International Journal of Clinical Oncology (2019) 24:1536–1542
https://doi.org/10.1007/s10147-019-01496-w

ORIGINAL ARTICLE

Phonatory function in patients with well-differentiated thyroid carcinoma following meticulous resection of tumors adhering to the recurrent laryngeal nerve

Satoru Miyamaru[1] · Yoshihiko Kumai[1] · Daizo Murakami[1] · Narihiro Kodama[2] · Takumi Miyamoto[1] · Eiji Yumoto[3] · Yorihisa Orita[1]

Received: 4 March 2019 / Accepted: 18 June 2019 / Published online: 24 June 2019

Abstract

Background Well-differentiated thyroid carcinomas (WDTCs) sometimes adhere firmly to the recurrent laryngeal nerve (RLN), while allowing normal mobility of the vocal fold (VF). Meticulous dissection of the adhered tumor from the RLN is known to be effective, preserving VF mobility and oncological safety. However, phonatory function following this preservation procedure has yet to be evaluated sufficiently. The objective of this study was to examine phonatory function following the preservation procedure.

Methods Ten patients with WDTCs, demonstrating normal preoperative VF mobility with tumors adhering to the RLN, underwent the preservation procedure between 2000 and 2013 (preservation group). During the same period, nine patients with WDTCs demonstrating normal VF mobility underwent resection and reconstruction of the tumor-invaded RLNs (reconstruction group). Phonatory function, including maximum phonation time (MPT), mean flow rate (MFR), jitter, shimmer, harmonics-to-noise ratio, and GRBAS scale score, was evaluated and compared statistically between the two groups.

Results The mean values of MPT and MFR in the preservation group were at normal levels. Both G and B scores of GRBAS scale were at near-normal levels. Additionally, the mean B score of the GRBAS scale was significantly better in the preservation group than in the reconstruction group.

Conclusions When normal VF mobility is observed preoperatively, meticulous resection for preserving RLN would contribute to maintain not only normal level of MPT and MFR, but also to provide better B score of GRBAS scale than RLN resection followed by immediate reconstruction.

Keywords Well-differentiated thyroid carcinoma · Recurrent laryngeal nerve · Phonatory function

Introduction

Well-differentiated thyroid carcinoma (WDTC) is a predominantly curable disease with a low mortality rate. However, some biologically aggressive WDTCs invade the surrounding tissues, including the strap muscles, larynx, trachea, esophagus, and recurrent laryngeal nerve (RLN) [1]. After the strap muscles, the RLN is the second most common structure to be invaded by a primary thyroid tumor or lymph node metastasis [2].

Although presenting with normal mobility of the vocal fold (VF), WDTCs are sometimes found to adhere firmly to the RLN during surgery. In such cases, patients undergo RLN resection accompanied by tumor resection for oncological safety. Once the RLN is resected, the resected side of the VF should be paralyzed permanently and the patient would suffer breathy dysphonia. Some previous reports regarding the preservation of the intact RLN with meticulous tumor resection in advanced cases of WDTC have suggested that the combined resection of the tumor and its adhered RLN did not improve survival [3–6]. Additionally,

✉ Satoru Miyamaru
smiyamaru@gmail.com

[1] Department of Otolaryngology-Head and Neck Surgery, Graduate School of Medicine, Kumamoto University, 1-1-1, Honjo, Chuo-ku, Kumamoto 860-8556, Japan

[2] Department of Rehabilitation, Kumamoto Health Science University, Kumamoto, Japan

[3] Department of Otolaryngology, Asahino General Hospital, Kumamoto, Japan

normal postoperative VF mobility with preservation of the intact nerve was restored in many cases. Based on these perspectives, when preoperative VF mobility is normal and the tumor is found to adhere to the RLN during surgery, we usually try to preserve the RLN intact using meticulous tumor resection, which we call the 'preservation method' in this study.

Good vocal quality can be expected with preservation of an intact RLN. However, to our knowledge, few articles have described the vocal outcome following the use of the RLN preservation method after advanced WDTC surgery [6]. As the parameters of phonatory function evaluated in the literature [6] are solely aerodynamic, detailed evaluation of vocal quality is difficult. Therefore, we evaluated not only aerodynamic parameters, but also acoustic and perceptual parameters of postoperative phonatory function in this study. Additionally, as a control group, we included patients who underwent resection and reconstruction of RLNs that had been invaded by the tumors (which we call the 'reconstruction method' in this study) during the same period.

The objective of this study was to evaluate the postoperative phonatory function, oncological safety, and VF mobility achieved with the preservation method and to compare postoperative phonatory function between patients who underwent preservation and reconstruction procedures for advanced WDTC. The study findings would be helpful for thyroid cancer surgeons, aiding determination of the proper surgical indication in terms of postoperative vocal outcome and oncological safety.

Patients and methods

During the period 2000–2013, we operated on 179 patients with WDTC at Kumamoto University Hospital. Written consent was obtained from all patients. Patients agreed that we could use clinical data obtained from this study for diagnosis and evaluation for the purpose of research. Ethical approval was not necessary because this was a retrospective study and included no additional examination of the patients. Twenty-five patients were found to have tumors adhering firmly to the RLN along with normal preoperative VF mobility. Ten patients were treated with the RLN preservation method (preservation group); they were two males and eight females aged 35–79 years (median age, 58.5 years). The median follow-up period was 106 months (range, 39–182 months). Histology of WDTC were papillary carcinomas for 8 and follicular carcinomas for two patients (Table 1).

The remaining 15 patients underwent resection of the RLNs along with the tumors. The RLN reconstruction method was applied during the same operation in nine of these patients (reconstruction group). Histology of WDTC was papillary carcinoma for all patients (Table 2). RLN

Table 1 Clinical data and phonatory function in the preservation group

	Age	Sex	Histopathology	Tumor recurrence	Vocal fold movement	Restoration period	MPT (s)	MFR (ml/s)	*G* score	*B* score	Jitter	Shimmer	HNR
1	63	Male	Follicular	–	Full recovery	2 m	–	–	–	–	–	–	–
2	42	Female	Papillary	–	Partial recovery	8 m	–	–	–	–	–	–	–
3	37	Female	Follicular	–	Full recovery	3 m	20.5	100.7	0	0	0.512	1.437	8.539
4	70	Female	Papillary	–	Partial recovery	9 m	–	–	–	–	–	–	–
5	76	Female	Papillary	–	Full recovery	3 m	25.2	79.2	0	0	4.279	10.267	7.423
6	54	Female	Papillary	–	Normal	–	–	–	–	–	–	–	–
7	35	Male	Papillary	–	Full recovery	2 m	33.4	189	1	0	0.283	4.103	8.416
8	73	Female	Papillary	–	Normal	–	11.9	128	0.6	0	3.464	9.75	4.237
9	41	Female	Papillary	–	Paralysis	×	9.8	141	1	0.6	1.116	6.09	8.125
10	79	Female	Papillary	–	Normal	–	5.0	172	0.6	0.6	0.806	6.717	6.364
Average	57					Average	17.6 ± 10.7	135.0 ± 41.6	0.53 ± 0.45	0.20 ± 0.31	1.743 ± 1.69	6.394 ± 3.36	7.184 ± 1.65

Table 2 Clinical data and phonatory function in the reconstruction group

	Age	Sex	Histopathology	MPT (s)	MFR (ml/s)	*G* score	*B* score	Jitter	Shimmer	HNR
1	68	Female	Papillary	22.2	61	1	0.6	0.561	1.377	8.508
2	72	Male	Papillary	10.4	146	1.6	1.3	2.954	8.768	8.539
3	61	Male	Papillary	24.3	101.8	0.3	0	2.859	9.849	7.545
4	18	Male	Papillary	12	327.1	0.6	0.6	1.31	7.343	9.469
5	71	Male	Papillary	17.7	168.1	0.3	0	1.223	8.755	7.825
6	81	Female	Papillary	18.2	166.3	1	1	12.071	20.236	3.08
7	63	Female	Papillary	16.5	114.8	1.3	1.3	0.598	4.472	7.305
8	33	Female	Papillary	6	202.4	0.6	0.6	2.911	6.967	9.431
9	46	Female	Papillary	11.3	138.2	0.6	0.6	4.735	8.677	7.077
Average	57			15.4 ± 5.9	158.4 ± 75.6	0.81 ± 0.45	0.67 ± 0.48	3.247 ± 3.58	8.494 ± 5.13	7.642 ± 1.92

reconstruction techniques used were direct RLN anastomosis, ansa cervicalis—RLN anastomosis, and free nerve grafting (in two, three, and four patients, respectively).

For the preservation method, we attempted to preserve the RLN by scrutinizing it carefully under magnification. The nerve was shaved carefully from the tumor using a scalpel. Technical issues were secured since, limited two surgeons (DM and EY) who had abundant experiences of thyroid cancer surgery, performed this surgery using a nerve monitoring device. When preservation of the RLN intact was difficult, we attempted to resect perineural tissue only, preserving the core portion of the nerve as far as possible. In cases with signs of invasion to the nerve fiber, such as color alteration, the RLN was extirpated along with the tumor.

In this study, we examined the following three outcomes to evaluate the effectiveness of the RLN preservation method: (1) local recurrence; (2) postoperative VF mobility, and (3) postoperative phonatory function. VF mobility was assessed by inspection of the larynx with a flexible fiberscope in all patients immediately after the operation and at follow-up clinic visits. We also recorded the restoration period in patients who experienced postoperative VF paralysis. Postoperative phonatory function was assessed using aerodynamic, acoustic, and perceptual analyses.

For aerodynamic analyses, patients were instructed to produce a sustained vowel ('a') at a comfortable pitch and volume for as long as possible. The maximum phonation time (MPT) was measured for each patient using a stopwatch, and the greatest values were included in the analyses. The mean flow rate (MFR) was measured using a phonation analyzer (PS-77E; Nagashima, Tokyo, Japan). During the procedure, patients were instructed to produce the 'a' vowel sound at a comfortable pitch and volume while holding a mouthpiece tightly to their lips and wearing a nose clip. Normal speakers usually have MPTs > 10 s and MFRs of 50–200 ml/s.

Acoustic analysis was conducted using the Multi-dimensional Voice Program Model 5105 (version 3.1.7; Kay Elemetrics, Lincoln Park, NJ, USA). The vowel segment was cut from the complete voice sample, and 0.5–1 s from a stable portion of the vowel utterance was then trimmed and analyzed. The acoustic parameters were jitter (normal, < 1.040%), shimmer (normal, < 3.810%), and the noise-to-harmonics ratio (NHR; normal, > 7.2 dB). The NHR was converted to the harmonics-to-noise ratio (HNR) using the equation $\mathrm{HNR} = 10 \times \log_{10}(1/\mathrm{NHR})$ [7].

Patients' voices were recorded in a sound-proofed room using a digital recorder (Model PMD 670; Marantz, Sagamihara, Japan) connected to a microphone (Model WM-421; Panasonic, Osaka, Japan). The microphone was held at a distance of 20 cm from the mouth during recording. Patients produced sustained phonation of the 'a' vowel sound at a comfortable pitch and volume. The voice was sampled at 45 kHz through an anti-aliasing filter and stored in a pulse-code modulation format. The speech segments of the recordings were used for auditory perceptual analysis. Perceptual voice evaluations were conducted using the grade (G), roughness (R), breathiness (B), asthenia (A), and strain (S) (GRBAS) scale [8]. All speech samples were anonymized before auditory perceptual assessment to avoid bias. The mean *G* and *B* values were analyzed because unilateral VF paralysis causes breathy hoarseness. One experienced otolaryngologist (YK) and two speech and language pathologists (NK and TM) rated the parameters using a four-point scale (0 = normal, 1 = slight disturbance, 2 = moderate disturbance, 3 = severe disturbance).

Phonatory function was compared between the preservation and reconstruction groups. Six patients in the preservation group (total, $n = 10$) underwent phonatory function evaluations. The reasons for lack of data for phonatory functional parameters were as following: patient no. 2 and 4 presented bilateral VF paralysis due to not only the manipulation of the ipsilateral RLN with meticulous resection but also the contralateral RLN resection with invaded tumor. Patient no. 1 and 6 refused the examination of phonatory function. All parameters were evaluated in all nine patients

in the reconstruction group. Clinical data and phonatory functional outcomes in all patients in both groups are summarized in Tables 1 and 2. These assessments were performed more than 6 months after surgery as performed in our previous study [9] in all patients. The ranges of examination periods were 6–100 months (median period, 70 months) in the preservation group and 6–158 months (median period, 27 months) in the reconstruction group.

All data are presented as mean values ± standard deviations. Statistical analyses were performed using the Mann–Whitney *U* test (StatView 5.0 for Windows; SAS Institute, Cary, NC, USA). p values < 0.05 were considered to indicate statistical significance.

Results

Local control

In the preservation group, one patient experienced local recurrence at the ipsilateral tracheal ring (Table 1). We were able to completely extirpate it while leaving the RLN intact. Since the operation, the patient has survived without recurrence for > 10 years.

Vocal fold mobility

Three patients had normal VF mobility immediately after the operation. Paralyzed VFs recovered fully over a period of 2 or 3 months after the operation in four of seven patients. In one patient, VF mobility was not recovered. The paralyzed VFs of the remaining two patients recovered partially at 8 and 9 months after the operation, respectively (Table 1). Both of these patients underwent tracheotomy during the operations because their contralateral RLNs were resected due to invasion of the carcinomas. One patient was able to close her tracheostoma after the partial recovery of unilateral VF mobility. Ten years after tracheostoma closure, she underwent Ejnell's operation [10], in which the paralyzed VF is pulled laterally, due to the gradual deterioration of dyspnea. The other patient did not close her tracheostoma.

Phonatory function

The mean MPT and MFR values in the preservation group were 17.6 ± 10.7 s and 135 ± 41.6 ml/s, respectively. Both values were within the normal ranges. In the reconstruction group, the mean MPT and MFR values were 15.4 ± 5.9 s and 158.4 ± 75.6 ml/s, respectively. Neither parameter differed significantly between the preservation and reconstruction groups ($p = 0.304$ and 0.252, respectively; Fig. 1). The values of MPT in two patients were below normal level. These might be based on the permanent VF paralysis (no. 9) and low vital capacity because of aged and small stature female (no. 10), respectively.

The average jitter, shimmer, and HNR values in the preservation group were 1.743% ± 1.69%, 6.394% ± 3.36%, and 7.184 ± 1.65 dB, respectively. These values did not differ significantly from those in the reconstruction group ($p = 0.179$, 0.198, and 0.320, respectively; Fig. 2).

The mean *G* and *B* scores of the GRBAS scale were 0.53 ± 0.45 and 0.20 ± 0.31, respectively, in the preservation group and 0.81 ± 0.45 and 0.67 ± 0.48, respectively, in the reconstruction group. The mean B score in the preservation group was significantly better than that in the reconstruction group ($p = 0.028$; Fig. 3).

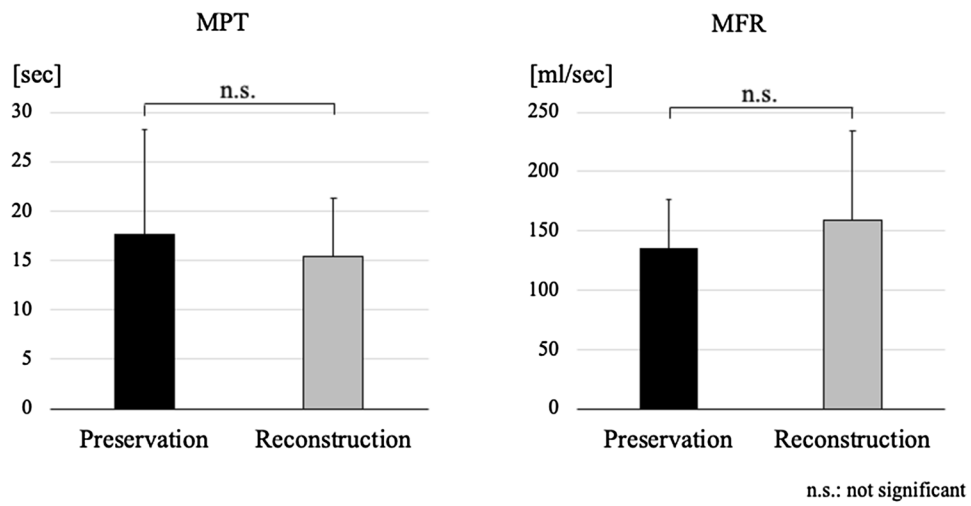

Fig. 1 Aerodynamic measurements in both groups. *MPT* maximum phonation time, *MFR* mean flow rate

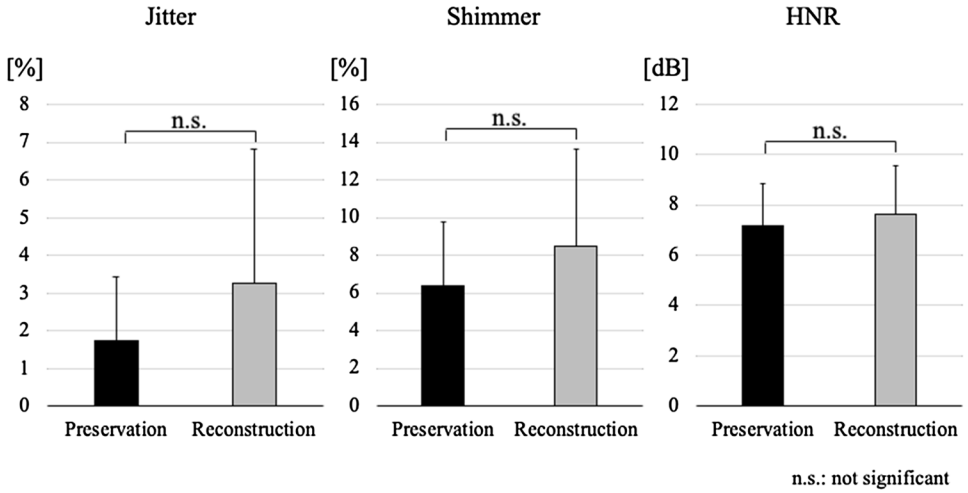

Fig. 2 Acoustic analyses in both groups. *HNR* harmonics-to-noise ratio

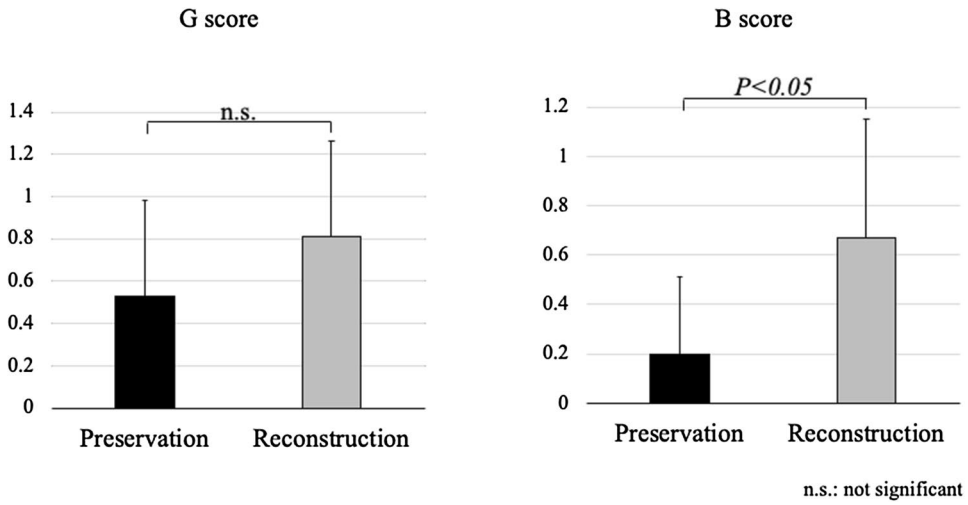

Fig. 3 Perceptual evaluation in both groups. *G* grade, *B* breathiness

Discussion

Although WDTC is one of the most treatable malignancies, it occasionally invades regional structures. Approximately 7–16% of WDTCs were reported to invade surrounding structures, including the strap muscles, larynx, trachea, esophagus, and RLN [11–13]. Although complete surgical resection clearly should be attempted in all cancer surgeries, it is not always technically feasible and safe in cases of locally advanced WDTC. Therefore, conservative and minimally invasive surgery to maintain structural function and patients' quality of life has recently become common practice and been advocated [1, 14]. Following this principle, the decision to undertake preservation or resection of the RLN accompanied by advanced WDTC tumor resection remains controversial.

Some studies have suggested that complete excision with resectional management of the RLN did not improve survival in cases in which the WDTC infiltrated into the preoperatively functioning RLN [3–6]. In the current study, one of ten patients experienced tumor recurrence on the tracheal ring near the primary tumor. However, we were able to salvage this case with additional surgery, and the patient has remained cancer-free with normal VF mobility for > 10 years. Our results support the previously reported oncological safety of this method.

Some reports in the literature describe VF mobility after meticulous tumor resection [4–6]. Nishida et al. [4] reported the restoration of normal VF function in 14 (61%) of 23 patients with WDTC. Some functional VF mobility was recognized in 18 (78%) of 23 patients. Lang et al. [5] reported 6 (15%) cases of temporary and 3 (8%) cases of permanent paralysis of the VF among 39 patients with WDTC. Kihara et al. [6] reported that 15 of 18 (83%) patients with WDTC had functioning VFs 1 year after surgery. In our study, normal VF mobility was preserved in 7 (70%) of 10 patients, and partial VF mobility was confirmed in 2 (20%) of all

patients eventually. Once the RLN has been resected, even with use of the RLN reconstruction method, VF mobility on the resected side is never recovered. We therefore emphasize the necessity of preserving normal postoperative VF mobility when feasible. The advantage of preserving postoperative VF mobility when the tumor adheres to the unilateral RLN lies in the ability to avoid tracheostomy for bilateral RLN paralysis due to subsequent tumor invasion of the contralateral RLN. The avoidance of this procedure would maintain the patient's quality of life.

Another advantage of RLN preservation is the avoidance of hoarseness caused by unilateral VF paralysis. Therefore, the examination of phonatory function following RLN preservation surgery is important. However, few reports describe the detailed examination of postoperative phonatory function. Kihara et al. [6] examined the phonatory function of patients who underwent partial-layer RLN resection the same with our meticulous resection procedure. To our knowledge, this report is the only one to describe phonatory function outcomes after meticulous resection of WDTCs from adhered RLNs. In that study, the authors used the MPT/vital capacity ratio to evaluate phonatory function because the MPT value tends to be affected by the vital capacity [15]. The MPT/vital capacity ratio at 1 year after surgery was in the normal range [6]. This ratio can be used to characterize the degree of breathy hoarseness, but the estimation of proper voice quality with this parameter alone is difficult. Perceptual and acoustic analyses, as well as aerodynamic analyses, are indispensable for the accurate evaluation of postoperative phonatory function.

In perceptual analysis using the GRBAS scale, the mean *G* and *B* scores in the preservation group were almost normal (0.53 ± 0.45 and 0.20 ± 0.31, respectively), and the mean B score was significantly better in the preservation group than in the reconstruction group ($p = 0.028$). We previously reported excellent postoperative vocal outcomes in the reconstruction group [9, 16]. We assume that the significant difference between the preservation and reconstruction groups in the present study may depend on the presence or absence of RLN paralysis and/or the degree of RLN damage. One report in the literature notes that the severity of RLN injury dictates the functional recovery of the laryngeal motor system [17].

In general, aerodynamic parameters deteriorate with insufficient glottic closure due to unilateral VF paralysis. The mean MPT and MFR values in the preservation group in our study were within normal ranges. Although no significant difference was observed between groups, the average values of MPT and MFR were better in the preservation group than in the reconstruction group. If a sufficient number of patients can be obtained in the future, significant differences in these parameters could be detected. Acoustic parameters (jitter, shimmer, and the HNR) are used to quantitatively and objectively evaluate the degree of voice disorder and are easily influenced by other factors, such as age and sex [18, 19]. As the patients included in the current study were of various ages and both sexes, the results might have varied widely, leading to the lack of detection of a significant difference between groups.

The most important and significant clinical question for thyroid cancer surgeons is the degree to which the RLN can be dissected while preserving VF mobility. Unfortunately, no definitive criteria relevant to this clinical question have been established. Kihara et al. [6] examined the anatomical structures of resected RLNs following the resection of RLN-adhering tumors. They noted that 78–82% of the nerve cross section was composed of perineural connective tissue surrounding the nerve fibers. They attempted to resect perineural tissue only, preserving the core portion of the nerve as far as possible. Consequently, in some patients, the proportion of the thinnest diameter of the preserved RLN to its original size was less than 1/4. Postoperative VF paralysis recovered in 9 (75%) of 12 patients [6]. If the remaining nerve does not show color alteration, we suggest that the core portion of the RLN should be preserved as far as possible. To establish clear criteria regarding this issue, histological investigation of resected RLNs and examination of correlations with postoperative VF mobility should be performed with a sufficient number of patients as part of a multi-institutional research project.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. McCaffrey JC (2006) Aerodigestive tract invasion by well-differentiated thyroid carcinoma: diagnosis, management, prognosis, and biology. Laryngoscope 116:1–11
2. Tumori T, Nakao K, Miyata M (1985) Clinicopathologic study of thyroid carcinoma infiltrating the trachea. Cancer 56:2843–2848
3. Falk SA, McCaffrey TV (1995) Management of the recurrent laryngeal nerve in suspected and proven thyroid cancer. Otolaryngol Head Neck Surg 113:42–48
4. Nishida T, Nakao K, Hamaji M et al (1997) Preservation of recurrent laryngeal nerve invaded by differentiated thyroid cancer. Ann Surg 226:85–91
5. Lang BH, Lo CY, Wong KP et al (2013) Should an involved but functioning recurrent laryngeal nerve be shaved or resected in a locally advanced papillary thyroid carcinoma? Ann Surg Oncol 20:2951–2957
6. Kihara M, Miyauchi A, Yabuta T et al (2014) Outcome of vocal cord function after partial layer resection of the recurrent

laryngeal nerve in patients with invasive papillary thyroid cancer. Surgery 155:184–189
7. Yumoto E, Gould WJ, Baer T (1982) Harmonics-to-noise ratio as an index of the degree of hoarseness. J Acoust Soc Am 71:1544–1550
8. Hirano M (1981) Clinical examination of voice. Springe, New York, pp 81–84
9. Sanuki T, Yumoto E, Minoda R et al (2010) The role of immediate recurrent laryngeal nerve reconstruction for thyroid cancer surgery. J Oncol 2010:1–7 **(Article ID 846235)**
10. Ejnell H, Mansson I, Hallen O et al (1984) A simple operation for bilateral vocal cord paralysis. Laryngoscope 94:954–958
11. McCaffrey TV, Bergstralh EJ, Hay ID (1994) Locally invasive papillary thyroid carcinoma: 1940–1990. Head Neck 16:165–172
12. Sillipphant WM, Levitin MS (1964) Thyroid carcinoma and death: a clinicopathological study of 193 autopsies. Cancer 17:513–525
13. Batsakis JG (1987) Laryngeal involvement by thyroid disease. Ann Otol Rhinol Laryngol 96:718–719
14. Kebebew E, Clark OH (2003) Locally advanced differentiated thyroid cancer. Surg Oncol 12:91–99
15. Miyauchi A, Inoue H, Tomoda C et al (2009) Improvement in phonation after reconstruction of the recurrent laryngeal nerve in patients with thyroid cancer invading the nerve. Surgery 146:1056–1062
16. Yumoto E, Sanuki T, Kumai Y (2006) Immediate recurrent laryngeal nerve reconstruction and vocal outcome. Laryngoscope 116:1657–1661
17. Tessema B, Roark RM, Pitman MJ et al (2009) Observations of recurrent laryngeal nerve injury and recovery using a rat model. Laryngoscope 119:1644–1651
18. Orlikoff RF (1990) The relationship of age and cardiovascular health to certain acoustic characteristics of male voices. J Speech Hear Res 33:450–457
19. Awan SN (2006) The aging female voice: acoustic and respiratory data. Clin Linguist Phon 20:171–180