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The Impact of Post-thyroidectomy Paresis on Quality of Life in Patients with Nodular Thyroid Disease

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

3
4 Abbreviated title

5 **Post-thyroidectomy paresis, voice, and quality of life**

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36
37 **Conflicts of interest**

38 None.

39
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46

47 **Abstract**

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

50 **Study design:** Observational study

51 **Setting:** University hospital

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

58 **Results:** Sixty-two patients were included, 55 of whom completed all examinations. Three weeks
59 after surgery, a blinded VLS examination showed signs of paresis of either the recurrent laryngeal
60 nerve- or the external branch of the superior laryngeal nerve (RLN/EBSLN) in 13 patients (24%). A
61 paresis corresponded to a 12 ± 28 point increase in VHI ($p=0.002$) and was associated with a
62 significant 4.3 ± 7.5 semitone (ST) decrease in the maximum fundamental frequency ($p<0.001$) and a
63 5.3 ± 8.2 dB reduction in maximum intensity. Further it was associated with a 4.5 ± 11.2 seconds
64 reduction in MPT ($p=0.001$), and a 0.40 ± 1.19 increase in grade, 0.42 ± 1.41 in roughness, and
65 0.36 ± 1.11 in breathiness. Signs of postoperative RLN/EBSLN paresis correlated with an 11.0 point
66 ($p=0.02$) poorer improvement in Goiter symptoms, at both three weeks and six months after
67 surgery.

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

71

72 **Introduction**

73 Thyroidectomy is a well-established treatment option for patients with thyroid nodularity, Graves'
74 disease, and thyroid malignancy¹⁻⁴. Thyroid surgery profoundly improves disease-specific quality of
75 life (DSQoL) for patients with benign as well as malignant thyroid disease⁵⁻⁹, and relieves both
76 tracheal and esophageal compression¹⁰⁻¹¹. When performed at high volume centers, thyroidectomy
77 is reported to be associated with a low rate of long-term complications, i.e. hypocalcemia and
78 recurrent laryngeal nerve (RLN) paralysis¹²⁻¹⁵. However, up to 40% of patients experience a
79 postoperative voice and/or vocal fold change¹⁶⁻²⁰ which can be caused by intubation injuries²¹,
80 paresis of the external branch of the superior laryngeal nerve (EBSLN)^{22, 23}, RLN paresis²⁰, or
81 maladaptive mechanisms¹⁶. Especially RLN or EBSLN (RLN/EBSL) paresis can cause permanent
82 voice changes^{20, 22-23}. The majority of postoperative voice and/or vocal fold changes disappear
83 within three to six months after surgery, but the frequency of paresis might be grossly
84 underestimated^{16-18, 24-26}. Previous studies have indicated a detrimental impact of voice disorders on
85 patients' quality of life (QoL)²⁷. Knowledge of how RLN/EBSLN paresis affects symptom
86 improvement based on DSQoL in patients with thyroid nodularity is sparse, yet pertinent to obtain,
87 as non-surgical treatment options have increasingly been implemented^{4, 28-35}.

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

91

92 **Materials and Methods**

93 **Patient characteristics**

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

96 up. Thyroid nodularity was defined as the presence of an enlarged thyroid gland on ultrasound with
97 at least one nodule confirmed by ultrasonography. Serum levels of total thyroxine (T₄) and total
98 triiodothyronine (T₃) had to be within the normal range (67-134 nmol/L and 1.35-2.33 nmol/L,
99 respectively), but subclinically hypo- or hyperthyroid patients were eligible. Patients were included
100 from November 2014 with the last visits in August 2017, after a follow-up period of six months.
101 The exclusion criteria were: 1) previous surgery to the neck, including thyroid surgery; 2) suspicion
102 of thyroid cancer, as these patients were managed in a fast track program³⁶; 3) age below 20 or
103 above 80 years; 4) neuromuscular disease; and 5) a preoperatively impaired voice with need for
104 specialist assessment¹⁶.

105

106 **Vocal fold and voice outcome measures**

107 Each patient underwent a preoperative multifactorial voice and vocal fold examination, which was
108 repeated three weeks and six months after surgery. It was performed by an experienced resident in
109 Ear- Nose- and Throat diseases. This program comprised a videolaryngostroboscopic (VLS)
110 examination conducted with a 70° rigid videolaryngoscope (Pulsar II, Karl Storz, Germany) with
111 stroboscopic light source. Two experienced laryngologists independently rated blinded videos after
112 completion of the study. The consultants addressed the vocal fold mobility, vocal fold lengthening
113 during intonation, and potential localized vocal fold lesion as dichotomized variables. Impaired
114 vocal fold mobility was interpreted as a RLN paresis, due to normal mobility preoperatively and
115 absence of long-term intubation or other disease that might cause immobility by fixation. Impaired
116 ability to lengthen the vocal folds was interpreted as “sign of EBSLN paresis”, because
117 postoperative discomfort and maladaptive mechanisms might mimic EBSLN palsy. The consultants
118 had no access to information on how well the patient had cooperated at the time of examination.
119 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 points⁴⁰.

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 questionnaire⁴¹ 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 patients⁴². 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

168 **Statistics**

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

181 The sample size was calculated to 52 patients, based on an improvement in DSQoL
182 after surgery of 10 points in ThyPRO scores with a standard deviation of 25 points⁹. Cohen's effect
183 sizes (ES) were used with ES of 0.2-0.5 defined as small, above 0.5 to 0.8 as moderate, and values
184 > 0.8 as large⁴⁵.

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

188

189 **Results**

190 **Patient characteristics**

191 Of 268 consecutive patients with benign nodular thyroid disease, 230 were assessed for eligibility,
192 62 of whom were included in the study (Figure 1). Fifty-five patients completed all examinations
193 while seven patients (11%) were lost to follow-up. The mean age of the patients was 52 ± 15 years
194 (Table 1) compared to 50 ± 13 years for the non-included, but eligible patients ($p=0.19$).

195

196 **Voice and vocal fold outcome measures**

197 None of the 55 patients had vocal fold changes at baseline, whereas VLS examination three weeks
198 after surgery revealed uni- or bilateral paresis of the RLN in seven patients (13%) and hereof two
199 with paralysis of the RLN (4%). In two of the seven patients and in an additional six patients, the
200 ability to lengthen the vocal folds was impaired suggesting EBSLN paresis (15%). In total 13
201 patients (24%) had signs of postoperative paresis. Five patients (9%) had a localized vocal fold
202 lesion (two with minor edema, two with contact granulomas, and one with a small leukoplakia), of
203 whom one also had RLN paresis. In total, 17 patients (31%) had VLS changes after surgery. Six
204 months after surgery, two of the seven patients with RLN paresis still had impaired vocal fold
205 mobility (4%). However neither of the two patients with initial RLN paralysees had any signs of
206 persisting nerve injury. Two of the six patients with signs of EBSLN paresis still had impaired
207 ability to lengthen the vocal folds (4%). One patient had a persistent localized vocal fold lesion
208 (2%). Thus, a total of five patients (10%) had VLS changes by six months after surgery. Neither
209 age, sex, thyroid volume, nor the extent of surgery, had an impact on these results.

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

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

218 A postoperative paresis was associated with a significant 4.3 ± 7.5 ST decrease in the
219 maximum f_0 ($p < 0.001$), a 4.7 ± 7.9 ST decrease in the frequency range ($p < 0.001$), a 5.3 ± 8.2 dB
220 reduction in maximum intensity, and a 4.3 ± 10.5 dB reduction in intensity range ($p = 0.002$). A
221 paresis was also associated with a 4.5 ± 11.2 seconds reduction in MPT ($p = 0.001$), a 0.89 ± 1.41
222 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
223 grade ($p = 0.01$), 0.42 ± 1.41 in roughness (0.02), and 0.36 ± 1.11 in breathiness ($p = 0.01$) (Table 3).
224 Patients with no sign of RLN/EBSLN paresis only experienced minor changes with difficulties
225 reaching the highest pitch three weeks after surgery (Table 4)

226

227 **The impact of thyroidectomy on voice handicap index**

228 At baseline, the median VHI score was 5 points (range 0 to 70 points). Despite a
229 statistically significant average increase of 7 ± 22 points ($p = 0.003$, $ES = 0.53$), it remained low three
230 weeks after surgery with a median score of 7 points (0 to 87 points) ($p = 0.003$, $ES = 0.53$) (Table 2).
231 The wide ranges indicate a very variable perceived voice handicap for the entire patient cohort.
232 Thus, 16 patients (29%) had a ≥ 10 point increase (more complaints) in VHI score, while seven
233 patients (13%) experienced a ≥ 10 point decrease (fewer complaints) in VHI scores, despite normal
234 voice function at baseline. Six months after surgery, the median VHI score of 9 points (range 4-80
235 points), ($p = 0.30$, $ES = 0.18$) was comparable to the baseline level. Six months after surgery, eight of
236 the patients (15%) had a VHI score ≥ 10 points higher than baseline values, while 11 patients (20%)
237 had ≥ 10 points lower VHI scores compared to baseline. Postoperative paresis corresponded to a
238 12 ± 28 point increase in VHI compared to patients with no paresis ($p = 0.002$). There was a negative

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

243

244 **The impact of thyroidectomy on quality of life**

245 The mean ThyPRO scale scores are shown in table 5. The data at baseline and 6 months
246 postoperatively have previously been published as part of a larger cohort investigating DSQoL in
247 comparison to the general population⁹. At three weeks after surgery, the Impaired Daily Life score
248 had increased (i.e. deterioration), ($p<0.001$, $ES=0.81$), while most other scores showed small
249 improvements ($ES<0.5$). Six months after surgery, symptoms were reduced significantly for all
250 scales, except Impaired Social Life, Impaired Daily life and Impaired Sex Life scales. Neither the
251 extent of surgery (hemithyroidectomy vs. total thyroidectomy) nor size of the thyroid correlated
252 significantly with the scores of the ThyPRO scales.

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

256

257 **Discussion**

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

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

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

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

273 A few previous studies have also examined postoperative vocal fold changes after
274 thyroidectomy^{17, 18, 24}. Vicente et al. identified VLS abnormalities in 21% of patients two weeks
275 after total thyroidectomy, but only in 6% of patients after a hemithyroidectomy¹⁷. At six months
276 after surgery, these figures were significantly reduced to 7% having VLS abnormalities after total
277 thyroidectomy, while hemithyroidectomized patients showed no VLS abnormalities¹⁷. Those data
278 lend credence to the theory that post-thyroidectomy RLN/EBSLN paresis is underestimated¹⁶. In
279 another study, Ryu et al. found a decrease in maximum f_0 of >10% in 57% of patients one month
280 after surgery, with no improvement 12 months postoperatively¹⁸. An increased VHI of $\geq 10\%$ was
281 found in 63% of patients one month postoperatively, and in 84% 12 months after surgery¹⁸. In
282 contrast, Maeda et al. found no change in subjective voice handicap using the VHI-10 questionnaire
283 in the first month following surgery²⁴. The above-mentioned studies^{17, 18, 24} also included patients
284 with thyroid malignancy, who may have a higher threshold for accepting any discomfort associated
285 with surgery⁴⁷. This may explain the more pronounced subjective voice handicap reported by the
286 patients in our study.

287 In line with a previously published study from our institution⁹, we found that patients
288 with thyroid nodularity experienced substantial symptom relief and improved QoL after
289 thyroidectomy. Importantly, RLN/EBSLN paresis three weeks after surgery was associated with
290 less improvement in the Goiter symptoms score, but did not correlate with the other ThyPRO scale
291 scores. This association may be explained by the fact that the Goiter Symptoms score includes the
292 item “Have you experienced hoarseness in the last weeks”. Our data therefore support the general
293 safety of thyroid surgery, as postoperative RLN/EBSLN paresis had only little negative impact on
294 quality of life. Importantly, RLN/EBSLN paresis seems to delay or reduce relief of the goiter
295 symptoms. Kuhn et al. retrospectively investigated the impact of post-thyroidectomy voice
296 disorders on QoL in thyroid cancer survivors using a non-validated 36-item questionnaire²⁷. Fifty-
297 one percent of patients reported post-thyroidectomy voice disorders, but the response rate was only
298 37%. A quarter of these patients reported a detrimental impact of the voice disorders on their QoL.
299 These results are not directly comparable to ours due to differences in study design. However, it is
300 evident from the study by Kuhn et al.²⁷ and supported by the present results, that postoperative
301 voice changes affect QoL. Thus, it is crucial to inform the patients about how relief of goiter
302 symptoms may depend on the occurrence of RLN/EBSLN paresis. With non-surgical goiter
303 treatment, such as radioiodine⁴⁸ or ultrasound-guided interventions³¹, side effects are more likely
304 avoided^{1, 29, 35, 49}. How such non-surgical interventions impact voice related QoL is, however, at
305 present unknown.

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

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

319

320 **Conclusion**

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

328

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332

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- 456
- 457

Table 1

Characteristics of patients with benign nodular thyroid disease

(n = 55)

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

SD: standard deviation

459

Table 2

460

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

461

thyroidectomy

Voice parameter	Baseline	3 weeks after surgery	<i>p</i> value ^a	Effect size	6 months after surgery	<i>p</i> value ^b	Effect size
Frequency Range (ST)	35 \pm 5	32 \pm 5	<0.001	0.56	34 \pm 5	0.13	0.20
Intensity Range (dB)	65 \pm 8	63 \pm 7	0.03	0.27	66 \pm 7	0.42	0.10
Maximum f_0 (ST)	69 \pm 5	65 \pm 5	<0.001	0.66	68 \pm 5	0.09	0.23
Maximum SPL (dB)	114 \pm 4	112 \pm 7	<0.001	0.57	114 \pm 5	0.43	0.03
Minimum f_0 (ST)	34 \pm 5	33 \pm 5	0.01	0.15	33 \pm 4	0.51	0.03
Minimum SPL (dB)	49 \pm 5	48 \pm 4	0.20	0.16	48 \pm 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

462

- Comparison of patient scores [mean \pm SD and median (range)] between baseline and three weeks (a), and between

463

baseline and six months (b) after surgery, using the linear mixed model.

464

- 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.

465

Fundamental frequency (f_0), semitone (ST), decibel (dB), noise to harmonic ratio (NHR), soft-phonation-index (SPI),

466

voice-turbulence-index (VTI), maximum phonation time (MPT) in seconds, and voice handicap index (VHI).

467

468

469

Table 3

470

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

471

thyroidectomy

Voice parameter	Baseline	3 weeks after surgery	6 months after surgery	<i>p</i> value
Frequency Range (ST)	35 \pm 6	28 \pm 6	33 \pm 5	<0.001
Intensity Range (dB)	66 \pm 7	60 \pm 8	65 \pm 7	0.002
Maximum f_0 (ST)	69 \pm 6	61 \pm 5	67 \pm 6	<0.001
Maximum SPL (dB)	113 \pm 4	107 \pm 8	112 \pm 5	<0.001
Minimum f_0 (ST)	33 \pm 4	32 \pm 4	33 \pm 4	0.83
Minimum SPL (dB)	47 \pm 4	47 \pm 4	47 \pm 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

472 - a linear mixed model was used to evaluate the impact of paresis on changes in voice parameters from baseline to three
473 weeks and six months after surgery. The independent variables were age, sex, thyroid volume, surgical procedure,
474 RLN/EBSLN paresis, and time point (baseline, three weeks after surgery, and six months after surgery)

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

477

478

Table 4

479

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

480

after thyroidectomy

Voice parameter	Baseline	3 weeks after surgery	6 months after surgery	<i>p</i> value
Frequency Range (ST)	35 \pm 5	34 \pm 5	34 \pm 5	0.01
Intensity Range (dB)	65 \pm 7	64 \pm 6	66 \pm 7	0.54
Maximum f_0 (ST)	69 \pm 5	67 \pm 5	68 \pm 5	<0.001
Maximum SPL (dB)	114 \pm 5	113 \pm 5	114 \pm 5	0.01
Minimum f_0 (ST)	34 \pm 5	33 \pm 5	33 \pm 5	0.02
Minimum SPL (dB)	50 \pm 5	49 \pm 4	48 \pm 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

481

- 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)

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- 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

490

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

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

491

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

493 Comparison of patient scores (mean \pm SD) between baseline and three weeks (a), and between baseline and six months
 494 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
 495 as moderate and above 0.8 as large. Deterioration of score (*)

496

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

498