastic carcinoma) included 61 NAR and were associated with eight RLN palsies (13.6%) ($p=0.013$).

There was no association found with CC nodal dissection. However, when cases having metastatic CC nodes ($n = 113$) were analyzed, 13 cases (11.5%) developed RLN ($p = 0.007$).

Between, IONM and without the IONM group, the RLN palsy rate was 11.3% ($n = 17$ NAR) and 4% ($n = 10$ NAR) respectively. Higher palsy rates were observed in the IONM group, which could be attributed to the selection of patients for its use at the time of surgery as brought out earlier in this article.

On multivariate analysis (Table 2) pT4 stage [$p < 0.001$, OR 8.5 (95% CI 3.6–10.1)], gross ETE [$p = 0.014$, OR 3.5 (95% CI 1.3–11.2)], and TEG involvement [$p = 0.05$, OR 2.8 (95% CI 1.0–8.1)] were the factors predisposing most for the development of RLN palsy.

## Discussion

In our series, the overall postoperative RLN palsy rate was 6.8% ($n = 27$), which is in concordance with other studies mentioned in the literature, related to postoperative RLN palsy with thyroid carcinoma. In an article by Sevim et al., on RLN palsy in thyroid carcinoma surgery, a transient palsy rate of 14.4% was mentioned [7]. In another series, the RLN palsy rate among thyroid carcinoma patients was mentioned as 5.2% (192 NAR) [13].

### Age

The median age of the patients was 40 years in our series, similar to the studies reported in the literature (41–44 years) [7]. We divided the patients into two groups with age $\leq 55$ years and $> 55$ years, as in the AJCC 2018 staging system, [12] and we looked for its influence on the palsy rates. This, however, was not significant ($p = 0.495$). Age overall had no influence on the RLN palsy rates in our series. A similar result of no association with age was reported by Sevim et al. in cases of thyroid carcinoma with respect to post-operative RLN palsy [7].

### Gender

The majority of our patients were females (62.5%), with a NAR distribution between female and male patients as 250 and 150 respectively. Interestingly, of the 150 NAR in males, there were a total of 16 nerve palsies (10.6%) with a significant $p$ value of 0.016 on univariate analysis (Table 2). However, this association was not significant in the multivariate analysis. Different series on thyroid surgeries in literature have also noticed a similar finding of no association of gender with post-operative RLN palsy rates [7, 14].

### Co-morbidities

Only 28% ($n = 71$) of the patients had some form of co-morbidities. Diabetes mellitus and hypertension were the most common associated co-morbidities either alone or in combination. In our series, the presence of co-morbidities did not have any influence on the NAR to develop RLN palsy ($p = 0.977$). Other studies in the literature which focus on thyroid surgeries in patients more likely to have co-morbidities i.e. geriatric patients, also did not find any association of post-operative RLN palsy with patients' co-morbidities [15].

### Case type

It is anticipated that the possibility of injury to the RLN is more in an already violated thyroid bed (central compartment). Literature mentions that a higher rate of RLN palsy rate is expected in cases involving second or completion thyroid surgeries [16]. Most patients in our series were treatment naïve ($n = 171$, NAR $= 265$, 67%). We in our series did not find a significant difference between the treatment naïve and the cases where already the patients had undergone prior thyroid surgery ($p = 0.190$).

### Pathological T-stage

As per the 8th edition AJCC staging system [12], we found the highest palsy rate of 26.8% ($n = 11$) was associated with pT4 tumors. Sevim et al. noted a similar rate of 25.4% in their series [7]. On multivariate analysis, we found the highest odds ratio (OR $= 8.5$) for pT4 and was the most likely factor influencing the development of RLN palsy in the post-operative period. pT3 was also associated with a 7.8% RLN palsy rate. However, with pT2 and pT1, the RLN palsy rates were as low as 2.6% and 2.3% respectively, with no statistically significant association.

### Gross extra-thyroidal extension (ETE)

The second highest risk associated with the development of RLN palsy in the post-operative period was with the presence of gross ETE (intra-operatively) (OR $= 3.5$). During the surgeries, a specific note of patients having gross ETE was made. This detail was captured and was used for the analysis. During analysis, 70 NAR were identified as having an ipsilateral gross ETE. Of these, 14 (20%) developed postoperative RLN palsy. Chiang et al., in their retrospective series consisting of 103 thyroid cancer patients, reported a temporary post-operative RLN palsy rate of 19.4% with ETE [17] while series by Sevim et al. found it to be 18.2% [7].

### Tracheo-esophageal groove (TEG) involvement

Tracheo-esophageal groove involvement was identified separately for each side, either pre-operatively on imaging (CECT) or was recorded if found intra-operatively. We found TEG involvement in 35 NAR. Out of these, a total of eight postoperative RLN palsies were observed (22.9%). with a statistically significant association [$p = 0.05$, OR 2.8 (95% CI 1.0–8.1)]. On review of literature, there are various studies, which mention the requirement of regular prophylactic clearance of TEG in thyroid carcinoma because of the possibility of nodal spread to this echelon [18–20]. However, we did not find any study bringing out a specific rate of involvement of TEG in cases of thyroid carcinoma or the associated risk of postoperative RLN palsy with it.

### Aggressive histology

Histopathological variants of papillary thyroid carcinoma such as tall, columnar, insular, solid and diffuse sclerosing were considered as aggressive in nature [21–23]. Other histopathologies included as aggressive were poorly differentiated thyroid carcinoma, medullary thyroid carcinoma, and anaplastic carcinoma. With this, there were a total of 61 NAR. Among these eight patients developed RLN palsy (13.6%). Sevim et al. in their series divided the histopathologies into three groups of well-differentiated, intermediately differentiated, and poorly differentiated (including anaplastic variants) with postoperative palsy rates of 8.1%, 4.5%, and 29.4% [7]. Most of the histopathologies which were included in the intermediate grade in the series by Sevim et al., were considered as aggressive variants in our study, and therefore with those two groups in their study combined.

### Central compartment lymph node (CCLN) involvement

On analysis of cases in which CC nodes were found to be metastatic, a total of 113 NAR were identified with a postoperative RLN palsy rate of 11.5% ($n = 13$). On review of literature, the incidence of RLN palsy following CC nodal dissection has been reported anywhere between 4–7.3% [24], but there are very few studies that mention rates of RLN palsy when CC nodes were found to be positive. One such study is by Pereira et al., where a transient RLN palsy rate of 13.3% was found when CC had metastatic nodes [25]. In another study from our own institution, on a different set of 153 patients of thyroid carcinoma who underwent surgery with CC neck dissection, out of the 11 RLN palsies in the series, 10 had positive central compartment nodes [26].

### Intra-operative neuro-monitoring (IONM)

A meta-analysis by Zheng et al. consisting of 36,487 NAR regarding IONM used during thyroid surgery mentioned a statistically significant difference in reducing rates of RLN palsy after thyroid surgeries, [27] while another meta-analysis by Pisanu et all consisting of 35,513 NAR did not find any statistically significant difference with the use of IONM [10]. In another study by Duclos et al., in fact, the authors found an increase in palsy rate with the use of IONM, which they attributed to the surgeon's learning curve with IONM [28]. As we started the use of IONM recently, we were interested to study its influence on the post-operative temporary nerve palsy rates. To our surprise, we found that the nerve palsy rates were higher in the IONM group in comparison to the group where it was not used (11.3% vs. 4%, respectively). We attribute the same to a selection bias of patients for IONM use. Due to the retrospective nature of our study, it is not possible to definitely comment that IONM should be used in such cases or not; but at our institution, we do prefer to use IONM as an adjunct to surgery in these scenarios.

## Limitations

Firstly, this is a retrospective study of a prospectively collected database and therefore, brings about limitations in making any strong observations or conclusions. Second, the follow-up for a significant number of patients in this cohort was for less than one year, so the permanent RLN palsy rates could not be reported.

## Conclusion

Factors such as pathological T4 stage, gross ETE (intra-operative), TEG involvement, aggressive histopathology, and positive central compartment nodes (in decreasing order) influence the development of RLN palsy following surgery for thyroid malignancy. We suggest that appropriate preoperative patient counseling is required in cases whenever these factors might be identified preoperatively. Also, a cautious approach during the dissection of the RLN nerve is advised in such cases. Though the palsy rates were higher in the IONM group, it could be due to the case selection for IONM use at our institute and may not be due to the use of IONM per se.

## Compliance with ethical standards

**Conflict of interest** No potential conflicts of interest to disclose for any author.

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