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The impact of post-thyroidectomy paresis on quality of life in patients with nodular thyroid disease

Abbreviated title

Post-thyroidectomy paresis, voice, and quality of life

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Conflicts of interest
None.

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Abstract

Objective: To investigate the impact of post-operative paresis on disease specific quality of life (DSQoL) after thyroidectomy in patients with benign nodular thyroid disease.

Study design: Observational study

Setting: University hospital

Subjects and Methods: Patients were evaluated before and three weeks, and six months after surgery in an individual prospective cohort study. Videolaryngostroboscopy (VLS), voice-range-profile, voice-handicap-index (VHI), multidimensional-voice-program (MDVP), maximum-phonation-time (MPT), and auditory-perceptual-evaluation. Changes in DSQoL were assessed by the Thyroid-specific Patient-Reported Outcome (ThyPRO). Cohen's effect size (ES) was used to evaluate changes.

Results: Sixty-two patients were included, 55 of whom completed all examinations. Three weeks after surgery, a blinded VLS examination showed signs of paresis of either the recurrent laryngeal nerve- or the external branch of the superior laryngeal nerve (RLN/EBSLN) in 13 patients (24%). A paresis corresponded to a 12±28 point increase in VHI ($p=0.002$) and was associated with a significant 4.3±7.5 semitone (ST) decrease in the maximum fundamental frequency ($p<0.001$) and a 5.3±8.2 dB reduction in maximum intensity. Further it was associated with a 4.5±11.2 seconds reduction in MPT ($p=0.001$), and a 0.40±1.19 increase in grade, 0.42±1.41 in roughness, and 0.36±1.11 in breathiness. Signs of postoperative RLN/EBSLN paresis correlated with an 11.0 point ($p=0.02$) poorer improvement in Goiter symptoms, at both three weeks and six months after surgery.

Conclusion: Signs of RLN/EBSLN paresis after thyroidectomy were associated with less pronounced improvement in Goiter Symptoms in patients with thyroid nodular disease. However, thyroidectomy was associated with an overall improved DSQoL by six month after surgery.

Introduction

Thyroidectomy is a well-established treatment option for patients with thyroid nodularity, Graves' disease, and thyroid malignancy[1-4]. Thyroid surgery profoundly improves disease-specific quality of life (DSQoL) for patients with benign as well as malignant thyroid disease[5-9], and relieves both tracheal and esophageal compression[10-11]. When performed at high volume centers, thyroidectomy is reported to be associated with a low rate of long-term complications, i.e. hypocalcemia and recurrent laryngeal nerve (RLN) paralysis[12-15]. However, up to 40% of patients experience a postoperative voice and/or vocal fold change[16-20] which can be caused by intubation injuries[21], paresis of the external branch of the superior laryngeal nerve (EBSLN)[22, 23], RLN paresis[20], or maladaptive mechanisms[16]. Especially RLN or EBSLN (RLN/EBSL) paresis can cause permanent voice changes[20, 22-23]. The majority of postoperative voice and/or vocal fold changes disappear within three to six months after surgery, but the frequency of paresis might be grossly underestimated[16-18, 24-26]. Previous studies have indicated a detrimental impact of voice disorders on patients' quality of life (QoL)[27]. Knowledge of how RLN/EBSLN paresis affects symptom improvement based on DSQoL in patients with thyroid nodularity is sparse, yet pertinent to obtain, as non-surgical treatment options have increasingly been implemented[4, 28-35].

We aimed at investigating the association between RLN/EBSLN paresis and symptom improvement, based on DSQoL, in patients with benign thyroid nodular disease undergoing thyroidectomy.

Materials and Methods

Patient characteristics

In a tertiary referral setting, patients with thyroid nodularity scheduled for thyroid lobectomy or total thyroidectomy, were consecutively included in a study with six months post-operative follow-

up. Thyroid nodularity was defined as the presence of an enlarged thyroid gland on ultrasound with at least one nodule confirmed by ultrasonography. Serum levels of total thyroxine (T_4) and total triiodothyronine (T_3) had to be within the normal range (67-134 nmol/L and 1.35-2.33 nmol/L, respectively), but subclinically hypo- or hyperthyroid patients were eligible. Patients were included from November 2014 with the last visits in August 2017, after a follow-up period of six months. The exclusion criteria were: 1) previous surgery to the neck, including thyroid surgery; 2) suspicion of thyroid cancer, as these patients were managed in a fast track program[36]; 3) age below 20 or above 80 years; 4) neuromuscular disease; and 5) a preoperatively impaired voice with need for specialist assessment[16].

Vocal fold and voice outcome measures

Each patient underwent a preoperative multifactorial voice and vocal fold examination, which was repeated three weeks and six months after surgery. It was performed by an experienced resident in Ear- Nose- and Throat diseases. This program comprised a videolaryngostroboscopic (VLS) examination conducted with a 70^{o} rigid videolaryngoscope (Pulsar II, Karl Storz, Germany) with stroboscopic light source. Two experienced laryngologists independently rated blinded videos after completion of the study. The consultants addressed the vocal fold mobility, vocal fold lengthening during intonation, and potential localized vocal fold lesion as dichotomized variables. Impaired vocal fold mobility was interpreted as a RLN paresis, due to normal mobility preoperatively and absence of long-term intubation or other disease that might cause immobility by fixation. Impaired ability to lengthen the vocal folds was interpreted as “sign of EBSLN paresis”, because postoperative discomfort and maladaptive mechanisms might mimic EBSLN palsy. The consultants had no access to information on how well the patient had cooperated at the time of examination. Any discrepancies were resolved by discussion until consensus was reached.

120 The dual-microphone phonetogram system Voice Profiler 5.0 (Alphatron Medical
121 Systems, Rotterdam, the Netherlands) was used for assessing the voice range profile (VRP)[37]. The
122 parameters of interest were the minimum and maximum fundamental frequencies (f_0), measured in
123 semitones (ST), the frequency range, the minimum and maximum voice intensity, defined as sound
124 pressure level (SPL), measured in decibel (dB), and the intensity range.
125 Jitter (%), shimmer (%), noise to harmonic ratio (NHR), voice turbulence index (VTI),
126 and soft phonation index (SPI) were assessed by the multidimensional-voice-program (MDVP;
127 Model 4400, KeyPENTAX, NJ, USA). Patients produced the sustained vowel /a:/ at a comfortable
128 frequency and intensity. The procedure was repeated three times, and the median value was used for
129 analyses.
130 The maximum-phonation-time (MPT) was recorded having the patient sustain the
131 vowel /a:/ for as long as possible on a single breath using a handheld recorder (LS-11, Olympus,
132 Japan). This was repeated three times and the longest sample used for analyses.
133 A blinded auditory-perceptual evaluation was performed by a speech-language
134 pathologist using the most reliable parameters of the GRBAS-scale system [grade (G), roughness
135 (R), and breathiness (B)][38]. The voice samples were 15 seconds of reading the Danish version of the
136 "North Wind and the Sun". Each voice sample was rated on the G, R, and B scales using a four-
137 point Likert scale (0-3) with higher scores indicating greater abnormality of the voice.
138 The voice handicap index (VHI) questionnaire was completed prior to the VLS
139 examination. This well-validated questionnaire[39, 40] comprises 30 statements regarding patient-
140 reported severity of voice handicap. Each statement is scored on a five-point Likert scale from 0
141 (never) to 4 (always), with a possible score of 120 point. Thus, a higher VHI score indicates a
142 greater self-reported impact or "handicap" of a voice problem. A validation study of the Danish
143 VHI found control persons having a VHI score of 6.5±8.3 points[40].

144

145 **Symptom improvement based on disease specific quality of life**

146 Symptom improvement, based on DSQoL was assessed before surgery and three weeks and six
147 months after surgery, using the Thyroid-specific Patient-Reported Outcome measure (ThyPRO).
148 This is a self-administered questionnaire[41] with 13 multi-item scales covering symptom
149 improvement after thyroidectomy (Goiter Symptoms, Hyperthyroid Symptoms, Hypothyroid
150 Symptoms, Eye Symptoms, Tiredness, Cognitive Complaints, Anxiety, Depressivity, Emotional
151 Susceptibility, Impaired Social Life, Impaired Daily Life, Impaired Sex Life, and Cosmetic
152 Complaints), as well as a single item measuring overall impact of thyroid disease on QoL. The
153 questionnaire includes eighty-five items rated on a five-point Likert scale from 0 (not at all) to 4
154 (very much). Each scale was scored as a summary score and linearly transformed to a range of 0-
155 100 points with a lowered score indicating improved health status. The Eye Symptom scale was
156 omitted as it was not relevant for these patients[42]. This study was part of a larger study investigating
157 changes in QoL with some of the data previously published, but in a different context[9, 10, 43, 44].

158

159 **Surgical procedure**

160 The thyroid surgery comprised either a thyroid lobectomy or a total extracapsular thyroidectomy,
161 and was performed under general anesthesia by a consultant head and neck surgeon. The RLN was
162 monitored using the NIM EMG tube (Medtronic, Minnesota, USA), and was exposed to the inferior
163 constrictor. Patients were discharged the first postoperative day in case of uncomplicated
164 lobectomy. After total thyroidectomy, levothyroxine was administered. These patients were
165 discharged when calcium levels approached the normal range. Patients were followed up at 2-4
166 weeks after surgery, and again 6-10 weeks after surgery.

167

Statistics

A three step statistical approach was used for assessing the impact of RLN/EBSLN paresis on DSQoL. Initially, a linear mixed model was used to evaluate the impact of paresis on changes in voice parameters from the multifactorial voice examination from baseline to three weeks and six months after surgery. The independent variables were age, sex, thyroid volume, surgical procedure, RLN/EBSLN paresis, and time point (baseline, three weeks after surgery, and six months after surgery). The linear mixed model was used to interpret the significance of the changed objective voice parameters (parameters with significant and moderate sized changes) on VHI score using age, sex, thyroid volume, surgical procedure, time, RLN/EBSLN paresis, maximum f_0, and maximum SPL as independent variables. A linear mixed model was used to evaluate the association of RLN/EBSLN paresis on changes in ThyPRO scales from baseline to three weeks and six months after surgery using age, sex, thyroid volume, surgical procedure, and RLN/EBSLN paresis as independent variables.

The sample size was calculated to 52 patients, based on an improvement in DSQoL after surgery of 10 points in ThyPRO scores with a standard deviation of 25 points[9]. Cohen's effect sizes (ES) were used with ES of 0.2-0.5 defined as small, above 0.5 to 0.8 as moderate, and values > 0.8 as large[45].

The study was approved by The Regional Scientific Ethical Committee for Southern Denmark (S-20130096), and registered at the Danish Data Protection Agency, and at www.clinicaltrials.gov (NTC02468921).

Results

Patient characteristics

Of 268 consecutive patients with benign nodular thyroid disease, 230 were assessed for eligibility, 62 of whom were included in the study (Figure 1). Fifty-five patients completed all examinations while seven patients (11%) were lost to follow-up. The mean age of the patients was 52±15 years (Table 1) compared to 50±13 years for the non-included, but eligible patients (p=0.19).

Voice and vocal fold outcome measures

None of the 55 patients had vocal fold changes at baseline, whereas VLS examination three weeks after surgery revealed uni- or bilateral paresis of the RLN in seven patients (13%) and hereof two with paralysis of the RLN (4%). In two of the seven patients and in an additional six patients, the ability to lengthen the vocal folds was impaired suggesting EBSLN paresis (15%). In total 13 patients (24%) had signs of postoperative paresis. Five patients (9%) had a localized vocal fold lesion (two with minor edema, two with contact granulomas, and one with a small leukoplakia), of whom one also had RLN paresis. In total, 17 patients (31%) had VLS changes after surgery. Six months after surgery, two of the seven patients with RLN paresis still had impaired vocal fold mobility (4%). However neither of the two patients with initial RLN paralyses had any signs of persisting nerve injury. Two of the six patients with signs of EBSLN paresis still had impaired ability to lengthen the vocal folds (4%). One patient had a persistent localized vocal fold lesion (2%). Thus, a total of five patients (10%) had VLS changes by six months after surgery. Neither age, sex, thyroid volume, nor the extent of surgery, had an impact on these results.

Three weeks after surgery, the patient cohort experienced an average frequency range decrease from 35±5 ST to 32±5 ST ($p<0.001$, ES=0.56) and the average intensity range decreased slightly from 65±8 dB to 63±7 dB ($p=0.03$, ES=0.27), along with a moderately reduced average maximum f_0 of 3±6 ST ($p<0.001$, ES=0.66) and an average reduced maximum SPL of 3±6 dB ($p<0.001$, ES=0.57) (Table 2). These findings reflect a reduced ability to shout/loudness, or reach

the highest pitch in the weeks after surgery. These parameters returned to baseline levels six months after surgery. No significant changes were observed in the MDVP parameters jitter, shimmer, NHR, VTI, and SPI or MPT, and GRB scales after surgery when analyzing the entire cohort.

A postoperative paresis was associated with a significant 4.3±7.5 ST decrease in the maximum f_0 ($p<0.001$), a 4.7±7.9 ST decrease in the frequency rage ($p<0.001$), a 5.3±8.2 dB reduction in maximum intensity, and a 4.3±10.5 dB reduction in intensity range ($p=0.002$). A paresis was also associated with a 4.5±11.2 seconds reduction in MPT ($p=0.001$), a 0.89±1.41 increase in jitter ($p<0.001$), a 0.01±0.04 increase in NHR ($p=0.02$), and an increase of 0.40±1.19 in grade ($p=0.01$), 0.42±1.41 in roughness (0.02), and 0.36±1.11 in breathiness ($p=0.01$) (Table 3). Patients with no sign of RLN/EBSLN paresis only experienced minor changes with difficulties reaching the highest pitch three weeks after surgery (Table 4)

The impact of thyroidectomy on voice handicap index

At baseline, the median VHI score was 5 points (range 0 to 70 points). Despite a statistically significant average increase of 7±22 points ($p=0.003$, ES=0.53), it remained low three weeks after surgery with a median score of 7 points (0 to 87 points) ($p=0.003$, ES=0.53) (Table 2). The wide ranges indicate a very variable perceived voice handicap for the entire patient cohort. Thus, 16 patients (29%) had a ≥10 point increase (more complaints) in VHI score, while seven patients (13%) experienced a ≥10 point decrease (fewer complaints) in VHI scores, despite normal voice function at baseline. Six months after surgery, the median VHI score of 9 points (range 4-80 points), ($p=0.30$, ES=0.18) was comparable to the baseline level. Six months after surgery, eight of the patients (15%) had a VHI score ≥10 points higher than baseline values, while 11 patients (20%) had ≥10 points lower VHI scores compared to baseline. Postoperative paresis corresponded to a 12±28 point increase in VHI compared to patients with no paresis ($p=0.002$). There was a negative

correlation between VHI and the maximum f_0 and maximum SPL, corresponding to increased subjective voice handicap with a decreased ability to shout, or to raise the voice pitch. Each reduction of one unit of ST in maximum f_0 or one dB in maximum SPL led to an increased VHI score of 0.76 points ($p=0.02$) and 1.36 points ($p<0.001$), respectively.

The impact of thyroidectomy on quality of life

The mean ThyPRO scale scores are shown in table 5. The data at baseline and 6 months postoperatively have previously been published as part of a larger cohort investigating DSQoL in comparison to the general population[9]. At three weeks after surgery, the Impaired Daily Life score had increased (i.e. deterioration), ($p<0.001$, ES=0.81), while most other scores showed small improvements (ES<0.5). Six months after surgery, symptoms were reduced significantly for all scales, except Impaired Social Life, Impaired Daily life and Impaired Sex Life scales. Neither the extent of surgery (hemithyroidectomy vs. total thyroidectomy) nor size of the thyroid correlated significantly with the scores of the ThyPRO scales.

Postoperative RLN/EBSLN paresis was significantly associated with the Goiter Symptom scale, with an 11.0 points poorer improvement in Goiter Symptoms ($p=0.02$) as compared to patients with no paresis, while no association with any other ThyPRO scale was found.

Discussion

Using multiple assessment points, well-validated questionnaires, and blinded VLS examinations, this study is the first to demonstrate how signs of postoperative RLN/EBSLN paresis relate to the degree of symptom relief in patients with benign thyroid nodular disease.

VLS is superior to indirect laryngoscopy or white light fiberlaryngoscopy, which often underestimates the frequency of vocal fold changes after thyroidectomy[16, 46]. This may explain the

high percentage (31%) of patients with vocal fold changes at three weeks after surgery in our study. Five of our patients had a minor oedema, granuloma or leukoplakia on the vocal folds, which might be related to a traumatic intubation procedure, use of large diameter NIM tubes, or post-operative voice abuse, whereas the remaining VLS changes (signs of RLN or EBSLN paresis) is more likely associated with the surgical procedure itself.

The multifactorial voice examination showed significantly reduced mean values of the maximum f_0 and maximum SPL, probably due to the high number of patients with signs of RLN/EBSLN paresis who experienced a more pronounced deterioration in voice parameters than the remaining patients. Neither age, sex, or goiter volume, nor surgical procedure was statistically correlated with RLN/EBSLN paresis, but this may be explained by lack of power in our study.

A few previous studies have also examined postoperative vocal fold changes after thyroidectomy[17, 18, 24]. Vicente et al. identified VLS abnormalities in 21% of patients two weeks after total thyroidectomy, but only in 6% of patients after a hemithyroidectomy[17]. At six months after surgery, these figures were significantly reduced to 7% having VLS abnormalities after total thyroidectomy, while hemithyroidectomized patients showed no VLS abnormalities[17]. Those data lend credence to the theory that post-thyroidectomy RLN/EBSLN paresis is underestimated[16]. In another study, Ryu et al. found a decrease in maximum f_0 of >10% in 57% of patients one month after surgery, with no improvement 12 months postoperatively[18]. An increased VHI of ≥10% was found in 63% of patients one month postoperatively, and in 84% 12 months after surgery[18]. In contrast, Maeda et al. found no change in subjective voice handicap using the VHI-10 questionnaire in the first month following surgery[24]. The above-mentioned studies[17, 18, 24] also included patients with thyroid malignancy, who may have a higher threshold for accepting any discomfort associated with surgery[47]. This may explain the more pronounced subjective voice handicap reported by the patients in our study.

In line with a previously published study from our institution[9], we found that patients with thyroid nodularity experienced substantial symptom relief and improved QoL after thyroidectomy. Importantly, RLN/EBSLN paresis three weeks after surgery was associated with less improvement in the Goiter symptoms score, but did not correlate with the other ThyPRO scale scores. This association may be explained by the fact that the Goiter Symptoms score includes the item "Have you experienced hoarseness in the last weeks". Our data therefore support the general safety of thyroid surgery, as postoperative RLN/EBSLN paresis had only little negative impact on quality of life. Importantly, RLN/EBSLN paresis seems to delay or reduce relief of the goiter symptoms. Kuhn et al. retrospectively investigated the impact of post-thyroidectomy voice disorders on QoL in thyroid cancer survivors using a non-validated 36-item questionnaire[27]. Fifty-one percent of patients reported post-thyroidectomy voice disorders, but the response rate was only 37%. A quarter of these patients reported a detrimental impact of the voice disorders on their QoL. These results are not directly comparable to ours due to differences in study design. However, it is evident from the study by Kuhn et al.[27] and supported by the present results, that postoperative voice changes affect QoL. Thus, it is crucial to inform the patients about how relief of goiter symptoms may depend on the occurrence of RLN/EBSLN paresis. With non-surgical goiter treatment, such as radioiodine[48] or ultrasound-guided interventions[31], side effects are more likely avoided[1, 29, 35, 49]. How such non-surgical interventions impact voice related QoL is, however, at present unknown.

The strengths of our study include a low number of patients lost to follow-up, the use of validated questionnaires, and blinded VLS and GRB analyses. A few limitations need to be addressed. Although our center receives patients with benign nodular goiter from a geographically well-defined area, a degree of selection bias is inevitable, as illustrated by the inclusion of only 62 of an initial 268 patients (23%) with benign nodular thyroid disease. In addition, our study might be

underpowered for analyzing the impact of age, sex, surgical procedure, and thyroid volume on RLN/EBSLN paresis and therefore, cannot conclude on subgroups of patients. In addition, electromyography examination was not used to confirm RLN/EBSLN paresis, implying that the reported incidence of paresis might be overestimated. Moreover, we excluded patients with thyroid malignancy as well as those with overt hyperthyroidism, in order to exclude the potential effects of fear of malignancy and that of increased metabolism on the perception of symptoms and QoL. Consequently, any conclusion of the impact of RLN/EBSLN paresis needs to be restricted to the thyroid phenotype investigated.

Conclusion

Signs of RLN/EBSLN paresis after thyroidectomy were associated with less pronounced improvement in Goiter Symptoms in patients with thyroid nodular disease. However, thyroidectomy was associated with reduced disease related symptoms and improved DSQoL by six month after surgery. This temporary side effect should be taken into account in the dialogue with the patient referred for benign thyroid nodular disease therapy. Comparison of surgical and non-surgical treatment modalities are awaited in order to further qualify recommendations for choice of therapy for future patients.

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Table 1

Characteristics of patients with benign nodular thyroid disease

(n = 55)

Age, *years, mean ± SD*	52 ± 15
Sex	
Female, *n* (%)	44 (80%)
Male, *n* (%)	11 (20%)
Surgery	
Total thyroidectomy, *n* (%)	15 (27%)
Thyroid lobectomy, *n* (%)	40 (73%)
Thyroid specimen, *gram, median (range)*	39 (8-280)
Previous radioiodine therapy	
Yes, *n (%)*	5 (9%)
No *n (%)*	50 (91%)
Thyrotropin (mU/L)	
Before surgery, *median (range)*	1.00 (0.00-3.40)
After surgery, *median (range)*	2.00 (0.22-6.00)
Postoperative levothyroxine	
Thyroid lobectomy, n (%)	9 (23%)
Total thyroidectomy, n (%)	15 (100%)
Permanent hypoparathyroidism	
Six months after surgery, *n (%)*	1 (2%)

SD: standard deviation

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Table 2

Voice scores [mean ± SD and median (range)] for 55 patients with benign nodular thyroid disease undergoing thyroidectomy

Voice parameter	Baseline	3 weeks after surgery	*p* value[a]	Effect size	6 months after surgery	*p* value[b]	Effect size
Frequency Range (ST)	35 ± 5	32 ± 5	<0.001	0.56	34 ± 5	0.13	0.20
Intensity Range (dB)	65 ± 8	63 ± 7	0.03	0.27	66 ± 7	0.42	0.10
Maximum f_0 (ST)	69 ± 5	65 ± 5	<0.001	0.66	68 ± 5	0.09	0.23
Maximum SPL (dB)	114 ± 4	112 ± 7	<0.001	0.57	114 ± 5	0.43	0.03
Minimum f_0 (ST)	34 ± 5	33 ± 5	0.01	0.15	33 ± 4	0.51	0.03
Minimum SPL (dB)	49 ± 5	48 ± 4	0.20	0.16	48 ± 5	0.04	0.25
Jitter	0.84 (0.23-2.94)	0.75 (0.28-5.90)	0.26	0.26	0.82 (0.29-3.40)	0.53	0.14
Shimmer	3.17 (1.35-8.38)	3.38 (1.36-9.54)	0.13	0.25	3.32 (1.6-6.84)	0.36	0.13
NHR	0.12 (0.08-0.22)	0.13 (0.09-0.23)	0.11	0.30	0.13 (0.07-0.24)	0.76	0.05
VTI	0.04 (0.02-0.10)	0.04 (0.03-0.08)	0.10	0.50	0.04 (0.02-0.09)	0.36	0.48
SPI	9.37 (2.43-43.54)	8.52 (2.89-42.50)	0.09	0.19	10.20 (2.40-29.96)	0.71	0.04
Grade	1 (0-2)	1 (0-3)	0.06	0.43	1 (0-2)	0.95	0.04
Roughness	1 (0-3)	1 (0-3)	0.75	0.05	1 (0-3)	0.68	0.04
Breathiness	1 (0-1)	1 (0-3)	0.70	0.08	1 (0-2)	0.95	0.00
MPT (seconds)	22 (7-50)	19 (6-47)	0.24	0.12	20 (12-50)	0.94	0.01
VHI	5 (0-70)	7 (0-87)	0.003	0.53	9 (4-80)	0.30	0.18

- Comparison of patient scores [mean ± SD and median (range)] between baseline and three weeks (a), and between baseline and six months (b) after surgery, using the linear mixed model.
- Effect sizes of 0.2-0.5 were considered as small, values above 0.5 to 0.8 as moderate and above 0.8 as large.

Fundamental frequency (f_0), semitone (ST), decibel (dB), noise to harmonic ratio (NHR), soft-phonation-index (SPI), voice-turbulence-index (VTI), maximum phonation time (MPT) in seconds, and voice handicap index (VHI).

Table 3

Voice scores [mean ± SD and median (range)] for the 13 patients with signs of RLN/EBSLN paresis three weeks after thyroidectomy

Voice parameter	Baseline	3 weeks after surgery	6 months after surgery	*p* value
Frequency Range (ST)	35 ± 6	28 ± 6	33 ± 5	<0.001
Intensity Range (dB)	66 ± 7	60 ± 8	65 ± 7	0.002
Maximum f_0 (ST)	69 ± 6	61 ± 5	67 ± 6	<0.001
Maximum SPL (dB)	113 ± 4	107 ± 8	112 ± 5	<0.001
Minimum f_0 (ST)	33 ± 4	32 ± 4	33 ± 4	0.83
Minimum SPL (dB)	47 ± 4	47 ± 4	47 ± 4	0.34
Jitter	1.27 (0.33-1.64)	1.64 (0.41-5.90)	1.25 (0.48-3.40)	<0.001
Shimmer	3.77 (2.61-8.38)	3.93 (2.13-9.54)	4.50 (2.45-6.84)	0.18
NHR	0.13 (0.08-0.22)	0.14 (0.09-0.23)	0.13 (0.09-0.24)	0.02
VTI	0.04 (0.03-0.07)	0.04 (0.03-0.08)	0.04 (0.02-0.06)	0.10
SPI	13.58 (2.60-34.93)	8.52 (2.89-42.50)	12.63 (5.59-25.00)	0.46
Grade	1 (0-1)	1 (0-3)	1 (0-2)	0.01
Roughness	1 (0-3)	1 (0-3)	0 (0-3)	0.02
Breathiness	1 (0-1)	1 (0-3)	1 (0-2)	0.01
MPT (seconds)	21 (12-50)	19 (6-47)	20 (12-50)	0.003
VHI	8 (0-41)	28 (0-87)	6 (0-80)	<0.001

- a linear mixed model was used to evaluate the impact of paresis on changes in voice parameters from baseline to three weeks and six months after surgery. The independent variables were age, sex, thyroid volume, surgical procedure, RLN/EBSLN paresis, and time point (baseline, three weeks after surgery, and six months after surgery)
- Fundamental frequency (f_0), semitone (ST), decibel (dB), noise to harmonic ratio (NHR), soft-phonation-index (SPI), voice-turbulence-index (VTI), maximum phonation time (MPT) in seconds, and voice handicap index (VHI).

Table 4

Voice scores [mean ± SD and median (range)] for the 42 patients without signs of RLN/EBSLN paresis three weeks after thyroidectomy

Voice parameter	Baseline	3 weeks after surgery	6 months after surgery	*p* value
Frequency Range (ST)	35 ± 5	34 ± 5	34 ± 5	0.01
Intensity Range (dB)	65 ± 7	64 ± 6	66 ± 7	0.54
Maximum f_0 (ST)	69 ± 5	67 ± 5	68 ± 5	<0.001
Maximum SPL (dB)	114 ± 5	113 ± 5	114 ± 5	0.01
Minimum f_0 (ST)	34 ± 5	33 ± 5	33 ± 5	0.02
Minimum SPL (dB)	50 ± 5	49 ± 4	48 ± 5	0.20
Jitter	0.77 (0.23-2.94)	0.64 (0.28-3.21)	0.77 (0.29-2.63)	0.50
Shimmer	2.98 (1.35-7.91)	3.36 (1.36-6.51)	3.14 (1.60-5.85)	0.08
NHR	0.12 (0.09-0.22)	0.13 (0.10-0.17)	0.12 (0.07-0.17)	0.05
VTI	0.04 (0.02-0.10)	0.04 (0.03-0.08)	0.04 (0.03-0.09)	0.09
SPI	10.06 (2.43-43.54)	8.43 (2.89-19.64)	9.16 (2.40-29.96)	0.18
Grade	1 (0-2)	1 (0-2)	1 (0-2)	0.41
Roughness	1 (0-3)	1 (0-2)	0 (0-3)	0.56
Breathiness	1 (0-1)	1 (0-2)	1 (0-1)	0.49
MPT (seconds)	22 (7-41)	20 (12-47)	20 (12-42)	0.50
VHI	5 (0-70)	7 (0-80)	2 (0-62)	0.32

- a linear mixed model was used to evaluate the changes in voice parameters from baseline to three weeks and six months after surgery in patients without RLN/EBSLN paresis. The independent variables were age, sex, thyroid volume, surgical procedure, and time point (baseline, three weeks after surgery, and six months after surgery)
- Fundamental frequency (f_0), semitone (ST), decibel (dB), noise to harmonic ratio (NHR), soft-phonation-index (SPI), voice-turbulence-index (VTI), maximum phonation time (MPT) in seconds, and voice handicap index (VHI).
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Table 5

Mean ± SD ThyPRO scale scores for patients with benign nodular thyroid disease (n = 55)

ThyPRO domain	Baseline	3 weeks after surgery	*p* value[a]	Effect size	6 months after surgery	*p* value[b]	Effect size
Goiter Symptoms	43 ± 23	34 ± 23	<0.001	0.39	9 ± 9	<0.001	1.47
Hyperthyroid Symptoms	23 ± 18	16 ± 18	0.003	0.39	14 ± 14	<0.001	0.49
Hypothyroid Symptoms	21 ± 19	16 ± 20	0.09	0.23	15 ± 18	0.02	0.29
Tiredness	51 ± 27	47 ± 29	0.42	0.17	36 ± 25	<0.001	0.56
Cognitive Complaints	20 ± 21	15 ± 23	0.08	0.25	14 ± 21	0.02	0.32
Anxiety	22 ± 22	14 ± 16	<0.001	0.33	14 ± 21	<0.001	0.60
Depressivity	26 ± 22	21 ± 18	0.07	0.25	18 ± 25	0.003	0.38
Emotional Susceptibility	30 ± 23	26 ± 24	0.20	0.18	22 ± 22	0.008	0.35
Impaired Social Life	7 ± 13	7 ± 13	0.92	0.04	5 ± 12	0.23	0.19
Impaired Daily Life	13 ± 18	28 ± 24	<0.001*	0.81	7 ± 16	0.06	0.31
Impaired Sex Life	15 ± 23	16 ± 24	0.91	0.03	10 ± 23	0.07	0.27
Cosmetic Complaints	20 ± 20	19 ± 16	0.59	0.04	11 ± 16	<0.001	0.45
Overall Quality of Life	34 ± 28	26 ± 28	0.03	0.31	12 ± 25	<0.001	0.80

Data achieved at baseline and at 6 months after surgery have in part been published previously [9].

Comparison of patient scores (mean ± SD) between baseline and three weeks (a), and between baseline and six months after surgery (b), using the linear mixed model. Effect sizes of 0.2-0.5 were considered as small, values above 0.5 to 0.8 as moderate and above 0.8 as large. Deterioration of score (*)

497 **Figure 1:** Flow diagram of patient inclusion and follow-up.

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