VOCAL AFFECTION IN THYROID SURGERY

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Dedico esta Tese ao Daniel e ao Miguel.

If you are the smartest person in the room, then you are in the wrong room.

Confucius

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I. Abstract

Vocal affection in thyroid surgery

Voice production results from the complex function of the vocal mechanism. The vocal mechanism involves the larynx (commonly called the “voice box”) and the infralaryngeal, supralaryngeal and circunlaryngeal structures. The thyroid gland embraces the larynx and trachea, and laryngeal neurovascular structures are deeply connected to the thyroid gland.

Thyroid pathology may induce changes in laryngeal function from anatomical and/or functional compromise. In modern medicine, when proposing thyroid surgery to a patient, the goal is focused both on disease control and in quality-of-life preservation or improvement strategies. Focusing on the patients´ needs in thyroid surgery involves voice quality preservation, because this is a pre-operative concern in self-aware patients and therefore a patient related outcome measure (PROM) to be taken into account.

The importance of early diagnosis of laryngeal dysfunction in thyroidectomy patients derives from the reduced quality of life these patients experience from symptoms such as voice and swallowing disorders. Mechanisms of vocal affection in thyroid surgery are still not clear.

This study wants to quantify pre-operative and post-operative long term voice changes in thyroidectomy patients without vocal fold (VF) immobility and to confirm the hypothesis that an increased thyroid volume is a risk factor for post-operative voice changes.

The clinical practice improvement pretended with this investigation was the need to stratify risk factors more finely in statement 2b from 2010 American Academy of Otolaryngology – Head and Neck Society published guideline “Best Practice Guidelines for Voice Preservation in Thyroid Surgery”, establishing whether goiter surgery should be included in the conditions to refer for pre-operative laryngeal assessment in voice preservation strategies.

If bigger thyroid volume in goiter relates to increased risk for voice change post-operatively, then early referral to voice clinics of patients with increased volume thyroids, submitted to surgery, should be promoted, permitting timely intervention for better voice outcomes.

The more relevant conclusions from this PhD research work were the following:

1. There are relevant voice and laryngeal changes pre-operatively in patients proposed for thyroidectomy.
2. Most patients who seek medical advice related to voice changes post-operatively don´t have vocal fold mobility impairment.
3. Patients without thyroid cancer have more voice changes pre- and post-operatively than patients with thyroid cancer. This factor should prompt a revision of statement 2b, including non-malignant thyroid disease in peri-operative voice evaluation in thyroidectomy.

4. In patients with dysphonia, but without post-operative VF immobility, dysphonia in the first post-operative year is more frequent in the first three months.
5. In patients with dysphonia but without post-operative VF immobility, the voice improves to a level better than the pre-operative voice condition 6 months after surgery. Follow up and intervention for these patients is probably cost-effective in the first 3 post-operative months because, 6 months after surgery, voice improves in every patient without post-operative VF immobility, comparing to the first 3 post-operative months.
6. Post-operative dysphonia in thyroidectomy patients without VF immobility is characterized by reduced f0/a/ and reduced HPf0/i/ comparing to pre-operative results. These data confirms that dysphonia perceived by patients without VF immobility is objectively caused by a quantifiable change in objective voice analysis parameters.
7. Mean HPf0/i/ reduction post-operatively in patients without VF immobility is 60Hz. Reduced HPf0/i/ post-operatively is certainly one of the factors causing reduced singing ability perceived by the patients, when high pitch tones are required.
8. In patients without post operative VF immobility, both dysphonia, reduced f0/a/ and HPf0/i/ correlate to bigger thyroid volumes
9. Thyroid volume (cc) and weight (gram) is correlated to thyroid echography volume determination (cc) and both measures directly correlate to dysphonia, reduced f0/a/ and HPf0/i/ post-operatively.
10. These findings provide justification for considering increased echography thyroid volume as a risk factor for voice compromise in thyroidectomy patients. Increased thyroid volume pre-operatively should prompt early referral for voice clinics in the peri-operative period aiming at early and tailored voice re-habilitation when proven necessary, promoting a better voice related quality of life (QoL) in thyroidectomy patients.
11. Statement 2b in Best Practice Guidelines for Voice Preservation in Thyroid Surgery should include patients with increased volume goiter in peri-operative laryngeal evaluation.
12. Even without loss of sign (LOS) in intra-operative neuromonitoring (NIM) of recurrent nerve in thyroidectomy, patients with goiter should be referred for voice and laryngeal evaluation post-operatively.

The study was conducted in Hospital da Luz in Lisbon and in the Voice Department of Mayo Clinic Arizona in USA. All patients consented and the study was approved by the Hospital da Luz Ethic Committee CES/017/2014/PA and Nova Medical School Ethic Committee 38/2014/CEFCM.

Afeção vocal na cirurgia da tiroideia

A produção da voz deriva da função complexa do aparelho fonatório. O aparelho fonatório inclui a laringe (comumente chamada a "caixa de voz") e as estruturas supra, infra e cicunlaríngeas. A glândula tiroideia abraça a laringe e a traqueia e as estruturas neurovasculares da laringe apresentam uma estreita relação com a glândula tiroideia,

A patologia tiroideia pode condicionar alterações na função laríngea através de um compromisso anatómico e/ou funcional. Na medicina moderna, quando se propõe uma cirurgia tiroideia, o objetivo foca-se no controle da doença, mas também na preservação ou melhoria da qualidade de vida. O foco nas necessidades do doente na cirurgia da tiroideia implica a preservação da sua qualidade vocal, já que esta é uma preocupação dos doentes e como tal um *outcome* centrado no doente (PROM) a ser considerado.

A importância do diagnóstico precoce da disfunção laríngea nos doentes submetidos a tiroidectomia resulta da redução da qualidade de vida que estes doentes experienciam com o compromisso vocal ou da deglutição. Os mecanismos da afeção vocal na cirurgia da tiroideia não estão ainda totalmente claros.

Este estudo pretende quantificar as alterações vocais pré-operatórias, bem como as alterações vocais a longo prazo, nos doentes submetidos a tiroidectomia sem imobilidade das cordas vocais e confirmar a hipótese de que um aumento do volume da glândula tiroideia é um fator de risco nas alterações vocais pós-operatórias.

A melhoria na prática clínica pretendida com este estudo, foi a necessidade identificada de estratificar mais detalhadamente os fatores de risco constantes da afirmação 2b das *guidelines* para preservação da voz na cirurgia da tiroideia (emitidas em 2010 pela Academia Americana de Otorrinolaringologia e Cirurgia da Cabeça e Pescoço), estabelecendo se a cirurgia do bócio deve ser incluída nas situações a referenciar para avaliação laríngea pré e pós operatória, nas estratégias de preservação vocal.

Se o aumento do volume no bócio se relaciona com aumento do risco de alteração vocal no pós-operatório, então os doentes com tiroides aumentadas de volume por bócio, submetidos as tiroidectomias deverão ser encaminhados para consultas de voz, para atempada intervenção com vista a melhores resultados vocais.

As conclusões mais relevantes desta investigação ao abrigo do programa doutoral foram:

1. Existem alterações vocais e laríngeas significativas no pré-operatório de tiroidectomia
2. A maioria dos doentes, que procura apoio clínico por queixas vocais no pós-operatório de tiroidectomia, não apresenta alterações na mobilidade das pregas vocais (PV)
3. Doentes com patologia benigna têm mais alterações vocais no pré e pós-operatório do que os doentes com carcinoma da tiroideia. Este facto deve promover uma revisão da afirmação 2b, incluindo a patologia benigna da tiroideia na avaliação vocal pré-operatória de tiroidectomia
4. Em doentes com disfonia, mas sem imobilidade pós operatória das PV, a disfonia no primeiro ano é mais frequente nos primeiros 3 meses

5. Em doentes com disfonia mas sem imobilidade das PV pós operatória, a voz melhora face ao pré operatório, 6 meses após a cirurgia. O *follow up* e intervenção nestes doentes será provavelmente justificado, em termos de custo-eficácia, nos primeiros 3 meses já que, 6 meses após a cirurgia a voz melhora em todos os doentes sem imobilidade das PV comparativamente aos primeiros 3 meses de pós-operatório
6. A disfonia no pós-operatório de tiroidectomia sem alteração da mobilidade das PV é caracterizada por uma redução da f0/a/ e HPf0/i/ comparativamente aos resultados pré-operatórios. Estes dados confirmam que a disfonia sentida pelos doentes é objetivamente causada por uma alteração quantificável nos parâmetros de análise vocal.
7. A média da redução da HPf0/i/ no pós-operatório de doentes com disfonia sem imobilidade das PV, é 60Hz. Esta redução da HPf0/i/ no pós-operatório é certamente um dos fatores que condicionam a limitação em cantar que os doentes referem, quando tentam cantar em registos mais agudos.
8. Em doentes sem imobilidade das PV no pós-operatório, a disfonia, a redução da f0/a/ e a redução da HPf0/i/, correlacionam-se com o aumento do volume da tiroideia
9. O volume da tiroideia (cc) e o seu peso (grama) correlacionam-se com o volume determinado por ecografia da glândula (cc) e ambos se correlacionam diretamente com a disfonia, a redução da f0/a/ e redução da HPf0/i/ no pós-operatório.
10. Estes resultados justificam considerar o aumento ecográfico da glândula tiroideia como um fator de risco para o compromisso vocal na tiroidectomia. O aumento do volume da tiroideia no pré-operatório de tiroidectomia deve condicionar a referenciação destes doentes a consultas de voz no peri-operatório com vista a implementar medidas precoces e individualizadas de reabilitação vocal, sempre que indicado, com vista a promover uma melhor qualidade de vida (QoL) nos doentes tiroidectomizados.
11. A afirmação 2b das *guidelines* para preservação da voz na cirurgia da tiroideia deve incluir doentes com bócio e aumento do volume da tiroideia na avaliação laríngea peri-operatória
12. Mesmo na ausência de perda de sinal (LOS) na monitorização intraoperatória (NIM) do nervo recorrente na tiroidectomia, os doentes com bócio devem ser referenciados para avaliação vocal e laríngea no pós-operatório de tiroidectomia.

A investigação decorreu no Hospital da Luz em Lisboa e no Departamento de Voz da Mayo Clinic, Arizona nos EUA. Todos os doentes assinaram o consentimento informado e o estudo recebeu a aprovação da Comissão de Ética do Hospital da Luz CES/017/2014/PA e da Comissão de Ética da Nova Medical School 38/2014/CEFCM.

II. Introduction

The thyroid gland is situated in the anterior cervical compartment and has a close relationship with the larynx and trachea in its proximal portion. Derived from this close relationship, laryngeal function and voice quality may be at risk in the peri-operative period of thyroid surgery.

Thyroid pathology may induce changes in laryngeal function which can be the result of histological, anatomical and/or functional compromise. In modern medicine, when proposing thyroid surgery to a patient, our goal should focus both on disease control but also in quality-of-life preservation. Focusing on the patients´ needs in thyroid surgery involves voice preservation because this is always a pre-operative concern in self-aware patients. However, there are no precise guidelines concerning the most relevant variables to analyze for laryngeal function preservation in thyroid pathology. A full voice record and analysis will take no less than 20-30 minutes with a full laryngostroboscopic and voice record and analysis being probably too demanding and non-cost effective for the general population proposed for thyroid surgery. It would be important, for both patient tailored intervention and cost control, to focus the voice record and analysis on the variables that more frequently change in thyroid surgery, permitting to tailor effective prognostic and treatment strategies. These variables are not defined.

The importance of early diagnosis of laryngeal dysfunction in thyroidectomy derives from the reduced quality of life these patients realize when symptoms such as swallowing disorders and reduced voice quality are taken lightly by their physicians. Mechanisms of vocal affection in thyroid surgery are still not clear.

We hypothesize that pre-existence of laryngeal pathology predisposes to a higher susceptibility to vocal dysfunction after surgery of the gland. We also hypothesize that, in goiter, increased thyroid volume is associated with worse vocal outcome.

Therefore, it is mandatory to identify before surgery, patients with thyroid disease and secondary laryngeal dysfunction as well as patients with thyroid disease and primary laryngeal dysfunction (when intrinsic disease of the larynx exists) as this coexistence will induce, as we suppose to a higher degree of secondary laryngeal dysfunction as well as a higher vocal risk after thyroidectomy.

STATE OF THE ART

Gregory W. Randolph confirmed in 2010 at Thyroid[1] editorial the importance of laryngeal evaluation in pre and post-operative period of thyroid surgery concluding that the larynx has central importance in modern thyroid surgery.

American Academy of Otolaryngology Head and Neck Surgery (AAO-HNS) Foundation published June 2013 "Clinical Practice Guideline: Improving Voice Outcomes after Thyroid Surgery"[2]. Recommendations were set to optimize patients care based on evidence and evaluation of risk according to literature at time of publishing. These guidelines are similar to our peri–operative protocol of thyroid surgery at Voice Pathology Clinic in Hospital da Luz implemented since 2010. We see now validated a procedure that, since 2010, we believe essential for better voice outcome in thyroid surgery. Having now twelve years´ experience, we know that team work is essential; we also know that a full evaluation takes no less than thirty minutes and there is not, until the moment, evidence concerning the most important and reproducible variables to rely on.

These guidelines were questioned by Surgery´s Editorial April 2014[3]. According to the panel of surgeons from the most prestigious American Surgery Centers, AAO-HNS guidelines are inadequate because they overstate vocal dysfunction in thyroid surgery inducing anxiety in patients.

We have now set a theoretical discussion between otolaryngologists with vocal outcome concerns in thyroid surgery in mind and surgeons who doubt these vocal dysfunctions have any real importance. Time is now for clarification, discussion and scientific evidence.

From patient´s perspective there is no doubt about thyroid surgery morbidity in voice and swallowing[4], reaching 39% deterioration in post-operative period.

The optimal timing for evaluation of laryngeal function in thyroid surgery and the methods required have not yet been determined. David E. Rosow evaluated the consistency of clinical findings of laryngoscopy in vocal fold paralysis[5]- inherent subjectivity to evaluation of recurrent nerve disease with video stroboscopy was evaluated. If in paralysis the diagnosis is certain, in more subtle vocal mobility disorders, the same cannot be said. Beyond the subjectivity inherent to the evaluation of vocal fold mobility, voice is much more than just the simple opening and closing of the vocal folds. In reality, what disturbs our patients is the change or limitation of their vocal quality, and not so much the preservation of vocal fold movement or anatomical wholeness. The preservation of vocal function should be our goal and no longer just the preservation of the anatomical integrity of the recurrent laryngeal nerve. In a surgery with virtually no mortality, focus is now in reducing morbidity[4].

When evaluating vocal function in thyroid patients, our goal should focus on quantifying how vocal compromise affects the quality of life of our patients. Only in this way can we anticipate and diagnose early dysfunction related directly with the underlying pathology or with therapeutic options. The precocity of diagnosis will lead to a more timely rehabilitation course.

Pauline Meek et al[6] published in 2007 the first prospective study concerning vocal affection in the post-operative period of thyroid and parathyroid surgery. Voice quality changes were identified in all patients in the first three postoperative months including patients with apparent improvement at the level of video-stroboscopy. An interesting conclusion was the fact that recurrent nerve suspected lesion not always resulted in dysphonia. Another important conclusion was the potential for undiagnosed neurological lesions in the pre-operative period what has obvious significance in medico legal and informed consent subjects. As this study limitation, we may mention the variability of pathologies with poor representation of each individually and the fact that they did not use vocal evaluation objective data but just quality of life questionnaires and subjective vocal assessment scale.

Leonard Henry[7] considered the Dysphonia Severity Index (DSI) as an objective criteria for evaluation of vocal function after thyroidectomy having used for comparison the

Consensus Auditory-Perceptual Voice Evaluation (CAPE-V) - which quantifies the changes considered relevant by the observer- and the Voice Handicap Index (VHI) which quantifies the vocal changes considered relevant by the patient. In our opinion, this study lacks objectivity and reproducibility as there are no numeric and objective data for comparison as all the data are deduced from the subjectivity of the patient or Speech Language Pathologist (SLP) evaluation. Even if up to this moment SLP accept the reproducibility of these data, the European Society of Laryngology (among other Laryngology Societies) consider that voice analysis should include acoustic numerical objective determinations and video-stroboscopy in addition to quality of life questionnaires.

There is one evidence - changes in vocal quality do exist, in the absence of injuries of the laryngeal nerve, in patients after thyroidectomy[8,9]. Diego Vicente et al[10] identified 46% of vocal negative outcomes after thyroidectomy.

The inverse may also be stated. There is undiagnosed thyroid pathology in patients with symptomatic vocal cord paresis. Yolanda Heman-Ackah et al[11] identified unknown thyroid pathology in 47.4% of patients with vocal fold paresis. Every patient with vocal fold paresis diagnosis presented with mobile but sluggish vocal cords.

Caroline et al [12] published in 2012 the conclusions concerning predictability of recurrent nerve paresis in patients submitted to thyroid surgery not being an inclusion criterion the existence of vocal symptoms. Goiter patients were the patients which more frequently presented with recurrent nerve disturbance in post-operative electromyography (EMG) in comparison to adenoma patients. The rebound of this affection in quality of life or vocal function was not determined. Recurrent nerve disturbance was confirmed by EMG in pre and post-operative period even though the importance of neuromonitoring of the recurrent nerve had not been established until the moment of publication, in vocal function affection[13,14].

Bianca Siegel et al [15] published in 2017, results focusing in radiologic/clinicopathologic features relation to compressive symptoms in benign thyroid disease. Dyspnea was significantly related to tracheal compression, tracheal deviation, and substernal extension. Dysphagia was related to tracheal compression and tracheal deviation. Final pathologic diagnosis was not related to compressive symptoms, whereas specimen weight was significantly related to dyspnea and dysphagia. Vocal change was not objectively assessed in the research and this study was a retrospective study focusing in compressive subjective symptoms alone. However, having established a relation between dysphagia and dyspnea with radiologically identified tracheal changes related to specimen weight, makes it highly probable that vocal changes will exist as well because dysphonia is the third compressive symptom classically associated with goiter.

Admitting there is voice disturbance in primary hypothyroidism[16], that 77% of patients with hypothyroidism may have dysphonia[17] including lower pitch, vocal fatigue and reduction of vocal amplitude[18] and that hormonal thyroid replacement therapy induces changes in objective vocal parameter[19] one more parameter must be taken in account – thyroid function – in what concerns to its relationship with vocal function.

Admitting a possible or probable affection of vocal function in patients with thyroid pathology, submitted to surgery or not, we assume the importance of evaluation of vocal function in these patients for an early diagnosis and a timely and effective rehabilitation. However, there are several proposed alternatives for the diagnosis of these affections [20,21,22,23,24], several proposed evaluation timing determinations [2,20,] and several rehabilitation proposed strategies [21,22,23,24].

Recent international research [25,26,27,28], over the years our study went through since 2013, have centered in neuromonitoring of the recurrent nerve and, more recently, superior laryngeal nerves in thyroid surgery [29]. All the focus has, again, been centered on neural anatomical and functional preservation. Even if preservation of neural function is primordial in modern thyroid surgery, it is reductor to focus voice quality only in nerve function because voice is much more than just opening, closing and stretching of the vocal folds. Industry has had a central role in this research, heavily funding research, promoting publications and developing neural monitoring devices and protocols with positive quantifiable increments in neural preservation results in experienced hands. However, devices are expensive and they focus only on preserving the nerve signal and preserving post-operative opening, closing and stretching of vocal folds. Again, voice production involves a complex vocal system and focusing exclusively on vocal fold movement is reductor when aiming at vocal function preservation.

With neural impairment in thyroid surgery being more objectively quantified by recent research [26,28,29] and with neural monitoring devices reducing the probability for vocal mobility compromise, we believe research should now also be focused in objectively quantifying vocal compromise in thyroid surgical patients past mobility preservation, identifying other possible variables impacting prognosis and defining strategies for early identification and timely rehabilitation of vocal function in these patients.

Recentering medical research in pursuing patients' needs is the trend in future clinical research.

CURRENT GUIDELINES

Present guidelines for voice preservation in thyroid surgery were published by American Academy of Otolaryngology Head and Neck Surgery (AAO-HNS) Foundation in June 2013 "Clinical Practice Guideline: Improving Voice Outcomes after Thyroid Surgery"[2], Full guidelines are detailed in this chapter´s attachment

STATEMENT 2B. PREOPERATIVE LARYNGEAL ASSESSMENT OF THE NONIMPAIRED VOICE: The surgeon should examine vocal fold mobility, or refer the patient to a clinician who can examine vocal fold mobility, if the patient's voice is normal and the patient has (a) thyroid cancer with suspected extrathyroidal extension, or (b) prior neck surgery that increases the risk of laryngeal nerve injury (carotid endarterectomy, anterior approach to the cervical spine, cervical esophagectomy, and prior thyroid or parathyroid surgery), or (c) both, once a decision has been made to proceed with thyroid surgery. Recommendation based on observational studies with a preponderance of benefit over harm. Aggregate evidence quality: Grade C

The costs and time involved in full vocal assessment for every patient pre-operatively, as a basis for referral to laryngeal assessment, are significant. Not all surgical departments have access to voice clinics with the full range of tools for voice assessment which in its turn is time consuming. Focusing on conditions at higher risk for vocal compromise post-operatively should, in our view, be the center for research permitting to identify high risk patients pre-operatively in places where voice clinics are not accessible. Statement 2b does not include in pre-operative laryngeal examination recommendation patients with goiter. even though goiter has been related with worse vocal outcomes related to vocal fold hypomobility [6,30,31].

The question subjacent to this research was the need to stratify risk factors more finely in statement 2b, establishing whether goiter surgery should be included in the conditions to refer for pre-operative laryngeal assessment. For this purpose, firstly we have to confirm if goiter surgery induces worse vocal outcomes in patients without vocal fold immobility post-operatively and if so, if there is any identifiable pre-operative risk factor related to goiter characteristics. If we could identify pre-operative risk factors in this subpopulation, we would be able to more finely tailor post-operative vocal care for these patients, aiming at better voice preservation and quality of life.

OBJECTIVES

General objective

To promote the improvement of the level of care in voice preservation strategies after thyroid surgery.

Specific objective

1. Test the first hypothesis - that patients proposed for thyroid surgery have pre-operative undiagnosed vocal and laryngeal compromise, through a retrospective study.
2. Analyse the second hypothesis - patients without post-operative vocal fold immobility, have post-operative vocal compromise, through a prospective cohort study with blind control of laryngeal assessment.
3. Investigate the third hypothesis - that bigger thyroid volume, quantified by pre-operative echography, results in worse long term post-operative vocal function in patients without post-operative vocal fold immobility, through a prospective cohort study over one year with blind control of laryngeal assessment.

DETAILED DESCRIPTION (METHODOLOGY)

1. **Test of first hypothesis – patients proposed for thyroid surgery have pre-operative un-diagnosed vocal and laryngeal compromise**

To test the first hypothesis, a retrospective descriptive study was performed in 171 consecutive adult patients (> 18 years of age) who underwent hemi or total thyroidectomy in Hospital da Luz in Lisbon, over a period of 5 years (2010-2014). Only patients who underwent thyroidectomy with pre-operative assessment in our Voice Clinic were included. None of the 171 patients was excluded as they all had full data recorded pre-operatively.

All patients were routinely instructed to return for a post-operative evaluation if they had disturbing vocal complaints at the end of the first post-operative month. Post-operative data was collected only for these returning patients.

All patients consented and the study was approved by the Hospital da Luz Ethic Committee CES/017/2014/PA and Nova Medical School Ethic Committee 38/2014/CEFCM.

Results were published in J Surg Res 2020 [32].

2. **Test of second hypothesis - patients without post-operative vocal fold immobility, have post-operative vocal compromise**

3. **Test of third hypothesis - bigger thyroid volume, quantified by pre-operative echography, results in worse long term post-operative vocal function in patients without post-operative vocal fold immobility**

Having answered positively to our first hypothesis with this retrospective study, we underwent a prospective cohort study of 90 patients proposed for thyroidectomy with blind control for laryngostroboscopic (LS) results, over one year time, to answer the second and third hypothesis in our research.

Other than full voice assessment and laryngeal assessment for immobility, we obtained results for validated quality of life questionnaire – VHI - to assess the importance of vocal function changes in quality of life of patients. Thyroid volume was also determined in the pre and post-operative period from echographic determinations and surgical specimen results. Relevant changes other than immobility present in LS were also registered. Hypothyroid function was assessed by thyroid stimulating hormone (TSH) determination. Specific vocal tasks, still not validated for voice analysis of superior laryngeal nerve (SLN), were included as a novel approach for identifying compromise of this nerve´s function.

In what concerns the timing for identification of vocal affection in the post-operative period, LS and vocal function analysis were done at the end of the first month as far as there was no respiratory compromise - dyspnea (in these cases, due to a potentially life-threatening situation, the exam was done as soon as respiratory compromise was suspected). LS and vocal function analysis were repeated at the end of the third month and at the end of the sixth post-operative month; by this time, adequate non-invasive vocal rehabilitation with a weekly speech pathology rehabilitation session were predictably concluded in patients with vocal compromise. As a conclusion for the process and previous to any rehabilitation laryngeal surgery, vocal function reevaluation and LS were repeated at the end of the first year.

Due to the proven affection of voice by thyroid function, blood sample analysis of TSH were monitored in the pre and post-operative evaluations. In the first post-operative month TSH determinations are not routinely done in surgical protocols, because thyroid hormone replacement therapy is still being tailored so we did not have access to it [5,213,28,31].

We believe it was useful to determine the correlation between these variables with the thyroid pathology (tumoral, goiter) as well as with the surgical procedure. These data were also collected.

We also evaluated the possible correlation of thyroid volume determination in echography with thyroid volume and weight of the surgical specimen, to establish if thyroid echographic volume could be used as an objective determination of thyroid gland volume. Even if this statement seems very obvious, it has not, as far as we are aware, been proven yet. We looked for correlation between thyroid volume and vocal function.

Impairment of SLN function is a new area in voice preservation studies in thyroid surgery. This nerve´s function evaluation is inseparable from the evaluation of inferior laryngeal nerve function. As SLN normal function deals with the high pitch range, we proposed, for the first time, Maximum Phonation Time (MPT) of the /i/ high pitch vowel in the *falsetto* range, as a measure for the function of this nerve in thyroid surgery. Not having normative values for the MFT of the /i/ high pitch vowel we had to compare it in a case control setting between pre and post-operative values. We proposed this vocal task based on the physiology of the nerve as, besides vocal gliding confirmation in endoscopy, there are no other defined protocols for its clinical evaluation. There is no data confirming the utility of external branch of the superior laryngeal nerve monitoring intraoperatively so, we didn´t use it; we used pooling of secretion (part of a secretion severity rating scale as proposed by Murray[33] in the LS as an indirect identification of endolaryngeal sensitivity compromise.

Every patient included in the study performed a full voice evaluation and laryngeal assessment (as proposed by current best practice guidelines) over one year period with some particular introductions for the purpose of this study alone. After obtaining informed consent, patients were anonymized in the first visit by the Ph. D. researcher and data was collected and stored exclusively by the Ph. D researcher without access of second parts involved in the study to personal data. All stored data was anonymized and there was only one copy in possession of the Ph. D researcher. When data was revised by Mayo Clinic Laryngologist for blind control, no identifiable data was present due to initial anonymization and exams were revised directly from the Ph. D researcher storage device which involved travelling to and from Phoenix.

The study was conducted in Hospital da Luz in Lisbon and in the Voice Department of Mayo Clinic Arizona in USA. All patients consented and the study was approved by the Hospital da Luz Ethic Committee CES/017/2014/PA and Nova Medical School Ethic Committee 38/2014/CEFCM.

The study was supported by the Ph. D. researcher.

The second hypothesis - that patients without post-operative vocal fold immobility, have post-operative vocal compromise - was confirmed by our results published in Journal of Voice January 2020. Preoperative voice characteristics in thyroid patients [34].

The third hypothesis in our study - that bigger thyroid volume, quantified by pre-operative echography, results in worse long term post-operative vocal function in patients without post-operative vocal fold immobility- , was confirmed with results published June 2022 in Annals of Otolaryngology and Rhinology. Is thyroid volume a new prognostic factor for voice outcome in patients without vocal fold immobility after thyroidectomy? [35]

Clinical Practice Guideline: Improving Voice Outcomes after Thyroid Surgery. American Academy of Otolaryngology Head and Neck Surgery (AAO-HNS) Foundation. June 2013[2]

STATEMENT 1. BASELINE VOICE ASSESSMENT: The surgeon should document assessment of the patient's voice once a decision has been made to proceed with thyroid surgery. Recommendation based on observational studies with a preponderance of benefit over harm. Aggregate evidence quality: Grade C

STATEMENT 2A. PREOPERATIVE LARYNGEAL ASSESSMENT OF THE IMPAIRED VOICE: The surgeon should examine vocal fold mobility, or refer the patient to a clinician who can examine vocal fold mobility, if the patient's voice is impaired (as determined by the assessment in Statement 1) and a decision has been made to proceed with thyroid surgery. Recommendation based on observational studies with a preponderance of benefit over harm. Aggregate evidence quality: Grade C

STATEMENT 2B. PREOPERATIVE LARYNGEAL ASSESSMENT OF THE NONIMPAIRED VOICE: The surgeon should examine vocal fold mobility, or refer the patient to a clinician who can examine vocal fold mobility, if the patient's voice is normal and the patient has (a) thyroid cancer with suspected extrathyroidal extension, or (b) prior neck surgery that increases the risk of laryngeal nerve injury (carotid endarterectomy, anterior approach to the cervical spine, cervical esophagectomy, and prior thyroid or parathyroid surgery), or (c) both, once a decision has been made to proceed with thyroid surgery. Recommendation based on observational studies with a preponderance of benefit over harm. Aggregate evidence quality: Grade C

STATEMENT 3. PATIENT EDUCATION ON VOICE OUTCOMES: The clinician should educate the patient about the potential impact of thyroid surgery on voice once a decision has been made to proceed with thyroid surgery. Recommendation based on preponderance of benefit over harm. Aggregate evidence quality: Grade B, RCTs on the value of patient education in general regarding surgery; Grade C, studies on the incidence of voice impairment following thyroid surgery in particular

STATEMENT 4. COMMUNICATION WITH ANESTHESIOLOGIST: The surgeon should inform the anesthesiologist of the results of abnormal preoperative laryngeal assessment in patients who have had laryngoscopy prior to thyroid surgery. Recommendation based on observational studies with a preponderance of benefit over harm. Aggregate evidence quality: Grade C

STATEMENT 5. IDENTIFYING RECURRENT LARYNGEAL NERVE: The surgeon should identify the recurrent laryngeal nerve(s) during thyroid surgery. Strong recommendation based on a preponderance of benefit over harm. Aggregate evidence quality: Grade B, RCTs and retrospective cohort studies.

STATEMENT 6. PROTECTION OF SUPERIOR LARYNGEAL NERVE: The surgeon should take steps to preserve the external branch of the superior laryngeal nerve(s) when performing thyroid surgery. Recommendation based on preponderance of benefit over harm. Aggregate evidence quality: Grade C

STATEMENT 7. INTRAOPERATIVE EMG MONITORING: The surgeon or their designee may monitor laryngeal electromyography during thyroid surgery. Option based on 1 RCT and observational studies with a balance of benefit versus harm. Aggregate evidence quality: Grade C.

STATEMENT 8. INTRAOPERATIVE CORTICOSTEROIDS: No recommendation can be made regarding the impact of a single intraoperative dose of intravenous corticosteroid on voice outcomes in patients undergoing thyroid surgery. No recommendation based on observational studies with limitations and a balance of benefit versus harm. Aggregate evidence quality: Grade D, observational studies with concerns over methodology and clinical importance

STATEMENT 9. POSTOPERATIVE VOICE ASSESSMENT: The surgeon should document whether there has been a change in voice between 2 weeks and 2 months following thyroid surgery. Recommendation based on systematic reviews, clinical practice guidelines, and prospective, observational studies with a preponderance of benefit over harm. Aggregate evidence quality: Grade C, cohort studes on the prevalence and duration of voice changes after thyroid surgery and the underreporting of voice changes if not specifically sought.

STATEMENT 10. POSTOPERATIVE LARYNGEAL EXAMINATION: Clinicians should examine vocal fold mobility or refer the patient for examination of vocal fold mobility in patients with a change in voice following thyroid surgery (as identified in Statement 9). Recommendation based on preponderance of benefit over harm. Aggregate evidence quality: Grade C, QOL data, early intervention data, diagnostic maneuver.

ATEMENT 11. OTOLARYNGOLOGY REFERRAL: The clinician should refer a patient to an otolaryngologist when abnormal vocal fold mobility is identified after thyroid surgery. Recommendation based on observational studies with a preponderance of benefit over harm. Aggregate evidence quality: Grade C, before and after studies showing voice improvement after surgical intervention.

STATEMENT 12. VOICE REHABILITATION: Clinicians should counsel patients with voice change or abnormal vocal fold mobility after thyroid surgery on options for voice rehabilitation. Recommendation based on systematic reviews and observational studies with a preponderance of benefit over harm. Aggregate evidence quality: Grade B, systematic reviews on the benefits of counseling in general on health care outcomes; Grade C, observational studies on the effectiveness of interventions for voice rehabilitation.

III. Relevant anatomy and physiology of the vocal mechanism. Assessment of voice.

The thyroid gland and its relevant connection to the vocal mechanism.

Introduction

The larynx is essential to normal voice production, but voice production is not limited to the larynx. The vocal mechanism encompasses the structures involved in voice production – larynx, supralaryngeal vocal tract and infralaryngeal vocal tract [36].

Besides the larynx (commonly called the voice box) the vocal mechanism also includes infralaryngeal structures (abdominal and back muscles, rib cage, trachea and lungs) supralaryngeal structures (pharynx, oral cavity, nose and paranasal sinuses) and circunlaryngeal structures (extralaryngeal muscles) Each component performs an important function in voice production. Supralaryngeal and infralaryngeal vocal tract are phisiopathologically referred to as supraglottic and infraglottic vocal tract respectively [36]. For consistency alignment with other publications in voice, we will use this latter classification in this thesis.

The thyroid gland is enclosed in layers of the *deep cervical fascia* in the anterior neck and is deeply connected to the larynx and trachea by the posterior suspensory ligament. Thyroid gland embraces the larynx and trachea; laryngeal neurovascular structures are deeply connected to the thyroid gland. This deep anatomical relation is the cause of laryngeal compromise induced by thyroid conditions.

Relevant anatomy and physiology of the vocal mechanism. Assessment of voice.

A. **Relevant Anatomy of the Vocal Mechanism** (adapted from Robert T. Sataloff [36] and · Neil Weir. In: Scott-Brown´s Otolaryngology [37])

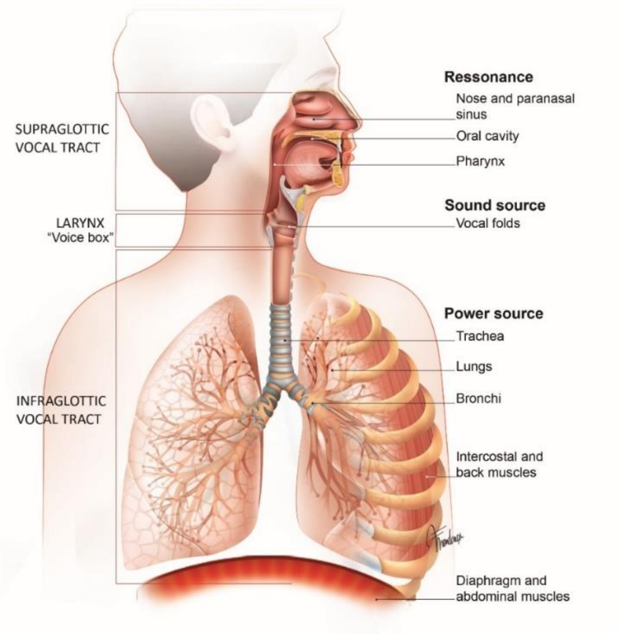

Figure 1 – Anatomy of the vocal mechanism (original)

1. The Larynx

The larynx is situated at the upper end of the trachea; it lies opposite the third to sixth cervical vertebrae in men while being somewhat higher in women and children. The skeletal framework of the larynx is formed by cartilages, which are connected by ligaments and membranes and are moved in relation to one another by both intrinsic and extrinsic muscles. It is lined with mucous membrane.

The larynx is composed of four basic anatomic units : skeletal framework, extrinsic muscles, intrinsic muscles and mucosa.

1. Skeletal framework

The laryngeal skeleton is composed by three single external cartilages - the leaf like epiglottis, the shield like thyroid cartilage and the ring like cricoid cartilage (the only complete ring in the airway) and by two interior paired cartilages – the pyramid like arytenoid cartilages and the accessory corniculate and cuneiform cartilages. Intrinsic ligaments connect the cartilages themselves and extrinsic ligaments connect the cartilages to the hyoid bone and trachea.

2. Extrinsic muscles

Extrinsic muscles can be divided in those below the hyoid bone (infrahyoid muscles) and those above the hyoid bone (suprahyoid muscles). They pull the larynx and change its vertical height. The infrahyoid muscles pull the larynx downwards and include the thyrohyoid, sternothyroid, sternohyoid and omohyoid. The suprahyoid muscles pull the larynx up and include the mylohyoid, geniohyoid, stylohyoid, stylopharingeus and salpingopharingeus. These muscles also change the vertical height of the external laryngeal framework.

3. Intrinsic muscles

In the interior of the larynx, intrinsic muscles interconnect laryngeal cartilages and the mucosa covers up all these structures. Vocal folds are defined as two fold-like structures which extend from the middle of the angle of the thyroid cartilage to the vocal process of the arytenoid cartilages; each fold is a layered structure of mucosa and muscle.

The free border of the vocal folds defines an anatomical reference point, the glottic space (glottis); above it lies the supraglotic space and below it the infraglottic space.

Intrinsic muscles of the larynx interconnect laryngeal cartilages and are of great importance in regulating the mechanical properties of the vocal folds as they control not only the position and shape of the vocal folds but also the elasticity and viscosity of each layer of the vocal fold. They may be divided into those that open -and close the glottis (posterior cricoarytenoids, lateral cricoarytenoids, oblique arytenoids and transverse); those that control the tension of the vocal folds (thyroaritenoids, also known as *vocalis* muscles, and the cricothyroids) and those that alter the shape of the inlet of the larynx namely the aryepiglottic and the thyroepiglottic . All intrinsic muscles are paired except the transverse. The posterior cricoarytenoid is the only muscle that opens the glottis and is also the only intrinsic laryngeal muscle that lies outside its cartilaginous framework; having just one muscle to open the vocal fold, makes vocal fold´s opening directly lost by loss of this muscle´s function.

Intrinsic ligaments of the larynx connect the cartilages themselves and strengthen the capsules of the intercartilaginous joints forming a broad sheet of fibroelastic tissue – the fibroelastic membrane - which lies beneath the mucous membrane forming an internal framework. It is divided into an upper and lower part by the laryngeal ventricle – an elongated recess below the vestibular fold (mucosal lined vestibular ligament) and the vocal fold. Anatomically, the vestibular folds limit inferiorly the vestibule of the laryngeal inside.

4. Mucous membrane

The mucous membrane lining the larynx is continuous above with that of the pharynx and below with that of the trachea. It is covered by either squamous, ciliated columnar or transitional. The vocal folds are covered by squamous epithelium.

The mucosa is subdivided in epithelium and *lamina propria* which consists of superficial, middle and deep layers. The superficial layer of *lamina propria* (also known as Reinke´s space) consists of loose fibrous substance similar to soft gelatin; it is this layer that vibrates most significantly during phonation. The intermediate layer of *lamina propria* consists mainly of elastic fibers and, together with the deep layer consisting of collagenous fibers form the vocal ligament deep to which is the *vocalis muscle* which constitutes the core of the vocal fold.

Mechanically, the vocal fold structures act more like three layers consisting of the cover (epithelium and superficial layer of the *lamina propria*), transition (intermediate and deep layers of the *lamina propria*) and body (the *vocalis muscle*).

The vocal folds act as the oscillator or voice source (noise maker) of the vocal tract. The intrinsic muscles alter the position, shape and tension of the vocal folds, bringing them together (adduction), moving them apart (abduction) or stretching them by increasing longitudinal tension. This change in space for airflow act as a blowing instrument for sound creation and the change in tension of the vocal folds act as a cord instrument in quality of sound generation; we may therefore consider the larynx as a complex blowing and cord instrument.

5. Nerve supply

The nerve supply of the larynx is from the vagus by its superior and inferior (recurrent) nerves.

The superior laryngeal nerve (SLN) divides, at the level of the greater horn of the hyoid bone in a small external and a larger internal branch.

The external branch of the superior laryngeal nerve provides motor supply to only one muscle of the larynx - the cricothyroid muscle - responsible for increasing longitudinal tension of the vocal folds (important in volume projection and pitch control of voice) while the internal branch pierces the thyrohyoid membrane (above the entrance of the superior laryngeal artery) dividing in two mainly sensory and secretomotor branches that provide sensibility (to the lower part of the pharynx, epiglottis, vallecula and vestibule of the larynx) participating in the cough reflex for protection of the airway. Again, having no redundancy in cricothyroid muscle innervation and the lack of protection of SLN external branch by the laryngeal framework, makes the loss of vocal fold tension an obvious consequence of diseases in thyroid.

All the remaining muscles on each side of the larynx are innervated by one of the two recurrent laryngeal nerves (RLN). The recurrent nerves are so called because they run a long course from the neck down into the chest and then backup to the larynx. Left recurrent nerve runs a longer course in the chest, hooking the aortic arch and this longer course is compensated by this nerve´s larger fibers which conduct stimulus faster [38]. so that left RLN neural stimulus reaches the left muscles of the larynx at the same time as the right RLN. In the neck, both nerves follow the same course and pass upwards accompanied by the inferior thyroid artery and enter the larynx behind the cricothyroid joint; they then divide in the motor branch and the sensory branch which supplies the mucous membrane below the level of the vocal folds. The recurrent nerves are easily injured by trauma, neck surgery and chest surgery mainly on the left side which may result in vocal cord paralysis. Injury of RLN affects all but one of intrinsic laryngeal muscles; its most obvious consequence is loss of vocal fold opening.

2. Supraglottic Vocal Tract

The supraglottic vocal tract includes the pharynx, tongue, palate, oral cavity, nose and other structures. Together, they act as a resonator (resonators) and are largely responsible for vocal quality (or timbre) of voice and all the perceived individual character of speech sounds. The vocal folds themselves produce only a “buzzing sound”.

3. Infraglottic Vocal Tract

The infraglottic vocal tract serves as the power source for the voice. It generates the force that directs the airflow between the vocal folds. Although in quiet breathing inspiration is actively drawn by the diaphragm and intercostal muscles, expiration is mainly passive. In forced expiration, the expiratory muscles (abdominal, intercostal, chest and back muscles) are active. In voice production, the expiratory muscles are active as well because they control the airflow of expiration across adducted vocal folds permitting glottic vibration to produce sound. Diseases that impair respiration such as asthma or laryngotracheal trauma undermine the power source of the voice; deficiencies in the infraglottic vocal tract may induce straining and overuse of the laryngeal muscles acting as a compensation mechanism to restore the power source for voice production, this resulting in glottic and supraglottic dysfunction.

B. Physiology of Voice Production (adapted from Robert T. Sataloff [36])

Intention to vocalize is transmitted to the motor cortex, a command for the vocal tract to produce sound is then transmitted from *motor nuclei* in the brainstem and spinal cord to the vocal tract; additional refinement of motor activity of the vocal tract involves extrapyramidal and autonomic nervous systems. These impulses produce a sound from the vocal tract muscular activation which is subject to auditory feedback from the individual´s auditory system, needed for controlling and modulating the impulses generated in the motor activity that produce the intended sound characteristics. We should regard voluntary quality of sound production as a complex arch involving motor impulses to vocal tract and auditory feedback for modulation of theses impulses.

1. Sound Production

Phonation – the production of sound – requires interaction among the power source, the oscillator and the resonator.

The power source composed by the infraglottic vocal tract (chest, abdomen and back musculature) produces a high pressure airstream.

Sound is then produced in the glottic space from oscillatory movements of the vocal folds produced by the airstream leaking out. These oscillatory movements of the vocal folds result from a very fast and active passage of air against an initially closed glottic space which opens in an upward direction collapsing immediately after passage of air, due to a myoellastic-aerodynamic mechanism promoted by the Bernouilli effect and by the elastic properties of the vocal folds. This complex mechanism results in very fast changes in glottic permeability, generated from the airstream actively pushing against the subglottic surface of the closed vocal fold forcing air out, while myoellastic properties of the vocal folds and aerodynamic mechanisms promote a reflex symmetric inactive closing of the vocal folds that squeezes air upwards This results in multi opening and closing cycles of the vocal folds, each one called a **vocal cycle**. These cycles mimic two symmetric flags flapping very fast at the same time as air goes by, touching each other for a very short time (a simplistic image used by the researcher for patients´ information).

The pressure exerted in the subglottic surface of the vocal folds necessary for its initial opening producing sound is called (subglottic) phonatory pressure. The frequency of vibration (number of vocal cycles per second) measured in Hertz (Hz) is dependent on the air pressure and the mechanical properties of the vocal folds, which are in part regulated by the laryngeal musculature. Pitch is the perceptual correlate of frequency of vibration - as pressure increases, the number of cycles also increase and pitch goes up. The sound produced by the vibrating vocal folds is a complex tone containing a fundamental frequency and many overtones or higher harmonic partials and is called the voice source signal; the voice source signal doesn´t show significant differences among individuals.

2. Resonance

Voice quality differences occur as the voice source signal passes through vocal tract resonance resonator system. The pharynx, oral cavity and the nasal and paranasal cavities act as a series of interconnected resonators. The vocal tract has four important resonant frequencies called formants.

3. Vocal Characteristics

The mechanisms that control two fundamental vocal characteristics – fundamental frequency and intensity – are particularly important:

Fundamental frequency of vibration, which corresponds to pitch, can be altered either by changing the air pressure (the higher the air pressure, the higher the fundamental frequency of vibration) or by changing the mechanical properties of the vocal folds (the more stretched or tense the vocal fold, the more frequently the vibrating cycles will occur, as far as vocal fold myoelastic properties are preserved).
Vocal intensity corresponds to loudness and depends on the degree of vocal fold motion - raising air pressure creates a greater amplitude of vocal fold displacement and increases vocal intensity.

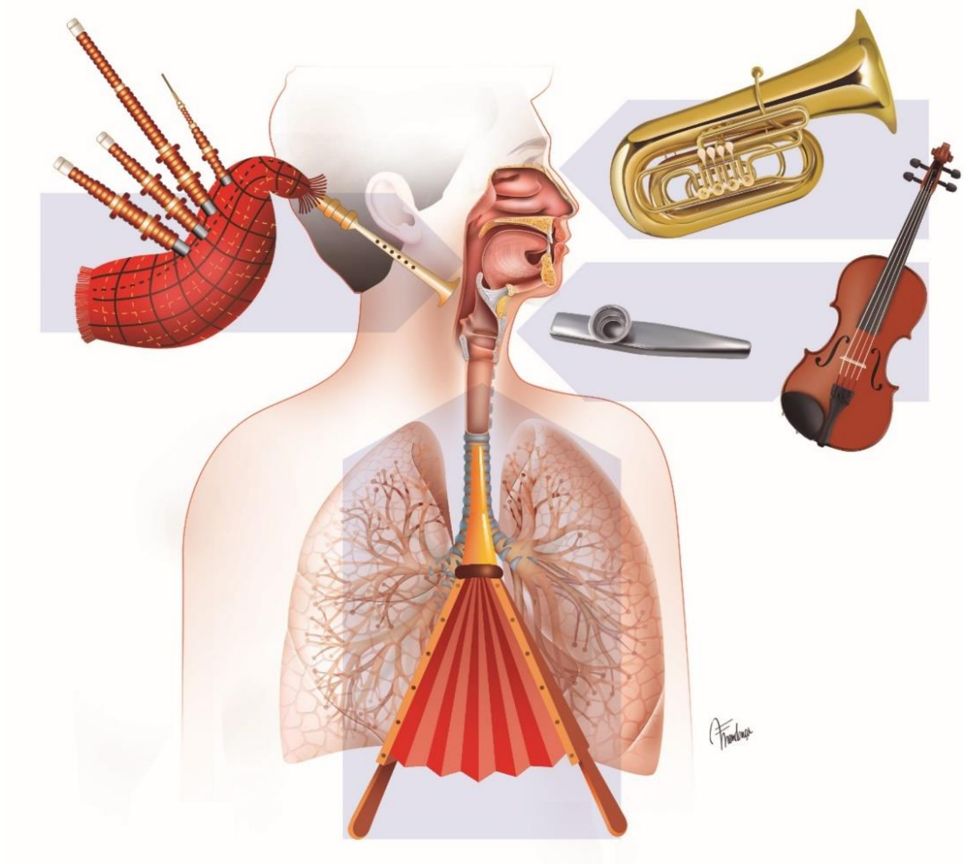

Figure 2 – Conceptual image of physiology of voice production using musical instruments. The infraglottic vocal tract acts as an air bellow when exhaling producing an air current; this exhaled air, squeezing between the closed vocal folds, generates a mucosal wave which produces a buzzing sound similar to that of a kazoo which can be changed in its fundamental frequency by changes in vocal fold length similarly to violin cords. This buzzing sound is then processed at the supraglottic vocal tract with the tongue and pharyngeal articulator/resonators acting as bagpipe and is then amplified by the air filled nose and paranasal sinus as sound passing over a trumpet (personal concept).

C. **Assessment of voice** (adapted from Philippe H. Dejonckere, M. Remacle, H.E. Eckel. In: Surgery of the Larynx and Trachea. Chapter 2. Assessment of Voice and Respiratory Function [39])

Voice production is multifactorial, and the respiratory function is directly involved in voice production. Audio recording is the most important requisite for voice quality assessment, permitting to use validated software voice assessment tools. Ideally the recordings are made in a sound-treated room or alternatively in an environment with ambient noise < 45dB. A miniature head-mounted microphone reduces aerodynamic noise from the mouth during speech. In regard to voice/speech material, protocol standard tasks are routinely assessed, including language specific and validated short reading passages.

1. Perception (Perceptive Analysis)

Auditory perceptual assessment follows a standard procedure; voice samples are classified using validated scales by experienced practitioners. A currently used scale for perceptual judgement of voice is the GRBAS scale which rates G-grade, R-roughness, B-breathiness, A-asthenicity and S-strain on a scale of 0-3. For reporting purposes, a four point grading scale (0-4) is used.

An important point in voice assessment is the fact that the term "dysphonia" should be used to any kind of perceived voice change and not only the commonly perceived roughness.

2. Vocal fold imaging

Laryngostroboscopy (LS) is the main clinical tool for vocal fold imaging. Rigid laryngoscopes and flexible videonasolaryngoscopes (VNL) with a continuous light source are available and videorecording is routinely provided with this equipment. LS involves using a pulsed light source in the scopes to visualize and record vocal fold movement in slow motion. It is classically recommended to observe and record LS under various voicing conditions.

LS involves a video-perceptual series of judgements and ratings. The basic parameters in LS are:

a. Glottic closure – complete, glottic insufficiency (type of insufficient glottic closure should be categorized) and straining.
b. Mucosal wave
    a. Symmetry
    b. Regularity
    c. Quality

3. Aerodynamics

3.1. Phonation Airflow

The simplest aerodynamic parameter of voicing is the maximum phonation time (MPT). It consists of the prolongation of an /a/ for as long as possible after maximum inspiration and at a spontaneous comfortable pitch and loudness; three trials are required, the longest being selected.

A reduction of possible bias from lung volume differences can be achieved using the phonation quotient (PQ) or averaged phonation airflow = vital capacity (ml) / MPT (s). Vital capacity (VC) can be measured using a hand-held spirometer.

MPT and PQ varies considerably among normal subjects. The method is especially useful for demonstrating changes in a single test subject over time.

3.2. Subglottic air pressure

Invasive measurements are reserved for research purposes.

Subglottal air pressure can be accurately estimated by measuring the intraoral air pressure produced during the repeated pronunciation of /pVp/ with a thin catheter introduced into the mouth.

4. Acoustics

Acoustic measures provide, in an objective and noninvasive way, a great deal of information about vocal function. Acoustic measures reflect the status of vocal function and do not relate specifically to certain voice disorders.

4.1. Visible Speech

Spectograms are visual representation of voice and can be used to make voice and speech visible.

4.2. Acoustical Parameters

Acoustic parameters are precise numerical values for many voice parameters. Factor analysis allows the large number of acoustical parameters to be reduced to a limited number of clusters.

- 4.2.1. Fundamental frequency of vibration – F0
- 4.2.2. Perturbation measures
  - 4.2.2.1. Jitter – mean difference between the periods of adjacent cycles divided by the mean period; it is a F0 related measurement
  - 4.2.2.2. Shimmer – mean difference between peak to peak amplitudes
  - 4.2.2.3. Harmonics to noise ratio (HNR)

5. Self-evaluation by Patients

Subjective self-evaluation determines the severity of voice disability in daily professional and social life and the possible emotional repercussions of the dysphonia. The voice handicap index (VHI) is a validated tool that permits to obtain a score of the disability produced by voice compromise based on the patients responses to a carefully selected list of questions. VHI questionnaires are validated for most languages and some dialects and are a reliable Patient Reported Outcome Measure (PROM).

6. Adjuvant techniques

6.1. Electroglottography

Electroglottography (EGG) is a method for monitoring vocal fold contact, rate of vibration, and perturbations of regularity during voice production. The signal originates from two electrodes lightly placed on the speaker´s neck at the level of the thyroid cartilage. EGG can only be used if there is vocal fold contact. One of the major applications of EGG is to trigger stroboscopic light source.

6.2. Electromyography

Electromyography (EMG) is an electrophysiological investigation of neuromuscular function. The main indications are mobility disorders, specially reduced mobility. A needle electrode is introduced through the cricothyroid ligament to approach the cricothyroid muscle; it is recommended that this exam is performed in cooperation with a general myography specialist. When the electrode is inserted in the muscle, a characteristic wave pattern is obtained from this muscle and it can be used either to guide correct substance injections or to quantify defibrillation percentage of muscular fibers if neuromuscular compromise is suspected (usually 14 days after neural lesion), defibrillation can be identified.

7. Basic protocol for functional assessment of voice recommended by the European Laryngological Society [40]

7.1. Perception
7.2. LS with video recording
7.3. Acoustics
7.4. Aerodynamics/Efficiency
7.5. Subjective Rating by Patients

The thyroid gland and its relevant connection to the vocal mechanism (adapted from Stephen Y. Lai, Susan J. Mandel, Randal S. Weber. In: Cummings Otolaryngology Head and Neck Surgery [41])

A. Relevant anatomy of the thyroid gland

The thyroid gland is composed of two lateral lobes connected by a central isthmus, weighing 15-25 g in adults. A thyroid lobe usually measures about 4 cm in height, 1.5 cm in width and 2 cm in depth. The superior pole lies posterior to the sternothyroid muscle and lateral to the inferior constrictor muscle and the posterior thyroid lamina. The inferior pole can extend to the level of the sixth tracheal ring. Approximately 40% of patients have a pyramidal lobe that arises from either lobe or the midline isthmus and extends superiorly.

The thyroid gland is enclosed between layers of the deep cervical fascia in the anterior neck. The true thyroid capsule is tightly adherent to the gland and the surgical capsule is a thin layer of tissue lying on the true thyroid capsule. Posteriorly, the deep cervical capsule condenses to form the posterior suspensory ligament or Berry´s ligament connecting the thyroid lobes to the cricoid cartilage and the first two tracheal rings.

Thyroid gland is composed of follicles which are the secreting functional units of the gland, together with a rich vascular, lymphatic and neural network.

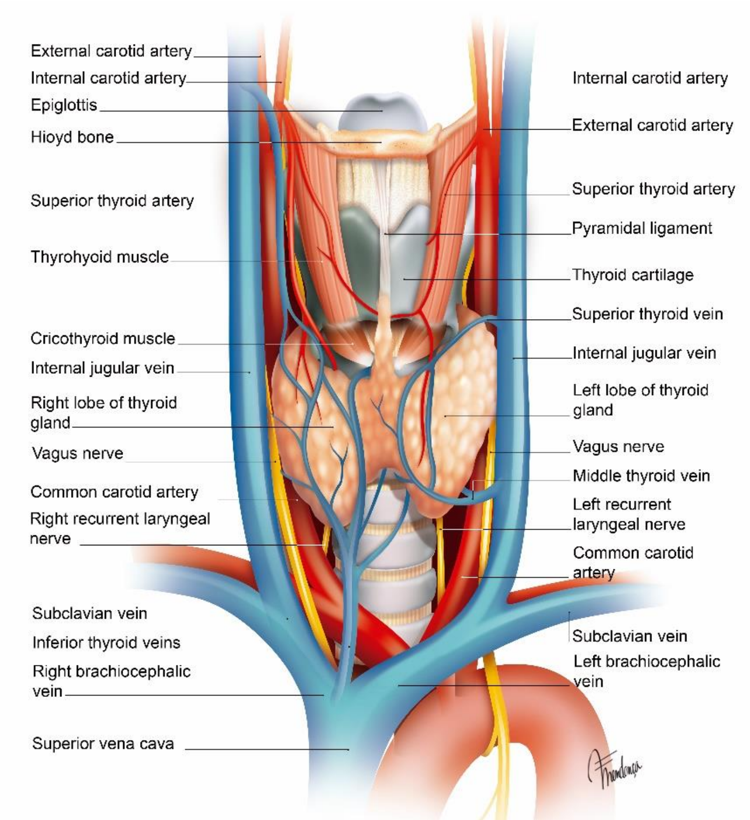

Figure 3 – Anatomy of the thyroid gland – laryngotracheal and vasculonervous connection

1. Vascular supply

The main arterial supply for the thyroid gland is from the superior and inferior thyroid arteries. Superior thyroid artery originates in the external carotid artery in the neck, it divides in a superior and inferior branch. Inferior thyroid artery originates from the thyrocervical trunk which is a branch of the subclavian artery; it also divides in a superior and an inferior branch. Inferior thyroid artery is an important surgical landmark for the recurrent laryngeal nerve ant he parathyroid glands. The recurrent laryngeal nerve will enter pass immediately superficial to the artery, deep to it or between its two terminal branches. Finding the artery during thyroidectomy provides the surgeon with a reliable indication of the depth to which the nerve should be sought.

2. Nerves

The recurrent laryngeal nerve on the right side ascends towards the gland just below the level of the inferior thyroid artery and assumes its classical position in the trachea-esophageal groove; it crosses the inferior thyroid artery either superficially, deeply or between its terminal branches and beyond those parts, lies immediately posterolateral to the ligament of Berry before disappearing behind the cricothyroid joint. It is not uncommon the nerve to divide in two and sometimes three terminal branches.

The left recurrent laryngeal nerve lies in the tracheoesophageal groove throughout its length. It is closely related to the inferior thyroid artery and may also divide in two or more terminal branches.

The external laryngeal nerve, which is a division of the superior laryngeal nerve, passes antero-inferiorly upon the superior constrictor muscle towards the cricothyroid muscle.

B. Physiology of the thyroid gland

The functioning unit of the thyroid gland is the follicle, which is made up of a single layer of cells surrounding a lumen which contains a variable amount of colloid. Thyroid concentrates iodine which is incorporated in thyroglobulin. Iodinated thyroglobulin is stored in the colloid and is selectively absorbed back into the cells, under the influence of thyroid stimulating hormone (TSH) where, by a process of hydrolysis it releases iodo-amino acids into the cell cytoplasm. Coupling reactions between these aminoacids lead to the formation of thyroxine (T4) and triiodothyronine (T3). Only T3 and T4 are released into the circulation. Free circulating T4 regulates TSH secretion. Thyroglobulin estimation, using its circulating antibody, which is detectable in the blood of all patients with differentiated thyroid cancer, is useful as a very sensitive marker of the extent of the disease.

Calcitonin is a peptide produced by the C cells of the thyroid gland. It reduces absorption of calcium from bone and lowers the serum calcium.

C. Thyroid function tests

Total T4 may be affected by thyroxine binding proteins in the circulation. Free T4 index can be obtained from a mathematical formula.

Serum TSH is useful in the diagnosis of hypothyroidism when its level is elevated at an early stage and also to monitoring adjustments to treatment with oral thyroxine. Hypothyroidism may induce changes in voice quality, namely slowing of speech, lower intensity of speech, lower F0 and edema in the vocal folds[88].

D. Imaging of the thyroid

Ultrasound permits to differentiate solid and cystic lesions and to distinguish between mono nodular and multinodular goiters. It is also used for guidance in fine needle aspiration biopsy.

Computed Tomography (CT) scan reveals features as compression of the trachea and esophagus and other distortions of anatomy in the neck including those of laryngeal framework.

E. Fine needle aspiration (FNA) biopsy

FNA is employed mainly in the work-up of patients with a solitary thyroid nodule or where suspicion of cancer exists. Cytopathology product is classified under the Bethesda classification system[89] in five recommended diagnostic categories:

I. Nondiagnostic or Unsatisfactory

II. Benign

III. Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance

IV. Follicular Neoplasm or Suspicious for a Follicular Neoplasm

V. Suspicious for Malignancy

VI. Malignant

F. Diseases of the thyroid gland

1. Enlargement of the gland

    a. Simple goiter – diffuse symmetrical enlargement of the gland
        i. Diffuse non-toxic goiter
        ii. Multinodular non-toxic goiter

    b. Metabolic diseases
        i. Diffuse toxic goiter – Graves' disease
        ii. Toxic nodular goiter – Plummer´s disease

2. Inflammatory conditions

    a. Hashimoto´s autoimmune thyroiditis
    b. Acute thyroiditis
    c. Subacute or Quervain thyroiditis

3. Thyroid neoplasms

    a. Papillary carcinoma comprises about 60% of all thyroid neoplasms, affects women in 2.4:1
    b. Follicular carcinoma comprises 18% of all thyroid neoplasms, affects women in 2.6:1
    c. Medullary carcinoma comprises between 5-10% of all thyroid neoplasms
    d. Anaplastic carcinoma comprises about 5% of all thyroid neoplasms
    e. Malignant lymphoma
    f. Follicular adenoma

G. Surgery of the thyroid gland

Surgery of the thyroid gland can involve either partial or total removal of the gland.

1. Hemithyroidectomy or subtotal thyroidectomy
2. Total thyroidectomy

Significant steps in surgical technique are briefly detailed. A midline transverse incision is done below cricoid cartilage level. Flaps are raised, the superior one up to the level of the thyroid notch. The midline raphe of the infrahyoid strap muscles is divided vertically. The plane between the sternohyoid and sternothyroid muscles is dissected allowing the sternohyoid muscle to be retracted laterally. The full width of the sternothyroid muscle (an external laryngeal muscle) is divided at its midpoint and elevated off the thyroid gland towards its origin in the thyroid cartilage. Superior and inferior thyroid arteries are identified and ligated and the recurrent laryngeal nerve and parathyroid glands are identified, either unilaterally in hemithyroidectomy or bilaterally in total thyroidectomy. Thyroid lobe mobilization off the nerve is most difficult at the ligament of Berry level, where most nerve injuries occur. Thyroid is then dissected away from the laryngotracheal cartilaginous skeleton.
The sternothyroid muscles are reapproximated in the midline. Drain (s) are inserted, and strap muscles and skin are sutured.

Recurrent laryngeal nerve paralysis is an unlikely complication when disease is purely within the thyroid gland. It is generally due to excessive traction, rough handling, coagulating vessels too close to the nerve or catching the nerve in a ligature. When disease is extra-thyroid, attempts to release disease out of the nerve contribute little to clearance of the disease and are likely to paralyze the nerve.

External laryngeal nerve paralysis is also more likely to occur when disease is extra thyroid. Isolated, it manifests as a limitation in the register of the voice or an inability to sing. In conjunction with ipsilateral recurrent laryngeal nerve paralysis, it manifests as a weak, breathy voice.

In total thyroidectomy, serum parathyroid hormone levels are measured immediately, and calcium levels are checked until stable levels are achieved. If total thyroidectomy is performed, patients start with thyroid hormone replacement on the first post operative day.

IV. Voice in thyroid surgery

1. Introduction

Voice disturbance after thyroidectomy may be identified, at least temporarily, in up to 39%[4] of patients and has classically been attributed to recurrent laryngeal nerve compromise. The incidence of temporary and permanent palsy varies in a wide range from 0-12% and 0-3.5% respectively[42]. Long lasting voice problems after thyroidectomy, irrespective of cause, are present in 29% of patients (personal data). Although temporary hoarseness is not uncommon in any surgery that involves general anesthesia, the potential for vocal tract injury in thyroid surgery mandates greater concern when hoarseness occurs after this type of procedure.

Voice production is multifactorial and with 0-3.5% reported incidence of long term recurrent laryngeal nerve injury causing mobility disorders, we still have 25% of long-lasting voice disorder in this surgery to account for.

Voice compromise impacts patients differently depending on their professional and/or social use of voice. Koufman scale[43] classifies patients according to professional voice use; its application to thyroidectomy patients may also permit to identify patients that will be most troubled by dysphonia.

2. Definition

Dysphonia is defined as the perception of voice change. It can be either perceived by the patient and family or by health care voice professionals. It is quantified by validated scales based in perceptive and objective voice analysis.

Any change in voice quality may be classified as dysphonia. Roughness, breathiness, asthenia and strain are all possible signs of dysphonia.

3. Clinical presentation and epidemiology

Dysphonia is perceived by patients as a modification in habitual voice characteristics. Change in voice quality after thyroidectomy is perceived by patients in 39% of cases[4].

Quantification of voice change is obtained by perceptive and objective voice analysis by trained professionals.

European Laryngological Society (ELS) proposed a new nomenclature for describing vocal fold motion impairment[44]. In the absence of proven section of the nerve or intra-operative neuromonitoring confirming complete loss of signal to the vocal fold, post-operative vocal fold immobility should be classified as paresis and not paralysis, until objectively confirming recurrent nerve function loss by post-operative electroneurography (ENG) or electromyography (EMG).

Most published data, repeatedly referred to by surgeons, present results for vocal fold paralysis (VFP) without objectively confirmed nerve function loss as they are inferred from post-operative vocal fold immobility. As VFP is diagnosed by post-operative immobility after thyroid surgery in many studies, the published results may be overrated. The average published VFP rate after thyroidectomy is 9.8% [28] and ranges from 0 to 18.6%. Goiter patients are the patients which more frequently present with recurrent nerve disturbance in post-operative EMG in comparison to adenoma patients. Traction and heating of the nerve conditioned by surgery are the usual identifiable causes for paresis. In thyroidectomies for malignant tumors, primary nerve invasion by tumor or the need for its section if macroscopically invaded, are causes for VFP.

From 1,381 RLN intraoperative neuromonitoring results published by Randolph in 2017[28], permanent and temporary RLN paralysis rates were 0% and 0.7%, respectively. These results are well under average VFP rates presented to patients in pre-operative counseling - data for pre-operative informed consent are well over Randolph results, which were obtained from ideal conditions.

In patients with post-operative dysphonia and no identifiable vocal fold immobility, SLN compromise and post-operative intubation injuries are the usual recognized causes. Both can be identified by standard laryngoscopic evaluation.

Intra-operative neuromonitoring of the RLN and more recently SLN, have led to prognostic advances concerning predictability of vocal immobility post operatively with tailored and rapid referral for voice rehabilitation protocols.

Intraoperative nerve monitoring of the RLN during thyroid surgery aids in nerve mapping, nerve identification, and prognostication of postoperative vocal fold function[28]. Neuromonitoring technique and algorithms in prediction of post-operative vocal fold mobility are well established but user and equipment related factors impact in its results. Published specificity of EMG loss of signal (LOS) in postoperative VFP detection is 99.9%, and sensitivity 33%. Negative predictive value of EMG LOS at the end of surgery in the prediction of postoperative VFP is 99.6%, whereas its positive predictive value for VFP is 75%.

4. Pathophysiology

When analyzing post thyroidectomy dysphonia, RLN injury is one possible cause but not the only possible cause. Voice production is a complex mechanism and reducing it to vocal fold mobility disorders is very restrictive. Pre-operative voice condition, intubation injuries, change in aerodynamic voice variables from decompressing thyroid pushing, external laryngeal muscles healing process and hypothyroid [18,19] post-operative status all may contribute to vocal post-operative results.

Presently, there is substantial literature suggesting that most nerve injuries from thyroidectomy are neuropraxic injuries that occur along the distal course of the RLN, most typically at the ligament of Berry, from stretch injury. When EMG waveform is preserved through the surgery, normal postoperative vocal fold function is assured, with negative predicting value over 99% [28].

Positive predictive value (PPV) is only 75% because intra-operative loss of signal, in addition to resulting from true nerve injury may, to some degree, result from equipment-related problems[28].

Intubation injuries may result in post-operative dysphonia. Most frequent causes are arytenoid cartilage luxation/subluxation impending thyroarytenoid muscle function, vocal fold lesion (hemorrhage or tracheal tube *lamina propria* indention) from tube compression and reduced sensitivity in subglottis (needed for phonation pressure recognition and fine control) secondary to cuff pressure in the subglottis.

Change in aerodynamic variables and external laryngeal muscle lesion resulting from surgery are a possibility for voice change but research is lacking.

Hypothyroid status induces a reduction in fundamental frequency of the voice resulting from edema of the lamina propria but cut levels for this condition are lacking [18,19].

5. Diagnosis

Dysphonia may be diagnosed by patients' symptomatic change in voice quality. Voice analysis by trained voice specialists can quantify dysphonia using either validated perceptive voice analysis scales and/or objective voice analysis software, both using validated voice tasks.

In dysphonic patients, laryngostroboscopy (LS) permits accurate identification of etiology [5].

Standard vocal tasks in LS permit diagnosis of RLN and SLN compromise. Intubation injuries are also diagnosed based on LS findings. Hypothyroid status may be suspected by *de novo* identification of lamina propria edema, but confirmation can only be achieved by thyroid hormone determination. Possible compromise of pre-laryngeal muscle function, resulting from surgery lesion and healing, can only be inferred by the temporal connection with surgery itself. External decompression of laryngotracheal structures by hypertrophic thyroid gland removal can be confirmed by CT scans, but in some patients, LS also permits to confirm re-establishing of normal anatomy of laryngotracheal structures. Aerodynamic changes from tracheal decompression after surgery can be confirmed from variation in results of quantifiable aerodynamic voice variables and respiratory function tests postoperatively.

6. Treatment

Vocal fold immobility treatment options vary in function of confirmation of intraoperative nerve section or LOS, presence of aspiration and patients voice quality.

If nerve loss is confirmed, presence of significant aspiration should prompt medialization procedures specially in elderly patients or those with impacted cough reflex or chronic pulmonary disease. If aspiration is absent, speech therapy may be offered and decision for medialization should be tailored according to patient´s vocal needs.

In the presence of immobility, without confirmed nerve loss, significant aspiration is also the trigger for decision in prompt medialization. If aspiration is absent, patients should be offered speech therapy and/or tailored medialization options according to vocal needs accomplishment.

Besides medialization, RLN reinnervation procedures may also be offered either during thyroid surgery or in deferred surgeries but results are not consistent in the literature; the objective of these procedures is to maintain some innervation to laryngeal intrinsic muscles reducing their atrophy but re-establishment of movement is not usually achieved, RLN and SLN pacing devices are also under investigation [45,46].

Intubation injuries usually respond to conservative measures. Speech therapy may be an option if voice does not recover. Surgery is usually reserved for vocal fold injuries or atrophy.

Thyroid hormone replacement therapy usually recovers voice characteristics in hypothyroid patients.

Post-operative external laryngeal muscle stiffening and aerodynamic changes usually respond to speech therapy and massage.

7. Conclusions

Voice change after thyroid surgery is frequent and compromises patients´ quality of life and professional capacities.

Prompt referral for tailored treatment permits to minimize these constraints. Early identification and referral of pre-operative risk situations to voice clinics will permit to offer a better risk assessment before surgery and earlier and tailored efficient treatment options for voice quality preservation after thyroid surgery.

V. RESULTS AND DISCUSSION

Voice in thyroid surgery without vocal fold immobility

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ABSTRACT

Introduction: Voice outcomes are of central importance in modern thyroid surgery. General Surgeons and Otolaryngologists (ENT) usually have different perspectives and value different criteria for successful assessment of voice issues.

Objective: Describe vocal changes in thyroid surgery patients

Methods: Retrospective descriptive study for 171 patients who underwent hemi or total thyroidectomy. Vocal complaints, vocal handicap indexes (VHI) scores and laryngostroboscopic (LE) results were assessed.

Results: 38% of patients reported laryngopharyngeal complaints preoperatively but only one patient had immobility.

Conclusions: Care must be taken when assuming that vocal changes in thyroid surgery result only or mainly from recurrent nerve injury. From 38% of patients with pre-operative vocal complaints only 0.5% of patients had immobility. Vocal changes in thyroid surgery are likely multifactorial and this study demonstrates that vocal fold immobility is not the only etiologic factor. Alternative causes for vocal changes in thyroid pathology and surgery must be investigated.

INTRODUCTION

Voice outcomes have a central importance in modern thyroid surgery[1]. Studies have reported a 39% voice and swallowing morbidity rate following thyroidectomy[4]. The thyroid gland is situated in the anterior cervical compartment and has a close relationship with the larynx and proximal trachea. Voice changes associated with thyroid disease may occur from the diseased thyroid gland or from surgery. However, primary laryngeal dysfunction may also coexist in patients with thyroid disease and its effect on vocal changes in patients assessed for thyroidectomy has not been fully quantified.

The American Academy of Otolaryngology Head and Neck Surgery (AAO-HNS) Foundation published the "Clinical Practice Guideline: Improving Voice Outcomes after Thyroid Surgery" in June 2013[2] which includes full voice assessment prior to surgery. However, these guidelines where questioned by an editorial in *Surgery* in April 2014[3]. The editorial stated that the AAO-HNS guidelines were considered inadequate by general surgeons due to concerns for overstating the incidence of vocal dysfunction in thyroid surgery, inducing anxiety in patients.

Given the differing views on the incidence of vocal dysfunction between ENTs and general surgeons, we performed a combined specialty study for clarification. Typically, patients undergo a preoperative complete voice evaluation only if there is current vocal dysfunction or if there is concern for possible damage to the recurrent laryngeal nerve during surgery.

Postulating that primary laryngeal dysfunction coexistent with thyroid disease may predispose thyroidectomy patients to a higher risk of poor voice outcome not related to immobility, we retrospectively revised data from 171 patients who underwent thyroidectomy in order to quantify pre-operative vocal problems.

MATERIALS AND METHODS

Patient Population

A retrospective descriptive study was performed on 171 consecutive adult patients (> 18 years of age) who underwent hemi or total thyroidectomy over a period of 5 years (2010-2014). Only patients who underwent thyroidectomy with pre-operative assessment in our Voice Clinic were included. None of the 171 patients was excluded as they all had full data recorded pre-operatively.

All patients were routinely instructed to return for a post-operative evaluation if they had disturbing vocal complaints at the end of the first post-operative month. Post-operative data was collected only for these returning patients.

All patients consented and the study was approved by the hospital´s Ethics Committee CES/017/2014/PA.

Data Collection

Since 2010, most thyroidectomy candidates in our hospital have been pre-operatively evaluated in our Voice Clinic. A full vocal functional evaluation, Voice Handicap Index (VHI) scores[47] and laryngostroboscopic examination (LE) are obtained and registered. Patients are informed of identified concomitant pre-operative organic or functional abnormalities and instructed to return post-operatively if they experience any concern regarding vocal quality post-operatively. Patients are evaluated within a maximum of a 7-day delay after their request for re-evaluation. All surgeries are performed by the same thyroid surgeon (general surgeon). Intra-operative neuromonitoring of the recurrent laryngeal nerve was not routinely used as an option of the Surgeon (this study was done before publishing of recurrent nerve neuromonitoring international study group results) ENT and Speech Language Pathologist (SLP) evaluations are all done by same ENT and SLP team.

Vocal Symptoms

Assessed vocal symptoms included chronic, new onset or a change in vocal quality or fatigue.

Voice Analysis

Vocal analysis was performed by the same speech and language pathologist using an headset omnidirectional microphone (PYLE PMEMI), with electret condenser, frequency response of 20Hz- 20KHz and -44dB ±3dB sensitivity, positioned at a constant distance of 4 cm lateral from the speaker's mouth and at a 45° angle from it (Dejonckere et al., 2001); a portable digital 16 bits mono recorder (TASCAM DR-05) was used, with a sample frequency of 44100 Hz; a digital sound level meter, model Rolls SLM305m was used, and ambient noise bellow 50 dB was assured (Dejonckere et al., 2001). Equipment was always tested and calibrated using a reference pure tone of 500 Hz, confirmed by acoustic analysis at the beginning of each recording day. Voice samples were recorded in a room with speakers, with the patient seated in a comfortable position.

Post-operative speech therapy

When indicated, post-operative speech therapy was given once weekly for 4 consecutive weeks, every other week in the second therapy month and monthly for the next 4 months. Patients were instructed for at home vocal exercises.

Laryngostroboscopic Examination

All patients were evaluated using Kay Pentax RLS 9100 B. Exams were evaluated for the presence of both structural abnormalities, functional changes and immobility. Structural abnormalities included nonspecific laryngeal inflammation and vocal fold lesions. Functional changes included both squeezing and insufficiency. Pitch glide was routinely assessed and registered if not present,

Statistical analysis

A descriptive analysis was performed for the pre-operative patients. A comparative analysis was done for patients who returned for post-operative evaluation using Excel for Windows.

RESULTS

Demographics

A total of 171 patients underwent thyroidectomy and pre-operative evaluation. Sex distribution included 29 male and 142 female patients. Patients were stratified by age (table 1) and voice use (table 2). Pathological results refer to post-operative specimen results (Graphic 1). As for surgery type, 135 patients had total thyroidectomy and 36 hemi-thyroidectomy. Tobacco smoking was present in 42 patients (25%). There were 29 patients who returned for re-evaluation post-operatively for relevant vocal complaints (17%).

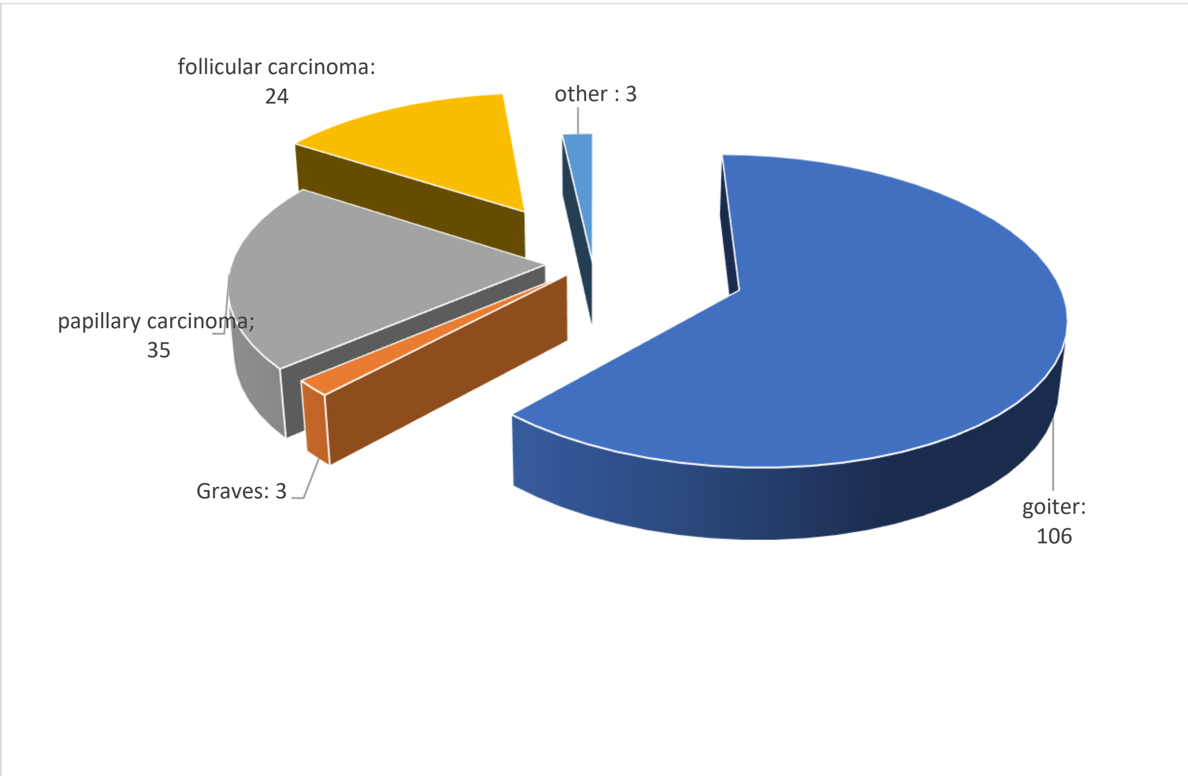
Table 1: participant's distribution according to age.

Age	
<30	8
30-50	78
51-70	80
>70	5

Table 2: participant´s distribution according to voice use

Voice professional	3
Habitual voice user	37
Sporadic user	131

Graphic 1: post-operative pathological results



Pre-Operative findings

Vocal Symptoms

Vocal complaints were present in 65/171 patients (38%), mainly vocal fatigue.

Voice analysis

VHI total score (VHI-T) median was 32 (normal <33). VHI-T results showed impairment in 5 patients (table 3). Maximal phonation time (MPT) was normal in 74/171 patients (46%) and reduced in 88/171 (54%) patients. Jitter was normal in 93% of the population and Shimmer was normal in 62%.

Table 3: VHI-T impaired results

VHI-T	
➢ 33	3
➢ 44	1
➢ 61	1

Laryngostroboscopic Examination

LE was considered abnormal in 106/171 (72%) patients (Table 4). Pitch glide in LE was present in patients with normal mobility.

Table 4: Abnormal LE (n=106)

Structural abnormality	68
Functional change	37
Vocal fold immobility	1

All the 5 patients with abnormal VHI-T results had abnormal findings in LE. In 3/171 patients with mild impairment, LE revealed structural change in 1 patient and laryngeal dysfunction in 2 patients; in 1/171 with moderate impairment, LE revealed structural change and in 1/171 with severe voice impairment, LE revealed laryngeal dysfunction. Interestingly, the patient with vocal fold immobility scored normal for VHI-T.

Post-Operative Results

Vocal Symptomatology

A total of 29 patients were re-evaluated for significant subjective post-operative vocal complaints (of which only 47% had pre-operative complaints). The complaints primarily included concerns of a different voice, weak voice or fatigue with vocal use. Twenty-five of these patients had surgery for goiter; as for type of surgery, 22/29 patients had total thyroidectomy.

All 29 patients underwent voice therapy. At the completion of voice therapy, all patients (100%) had subjective good vocal function (voice considered normal for daily use including professional needs), and no interest in complementary surgical therapy when offered.

Laryngostroboscopic Examination

Of the returning patients (29) with voice complaints, 23 showed positive findings on LE.

Eleven patients had vocal fold immobility (one had pre-operative immobility and 10 were de novo cases). At the 3 months follow up after the completion of voice therapy only one patient regained normal vocal fold mobility. All other patients showed compensated contralateral movement and no interest in complementary surgical therapy when offered.

Of the remaining 18 patients without immobility (62%), 6 had laryngeal dysfunction (2 had this diagnosis pre-operatively), 6 had structural changes (all present pre-operatively) and 6 were normal. Pitch glide was present in all these patients.

DISCUSSION

Voice complaints are common in patients undergoing thyroid surgery [6,8,9,10]. Voice results are therefore a primary concern for patients undergoing thyroidectomy. The current standard patient counseling for thyroidectomy is centered around the potential injury to the recurrent laryngeal nerve [12,13,14,25,28,48]. Most studies on voice and thyroid surgery focus mainly in post-operative results 6,[10,12,14,31]. Our study retrospectively described the incidence of vocal and endoscopic changes before thyroidectomy and the underlying etiologies causing vocal complaints.

In the present study, 38% of patients had some sort of vocal complaint prior to undergoing thyroid surgery. Only 0.5% resulted from vocal fold immobility. Interestingly, 72% of all patients had abnormal findings on laryngoscopic exam. It cannot be excluded that primary laryngeal dysfunction coexistent with thyroid disease and/or surgery may predispose thyroidectomy patients to a higher risk of poor voice outcome not related to immobility. The high percentage of abnormal findings may be reflective of the thyroid patient population, the inclusion of non-specific laryngeal inflammation in the structural changes category, the high population of smokers in the study (25%), or come from confirmation bias, the main limitation of our study (unblinded examiner)5. The lack of consistency between voice symptoms and exam findings is likely multifactorial. Both thyroid disease and laryngoscopic abnormalities develop slowly over time, which may cause an imperceptible vocal change for patients. Additionally, many laryngoscopic abnormalities do not cause vocal changes.

Twenty-nine patients returned postoperatively for considered subjectively significant vocal complaints, of which only 10 (35%) had a de novo vocal fold immobility. Therefore, a majority of patients had disturbing vocal complaints without vocal fold immobility, and so, care must be taken when assuming that vocal complaints related to thyroid surgery result only from recurrent nerve injury. This study showed that from our patients with pre-operative vocal complaints (38%), only 0.5% had immobility, and from the total 16.9% of patients with disturbing vocal complaints post-operatively, de novo immobility was present in only 35% of them.

The underlying etiology for these complaints is not fully understood23. Interestingly, one third of patients with vocal changes post-operatively without immobility had no abnormal finding on exam. This may be from sensory defects not perceived on typical in-office exam, or else be psychosomatic in nature.

All patients with post-operative voice changes had subjective improvement with voice therapy and no other procedural intervention. This highlights the high proportion of functional abnormalities in this patient population. Additionally, all patients with vocal fold immobility had subjective good voice quality with therapy alone. Given this finding, early vocal fold injection may not be necessary in every immobility patient and should be left to the shared decision of the surgeon and patient49.

One limitation of our study was that the classification of the LE results was done by the first author, who also assessed patient complaints and was aware of thyroid pathological results. Another was the possibility that patients were lost for follow up post-operatively. We may think that in some cases, voice change was not considered relevant enough by the patient, and so it didn’t trigger a second observation in voice clinic - as demonstrated by Kavookjan50, patients with lower VHI are less engaged in voice therapy even when prescribed. Distance and accessibility were not a limitation, for patients had an immediate appointment whenever requested, and all lived in a 50 km distance from the Hospital.

CONCLUSION

Care must be taken when assuming that vocal changes related to thyroid disease result only from recurrent nerve injury. This study showed that from 38% of patients with pre-operative vocal complaints, only 0.5% of patients had immobility and from the total 16.9% of patients with disturbing vocal complaints post-operatively, de novo immobility was present in only 35% of them. Alternative causes for vocal changes in thyroid disease and surgery must always be investigated.

Preoperative Voice Characteristics in Thyroid Patients

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ABSTRACT

Introduction: Thyroid surgery outcomes have evolved from mortality control strategies to morbidity control measures. Most vocal outcomes research in thyroid surgery are focused on recurrent nerve anatomic and functional preservation. However, there are likely multiple causes of vocal dysfunction in thyroid patients. We prospectively analyzed pre-operative patients with thyroid disease to define pre-operative vocal characteristics of this population.

Objective: Quantify vocal and laryngeal baseline conditions in thyroid surgical patients.

Methods: Prospective study of preoperative stroboscopy findings and vocal function assessing the correlation between thyroid disease, compressive symptoms, baseline vocal conditions and laryngoscopy results.

Results: Vocal quantitative scores were positive for dysphonia in 36% of patients and the Vocal Handicap Index confirmed either slight or moderate impairment in most patients. Stroboscopy results were abnormal in 60% of cases with no diagnoses of immobility. Correlation was established for diagnosis of cancer and the absence of symptoms.

Conclusions: These results point to a multifactorial cause for vocal impairment in thyroid surgery patients. Research on vocal impairment in thyroid surgery should not be centered exclusively on recurrent nerve neuromonitoring and functional preservation, but also on other variables that may contribute to vocal change in thyroid disease and surgery.

INTRODUCTION

Post-operative voice outcomes are one of the primary concerns for patients set to undergo thyroid surgery. It has been estimated that 39% of patients have a deterioration of voice and swallowing function following thyroidectomy4. A 2010 editorial in Thyroid stated the importance of laryngeal evaluation in the pre- and post-2operative period concluding that the larynx has central importance in modern thyroid surgery1 .The American Academy of Otolaryngology Head and Neck Surgery (AAO-HNS) Foundation's Clinical Practice Guideline on improving Voice Outcomes after Thyroid Surgery from June 20132 recommended, among others, that patients receive a pre-operative laryngeal examination if the voice is impaired or in the setting of a normal voice with suspected extrathyroidal extension. These guidelines were questioned by an editorial in Surgery in April 20143, where a panel of general surgeons wrote that those guidelines were inadequate because they overstate vocal dysfunction in thyroid surgery and induce anxiety in patients.

The disagreement between general surgeons and ENTs can be confusing to patients and needs to be rectified. In our mind, much of the disagreement is based on poorly defined risks of vocal outcomes following surgery, and differences in the types of post-operative complications managed by those specialties. Most general surgeons will typically evaluate only vocal fold immobility, whereas ENTs tend to manage a broader range of factors affecting voice, including anatomical lesions and functional changes.

The present study is a prospective study including ENTs, general surgeons, and speech – language pathologists, designed to rectify many of the details of this disagreement. Patients were evaluated pre-operatively for laryngeal symptoms and laryngeal stroboscopic examination findings. This current study was designed to determine the preoperative voice and laryngeal characteristics in thyroid patients to determine what other factors may be involved in their vocal abnormalities

MATERIALS AND METHODS

Patient Population

A prospective study was performed on a population of 48 consecutive patients over the age of 18 who were set to undergo either hemi or total thyroidectomy. Exclusion criteria were age below 18 years, previous thyroid surgery or radiotherapy of head and neck region, previous laryngeal or cervical surgery, known anatomic or functional laryngeal pathology with previous treatment, and cervical trauma.

All the patients gave their informed consent. Approval for the study was obtained from the hospital´s Ethics Committee (CES/017/2014/PA).

Variables analyzed were age, sex, occupation, fine needle aspiration (FNA) result of suspect thyroid nodule according to the Bethesda system for reporting thyroid cytopathology 2015, type of surgery, voice symptoms, swallowing symptoms, laryngeal stroboscopy examination (LS), and voice evaluation. Vocal use was assessed according to the Koufman classification[43].

Pre-Operative Evaluation:

Pre-operative symptomatology

Patient complaints relating to possible laryngeal dysfunction were assessed including dysphonia (voice change or vocal fatigue), dysphagia (limitation of swallowing or globus sensation) and dyspnea (tiredness or preferential sleeping position conditioned by breathing complaints).

Voice Evaluation

Voice evaluation was performed in every patient in the study by the same speech – language pathologist using a headset omnidirectional microphone (PYLE PMEMI), with electric condenser, frequency response of 20Hz- 20KHz and -44dB ±3dB sensitivity, placed at a constant position of 4 cm lateral to and at a 45° angle from the speaker's mouth (Dejonckere et al., 2001); a portable digital 16 bits mono recorder (TASCAM DR-05), with a sample frequency of 44100 Hz; a digital sound level meter, model Rolls SLM305m, and ambient noise bellow 50 dB was assured (Dejonckere et al., 2001). Equipment was always tested and calibrated using a reference pure tone of 500 Hz, confirmed by acoustic analysis at the beginning of each recording day. Voice samples were recorded with the patient seated in a comfortable position.

Voice evaluation included: auditory-perceptual evaluation of sustained vowel /a/ with the scale GRBAS (Hirano, 1981)[51]; self-evaluation with Voice Handicap Index (VHI)[46]; aerodynamic evaluation with the measurement of maximal phonation time (MPT, sec); acoustic evaluation for the parameters jitter (%) and shimmer (%) for sustained vowel /a/, vocal extension (VER, Hz) for reading the "Artur the Rat" (Guimarães, 2002)[52] and fundamental frequency for the high pitch sustained /i/ (HP f 0 /i/).

Laryngeal Stroboscopy Examination (Blinded)

LS recording was obtained using Kay Pentax RLS 9100 B. LS was performed either transorally or with a flexible endoscope according to patient choice and tolerance. LS evaluated the presence structural abnormalities, functional changes and immobility. Examination tasks were standardized and included visualization during quiet breathing, sustained /i/, repetitive /i/ and breath, and pitch glides. Structural abnormalities included nonspecific laryngeal inflammation and vocal fold lesions. Functional changes were assessed as present or absent and included both insufficiency (incomplete glottic closure at the onset of phonation) and squeezing (supraglottic laryngeal compression). Pitch glide was routinely assessed and registered. LS pooling of secretions as an indirect sign of swallowing impairment was assessed and considered positive if present.

LS examination recordings were blindly viewed and classified by a third-party fellowship trained laryngologist reviewer from another tertiary care hospital.

Statistics

Using SPSS 20 for Windows, a descriptive analysis was conducted. Normality of variables was tested. Variables had a non-parametric distribution, so the Spearman test for correlation of variables was applied. More than 20 % of expected frequencies of results were less than 5 so, even though similar Chi square test results were obtained, Spearman test results I□I are presented for consistency.

Possible correlations of pre-operative variables were analyzed: (1) pre-operative symptoms with age, sex and FNA result, (2) GRBAS total score (GRBAS-T) and Voice Handicap Index – total score (VHI-T), (3) VHI – T score with sex, occupation and FNA, (4) FNA with pre-operative symptoms, grade of dysphonia in GRBAS score (GRBAS-G), MPT, VER, HP f 0 /i/, jitter and shimmer.

Descriptive analysis was performed for LS, voice and swallowing results. Analysis was performed for the existence of possible single variable correlation between FNA and a) symptomology, b) LS vocal either normal or changed, c) LS vocal classification of normal, organic, nonspecific laryngeal inflammation (NSI) and functional, d) LS swallowing. The possible correlation of symptomology (either dysphonia and/or dyspnea) with LS vocal was assessed. Lastly, the correlation between dysphagia and LS vocal and LS swallowing results was evaluated.

RESULTS

Demographics

The population comprised 48 patients (41 women and 7 men) with a median age of 52.48 (STD 12.52), ranging between 31 and 85 years of age. As for vocal use, 22 (45.8%) were level 2 voice users and 26 (54.2%) level 3 voice users on the Koufman scale.

Surgical indications from FNA results are detailed in table 1. More detailed analysis of demographic data are presented in table 2; measure of the largest thyroid nodule determined by ultrasonography was included as thyroid nodules bigger than 3 cm have been related to laryngeal symptoms.

Table 1 - FNA results (n= 48)

FNA result	
Goiter	18
Suspicious	11
Papillary carcinoma	12
Follicular carcinoma	6
Anaplastic carcinoma	1

Table 2 – Population characteristics (n=48)

Legend: age, sex (F– female; M– male), FNA results according to Bethesda classification (1-goiter, 2 -papillary carcinoma, 3 -follicular carcinoma, 4-anaplastic carcionoma, 5-suspicious), type of surgery (1-hemithyroidectomy, 2-total thyroidectomy), biggest nodule dimension in cm (0- under 1cm; 2- 1cm to 3 cm; 3 bigger than 3 cm).

Patient	Age	Sex	FNA	Surgery
1	66	F	2	1
2	37	M	2	1
3	38	F	3	2
4	68	F	4	1
5	52	F	1	1
6	45	M	1	2
7	54	F	1	1
8	45	F	5	1
9	37	M	1	1
10	77	M	1	2
11	55	F	5	2
12	31	F	2	1
13	42	F	1	2
14	43	F	1	1
15	56	F	5	1
16	48	F	5	2
17	36	F	1	2
18	52	F	1	1
19	50	M	2	2
20	74	F	3	2
21	51	M	1	2
22	70	F	1	1
23	61	F	2	1
24	45	F	3	2
25	50	F	1	2
26	44	F	2	1
27	44	F	5	2
28	46	F	2	1
29	82	F	5	1
30	42	F	5	2
31	49	F	2	1
32	55	F	2	1
33	46	F	1	1
34	85	F	2	1
35	64	F	5	2
36	61	F	1	2
37	56	F	3	2
38	60	F	1	1
39	40	F	5	2
40	56	F	2	1
41	70	F	2	1
42	27	F	1	2
43	51	F	1	2
44	43	F	5	2
45	42	M	5	2
46	38	F	3	2
47	63	F	1	2
48	43	F	3	2

Pre-Operative Symptomatology

Great variation in answers was noted when patients were asked closed versus directed questions. Only 5.6% of patients reported having laryngeal symptoms (dysphonia, dysphagia, dyspnea) when asked closed questions, such as “have you noticed any change in voice or swallowing” or “do you have shortness of breath”. When asked direct questions such as if they felt “any voice change or vocal fatigue” to assess dysphonia, “any limitation in swallowing or globus sensation” to assess dysphagia, and “do you have tiredness, or a preferential sleeping position conditioned by breathing complaints” to assess dyspnea, positive answers obtained were higher and are detailed in table 3. Given the improved specificity, the answers to the direct questions were used for statistical analysis.

Table 3 – Pre-operative symptomatology (n=48)

Symptom	
Dysphonia	8 (16.7%)
Dysphagia	12 (25.9%)
Dyspnea	12 (25.9%)

Voice Evaluation

GRBAS-G score obtained was either 0 or 1; GRBAS-G score equal or higher than 1 was found in 35.8% of patients. VHI-T score revealed a slight handicap in 95.1% of patients for the entire age spread. A moderate handicap was observed in 4.9% of patients only within the 45-65 age group. MPT was within normal range for all patients. Jitter (median 0.51; STD 0.39) and shimmer (median 3.76; STD 1.84) were in the normal ranges. Vocal extension in reading (median 409.67; STD 41.4) was within the normal range, being higher (as expected) in women younger than 45 years old (median 416.04). HP f 0 /i/ median value was 415.37 (STD 91.23)

Laryngeal Stroboscopy Examination

LS was classified as normal in 40.4% of cases. From the 59.6% abnormal LS, 3.5 % had structural lesions, 19.3% had NSI, and 36.8% had functional changes (squeezing in 63.2% of cases and insufficiency in 36.8% of cases). There were no cases of vocal fold immobility. Pitch glide was present in all patients. LS was classified as positive for pooling of secretions in 6.3% of cases.

Correlation of pre-operative variables (table 4)

Correlation between demographics, symptoms and voice evaluation.

1. Correlation between pre-operative symptoms
    a. and age: correlation present, slight (for absence of symptoms and compressive symptoms individually)
    b. and sex: correlation present, slight (for absence of symptoms and compressive symptoms individually)
2. Correlation between GRBAS-T score
    a. and VHI-T score: correlation present, slight
3. Correlation between VHI-T
    a. and age: correlation present, slight
    b. and sex: correlation present, slight
    c. and FNA: correlation present, slight
4. Correlation between FNA (goiter or tumor)
    a. and Symptomatology (no symptoms, dysphonia, dysphagia, dyspnea): Correlation (IrI 0.05) between FNA tumor and absence of symptoms
    b. and GRBAS-G: correlation present, slight
    c. and VER: correlation present, slight
    d. and MPT: correlation present, slight
    e. and Shimmer: correlation present, slight
5. FNA with either GRBAS-G score, VER, HPf0/i/, MPT, Jitter or Shimmer:
    a. GRBAS-G, VER, MPT, Shimmer: correlation present, slight
    b. HP f0/i/, Jitter: correlation present, moderate

Laryngeal Stroboscopy Examination

1. Correlation between FNA (goiter or tumor)
    a. and LS vocal (either normal or changed): no correlation
    b. and LS vocal (either normal, structural, NLI or functional): no correlation
2. Correlation between LS pooling of secretions
    a. and FNA (tumor or goiter): no correlation
3. Correlation between symptomatology (dysphonia and/or dyspnea)
    a. and changed LS (either structural, NLI or functional): no correlation
4. Correlation between symptomatology dysphagia
    a. and LS pooling of secretions: no correlation
    b. and LS NLI: no correlation

Matrix of correlation between symptomology, FNA and LE Vocal (n=48)

Variáveis	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
FNA																
1 Goiter	1															
2 Tumor	-,600*	1														
Symptomology																
3 None	-,197	,331*	1													
4 Dysphonia	-,029	-,050	-,127	1												
5 Dysphagia	-,103	-,130	-,170	,392**	1											
6 Dispnoea	,091	-,226	-,170	,038	,288*	1										
Symptomology 1																
7 None	-,060	,246					1									
8 Symptoms	,060	-,246					-1,00**	1								
LE Vocal Changed																
9 Normal	,205	-,140							1							
e/ou 7	-,156	,022							,248	1						
LE Vocal Changed 1		10 Changed = 1 e/ou 2 e/ou 6														
11 Normal	,205	-,140									1					
12 Organic	-,162	,054									-,200	1				
13 NSI	-,218	,090									-,523**	-,114	1			
14 Functional (6/7)	-,183	,091									-,678**	-,147	,350*	1		
LE Swallowing																
15 Stasis	-,022														1	
16 No Stasis	,022														-1,00**	1

?p < 0.05 Correlation is significant at the 0.05 level (2-tailed); ??p < 0.01 Correlation is significant at the 0.01 level (2-tailed).

Table 4 – Correlation of pre-operative variables

DISCUSSION

Most of the research pertaining to patients who are candidates for thyroid surgery and have pre-operative voice symptoms has been centered on the recurrent laryngeal nerve. However, our clinical experience has suggested that most of these patients do have voice abnormalities and laryngeal changes without evidence of vocal fold immobility.

Several questions still exist related to the mechanisms of voice change in thyroid patients and to the pathological pathways therein involved. Most of the research has been centered on the recurrent laryngeal nerve26 and the anatomical variants that create the possibility for major and minor vocal changes5. However, again, considerable questions exist as to whether recurrent nerve injury is solely responsible for the patient´s vocal complaints. This current study was designed to determine the preoperative voice and laryngeal characteristics in thyroid patients to determine what other factors may be involved in their vocal abnormalities.

Higher symptom positive answers were found when patients were asked direct questions to ascertain voice complaints, dysphagia or dyspnea. Thyroid pathology usually evolves slowly, and so, it is possible that patients are unaware of “problems” or “issues” because they progressively adapted to their changes. When direct questions were asked, most answered positively (16.7% for dysphonia) in line with the results from validated tools for voice assessment - VHI scores (slight impairment in 95.5%, moderate impairment in 4.9%) and GRBAS-G score above 1 in 35.8% of cases. These results suggest that patients do have voice abnormalities pre-operatively, but they often unaware of them.

LS exams were abnormal in 59.6% of pre-operative evaluations. Having found a high percentage of abnormalities in a previous retrospective study for 171 patients (38%, unpublished data) we wanted to confirm these results. Blinded analysis of exams in this prospective study confirmed that most patients do have changes pre-operatively. From the abnormalities registered, none were related to immobility5,45. Structural lesions were present in 3.5%, NLI in 19.3 % and functional changes were present in 36.8%.

When correlating symptoms with FNA results, moderate correlation was found for cancer and absence of symptoms. One of the recommendations of the AAO-HNS guidelines is to perform a laryngeal examination pre-operatively in cancer patients only if they have voice complaints. Even though these recommendations relate to the risk of post-operative vocal changes, patients with cancer appear to not have voice symptoms pre-operatively. Additionally, our study showed that many patients have laryngeal abnormalities without any symptoms. No correlation was found between pre-operative diagnosis of tumor or goiter and changes found on laryngeal stroboscopy. This may be justified by a small sample limitation.

Given the high incidence of pre-operative voice pathology, none of which were found to have vocal fold immobility, hypotheses other than recurrent laryngeal nerve injury should be investigated. We believe aerodynamic distortion caused by laryngotracheal distortion may play a role in these cases10. No correlation was found for goiter and presence of symptoms, but it may be a question of sample size. We are currently performing a prospective blinded case-control study to test this hypothesis.

Additionally, the voice changes noted in this population may be from laryngeal sensory abnormalities and/or motor imbalances.

Our results are not in line with the present assumptions for the main mechanism of vocal changes in thyroid disease, for we did not find pre-operative vocal fold immobility in any of our dysphonic patients. Additionally, the fact that most patients had abnormal vocal parameters and were unaware of this, underscores the importance of performing a voice evaluation and laryngeal stroboscopy on all patients prior to a thyroidectomy. Without knowledge of the pre-operative vocal condition, the true cause of post-operative voice complaints may be unappreciated. Since many post-operative patients with voice complaints are found not to have a recurrent laryngeal nerve injury, it is possible the voice complaint may represent a worsening of an otherwise unaware vocal condition that has been exacerbated by the surgery. The findings of this study suggest the need for a broader outlook on the possible etiologies of thyroid-related voice changes and a more diligent evaluation of these patients in both the pre- and post-operative periods.

CONCLUSION

Vocal changes in pre-operative thyroid surgical patients are multifactorial and recurrent nerve involvement is only rarely an etiologic factor. Previous studies have mainly established the relationship between dysphonia and recurrent nerve damage with vocal fold immobility. However, care must be taken when assuming that vocal changes in thyroid surgery result only from nerve damage. A broader outlook on the possible etiologies of thyroid-related voice changes and a more diligent evaluation of these patients in both the pre- and post-operative periods is needed.

Is thyroid volume a new prognostic factor for voice outcome in patients without vocal fold immobility after thyroidectomy?

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ABSTRACT

Introduction: Thyroid pathology evolves slowly but its surgery suddenly modifies structures of vocal tract, what may elicit short and long-term voice changes in these patients, even when vocal fold mobility is not compromised.

Objective: The objective of this study was to analyze possible prognostic significance of thyroid specimen volume in long term voice outcomes of patients without vocal fold immobility after thyroidectomy.

Methods: Prospective cohort study of long-term vocal function and single blinded laryngoscopy results in patients without post-thyroidectomy vocal fold immobility. Correlation was assessed between voice outcomes and thyroid specimen volume over a one-year period time frame.

Results: A total of 90 patients were preparing to undergo a thyroidectomy and were enrolled in the study. In 84 patients without post-operative vocal fold immobility, perceived dysphonia increased in the first post-operative month, but it decreased to a level inferior to pre-operative evaluation after one year. LS functional changes decreased in the first post-operative month, but then increased at 3 months followed by a reduction compared to pre-operative results one year after surgery. GRBAS – G revealed a twofold increase of dysphonia in the first post-operative month, followed by a decrease comparing favorably to pre-operative results at one year. VHI- Fi subscore changes parallel that of GRBAS-G, as does f0 /a/ and HP f0 /i/ changes. HP f0 /i/ reveals a frequency reduction one month after surgery and it does not recover pre-operative mean frequency after one year. Correlation was established between dysphonia, surgical specimen weight and echographic thyroid volume. Correlation was also established for dysphonia, F0 /a/ change and HP f 0 /i/ reduction (mean 60Hz) with $p<0.01$ significance at one year.

Conclusions: Voice changes in patients without post-thyroidectomy vocal fold immobility involve F0/a/ change and HP f 0 /i/ reduction (mean 60Hz). These voice changes are related to thyroid volume and weight which, in turn, are correlated to echographic pre-operative thyroid volume. Increased echographic thryoid volume should be considered a prognostic factor for vocal compromise after thyroid surgery.

INTRODUCTION

Over the past ten years, voice outcomes in thyroid surgery have become of central importance in thyroid surgery. The American Academy of Otolaryngology Head and Neck Surgery (AAO-HNS) Foundation's Clinical Practice Guideline on improving Voice Outcomes after Thyroid Surgery from June 2013[2] recommended, among others, that patients receive a pre-operative laryngeal examination if the voice is impaired or in the setting of a normal voice with suspected extrathyroidal extension. These guidelines were questioned by an editorial in Surgery in April 2014[3], where a panel of general surgeons wrote that those guidelines were inadequate because they overstate vocal dysfunction in thyroid surgery and induce anxiety in patients.

Since 2010, international research on intraoperative recurrent laryngeal nerve neuromonitoring has received high interest and has resulted in the best practice recommendation to routinely use neuromonitoring in thyroid surgery [12,13,14,25,26,35,48]. The importance of routinely using intraoperative laryngeal nerve neuromonitoring cannot be overstated (not only on a clinical basis but also in malpractice defense). However, even though its use is recommended by AAO-HNS and the European Laryngology Academy, many surgeons still do not have routine access to this complimentary tool and many insurance companies still don´t cover its routine use.

A second point is that, not all post-operative thyroidectomy voice outcomes are related to vocal fold mobility issues [4,12,15,31,53]. Voice production involves other factors, such as mechanical, aerodynamic, resonance and emotional factors. Aerodynamic variables play an important role in voice production. Voluminous thyroid lesions can distort laryngotracheal anatomy by external compression, thereby altering airflow past the vocal folds. The majority of thyroid disease with surgical indication develop insidiously over time and anatomical structures in vicinity adapt to this increased volume over a long period. Surgery induces a sudden change of the involved and surrounding anatomy. This sudden change may also be perceived by the patient as a vocal change. Lastly, removal of the thyroid gland may induce irritation or cause minor damage to the external laryngeal muscles, resulting in altered phonatory function.

Baseline vocal and laryngeal conditions before surgery play a role as well. In a previous prospective study by the authors[34], vocal pre-operative quantitative scores were positive for dysphonia in 36% of patients and vocal handicap indices confirmed either slight or moderate impairment in most patients.

The primary objective of this one year long prospective cohort study in post-thyroidectomy patients was to analyze vocal function and laryngoscopy results in patients without post-thyroidectomy vocal fold immobility.

Our secondary objective was to analyze if thyroid specimen volume has prognostic significance in long-term post-operative voice quality in patients without vocal fold immobility after thyroid surgery

MATERIALS AND METHODS

Patient Population

A prospective cohort study was performed on a population of 90 consecutive patients over the age of 18 who were set to undergo either hemi or total thyroidectomy. Follow up was assessed over the first post-operative year. Exclusion criteria included age less than 18 years, previous thyroid surgery, radiotherapy of the head and neck region, previous laryngeal or cervical surgery, known anatomic or functional laryngeal pathology with previous treatment, and cervical trauma.

All patients gave their informed consent. Approval for the study was obtained from the Hospital da Luz Ethics Committee (CES/017/2014/PA).

Pre-Operative and post-operative evaluation

Variables analyzed were age, gender, occupation (vocal use), fine needle aspiration (FNA) result of suspect thyroid nodule, pre-operative determination of thyroid echographic volume (cm3,), type of surgery, thyroid surgical specimen histopathological diagnosis, thyroid surgical specimen volume (cm3,), total surgical thyroid specimen weight (gram), and thyroid stimulating hormone (TSH).

Thyroid

Thyroid volume was determined in cm3 (based in anteroposterior, lateral and transversal section dimensions) from both ultrasound determinations (eco volume) and from thyroid surgical specimen dimensions; weight in gram was determined from surgical specimen.

FNA result was classified according to the Bethesda system for reporting thyroid cytopathology 2015

TSH was registered pre-operatively and at three, six and twelve months post-operatively (before completion of the first post-operative month these results are not routinely assessed in our clinical practice).

Symptomatology

Patient complaints relating to possible laryngeal dysfunction were assessed including dysphonia (voice change or vocal fatigue), dysphagia (limitation of swallowing or globus sensation) and dyspnea (tiredness or preferential sleeping position conditioned by breathing complaints).

Voice Evaluation

Vocal use was assessed according to the Koufman classification [43].

Voice evaluation was performed for every patient in the study by the same speech – language pathologist using 1) a headset omnidirectional microphone (PYLE PMEMI), with electric condenser, frequency response of 20Hz- 20KHz and -44dB ±3dB sensitivity, placed at a constant position of 4 cm lateral to and at a 45° angle from the speaker's mouth (Dejonckere et al., 2001); 2) a portable digital 16 bits mono recorder (TASCAM DR-05), with a sample frequency of 44100 Hz; 3) a digital sound level meter, model Rolls SLM305m, with assurance of ambient noise bellow 50 dB (Dejonckere et al., 2001). Equipment was always tested and calibrated using a reference pure tone of 500 Hz and confirmed by acoustic analysis at the beginning of each recording day. Voice samples were recorded with the patient seated in a comfortable position.

Voice evaluation was performed and registered pre-operatively (time 0), one month after surgery (1 month), three months after surgery (3 month), six months after surgery (6 month) and twelve months after surgery (12 month).

Voice evaluation included: auditory-perceptual evaluation of sustained vowel /a/ with the scale GRBAS (Hirano, 1981)[51] self-evaluation with Voice Handicap Index (VHI)[46] ,aerodynamic evaluation with the measurement of maximal phonation time (MPT, sec); acoustic evaluation for the parameters fundamental frequency (f 0), jitter (%) and shimmer (%) for sustained vowel /a/, vocal extension (VER, Hz) for reading the "Artur the Rat" (Guimarães, 2002)[52] and fundamental frequency for the high pitch sustained /i/ (HP f 0 /i/ or F0/i/max).

Laryngeal Stroboscopy Examination (Blinded)

LS recording was obtained using Kay Pentax RLS 9100 B. LS was performed either transoral or with a flexible endoscope according to patient choice and tolerance. LS evaluated the presence of structural abnormalities, functional changes and immobility. Examination tasks were standardized and included visualization during quiet breathing, sustained /i/, repetitive /i/ and breath, and pitch glides. Structural abnormalities included nonspecific laryngeal inflammation (NSI) and vocal fold lesions. Functional changes were assessed as present or absent and included both insufficiency (incomplete glottic closure at the onset of phonation) and squeezing (supraglottic laryngeal compression). Pitch glide was routinely assessed and registered. Pooling of secretions as an indirect sign of swallowing impairment was assessed and considered positive if present.

LS was performed and recorded pre-operatively (time 0), one month after surgery (1 month), three months after surgery (3 month), six months after surgery (6 month) and twelve months after surgery (12 month). LS examination recordings were blindly viewed and classified by a third-party fellowship-trained laryngologist reviewer from another tertiary care hospital.

Statistics

Using SPSS 20 for Windows, a descriptive analysis was conducted. Normality of variables was tested. Tested variables had a non-parametric distribution, so the Spearman test for correlation of variables was applied. More than 20 % of expected frequencies of results were less than 5 so, even though similar Chi square test results were obtained, Spearman test results IρI are presented for consistency.

Long-term results of voice variables at times 0,1,3,6,12 months were obtained for the global study population. Voice assessment results were subsequently divided and analyzed independently in the subpopulation of patients without post-operative vocal fold immobility. Long-term results for symptoms and LS at times 0,1,3,6,12 months were assessed.

Graphic representation of voice assessment, symptoms and LS results was performed in the global study population and in the subpopulation without vocal fold immobility.

Correlation was assessed using Pearson correlation test. Correlation coefficient (R2 value) interval used for low degree correlation was [0.1-0.29]; for moderate degree correlation [0.3-0.49] and for high degree correlation [0.5-1]. When applicable, significance of correlation was determined at the 0.01 level (2-tailed) or at the 0.05 level (2-tailed). Analysis was performed for the existence of possible single variable correlation between thyroid volume and voice evaluation results: dysphonia symptoms, GRBAS – G subscore positive for dysphonia in perceptive analysis, acoustic variables (f 0 IaI, HP f 0 /i/), aerodynamic variable (MPT IaI), and self-evaluation (VHI-Fi subscore).

RESULTS

From a total of 90 patients included pre-operatively, 84 patients returned for re-evaluation at 1 month, 81 at 3 months, 68 at 6 months and 58 completed the study at 12 months.

Demographics

The population comprised 90 patients (74 women and 16 men) with a mean age of 50 years (s.d 13.76), ranging between 27 and 85 years of age. As for vocal use, 2 (2.2%) were professional voice users, 31 (34.1%) were habitual voice users and 57 (62.6%) were sporadic voice users based on Koufman scale (data was missing for 1 patient).

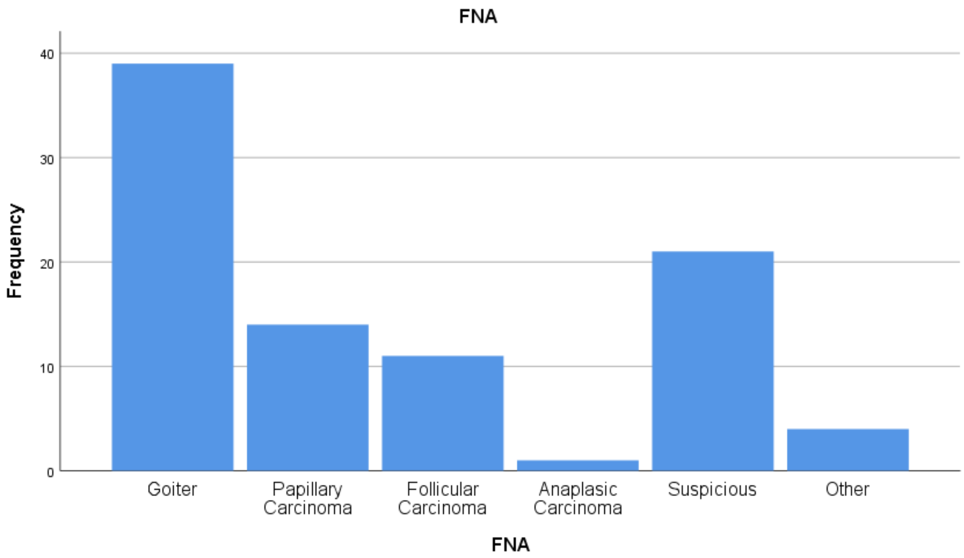
Thyroid disease related results

Pre-operative thyroid variables

FNA results are presented in graphic 1. The chi-square test for gender and FNA showed that there is no significant association in this population.

Mean thyroid echographic volume in cm3, revealed 50.47 cm3 on the left (s.d. 74,15), 34.85 cm3 on the right (s.d. 38.87) and 81.52 cm3 total (s.d. 86.13).

Graphic 1 – FNA results



Surgical procedure

From the baseline population of 90 patients, 6 did not ultimately undergo a thyroidectomy after referral to the voice clinic. Therefore, the post-operative population comprises 84 patients. Surgical procedures comprised 38 total thyroidectomies (41.8%) and 46 hemithyroidectomies (50.5%). A secondary total thyroidectomy was performed in 6 patients with a previous partial thyroidectomy for tumor.

Post-operative thyroid variables - surgical specimen

Histopathologic diagnosis

Thyroid specimen histopathologic results demonstrated a pre-operative preponderance of goiter (45.1%), with papillary carcinoma as the second most frequent diagnosis (24.2%). Malignant diagnoses (papillary, follicular and oncocytic carcinomas) were present in 39.6% of the patients.

Thyroid volume (cm3) and weight (g):

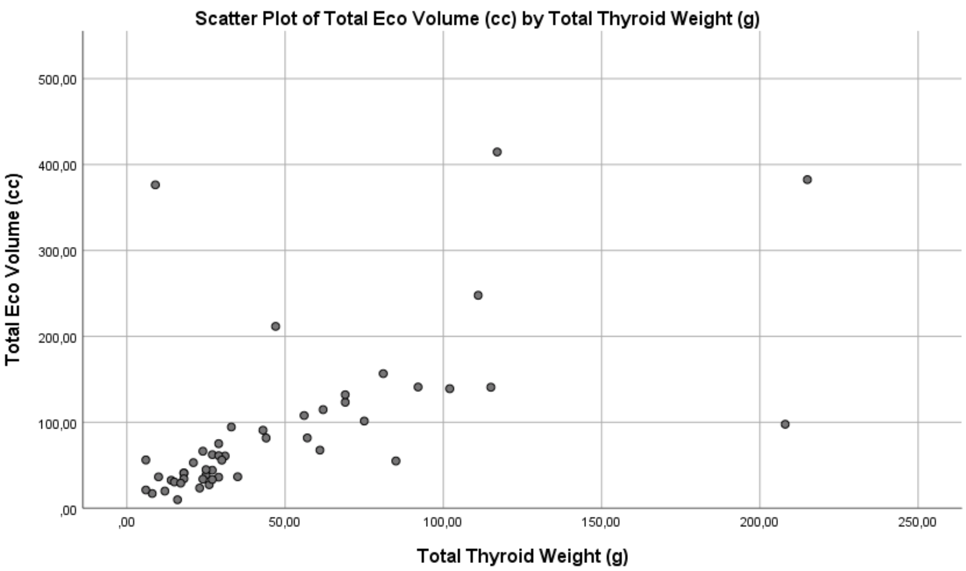
62 subjects underwent a pre-operative echographic analysis of the left lobe volume. The mean value of was 50.48 cm3 (s.d. 74.15).

60 subjects had a right lobe volume analysis with a mean value of 34.85 cm3 (s.d. 38.871).

60 subjects had a total thyroid weight analysis with a mean value of 81.52 g (s.d. 86.135).

There is a positive moderate correlation between pre-operative total thyroid echographic volume and total thyroid specimen volume ($r = 0.603$; $p < 0.01$). There is also a positive moderate correlation between pre-operative total thyroid echographic volume and post-operative total thyroid weight ($r = 0.603$, $p < 0.01$) – graphic 2.

Graphic 2 – Correlation between pre-operative echographic volume (cm3 = cc) and thyroid weight (gram=g)



<u>TSH determination</u>

TSH value determination was within normal range in 92% of patients pre-operatively. In the post-operative determinations, if the TSH value was changed it was increased, consistent with a hypothyroid status. In the 3-month evaluation, TSH was within normal range in 83% of patients and this value increased to a sustained 88% of cases after 6 months. The proportion of normal thyroid status was 12:1 pre-operatively and 7:1 at 12 months post-operatively.

Voice assessment in subpopulation without post-operative vocal fold immobility

There was no diagnosis of immobility pre-operatively. From patients who returned for follow up, immobility was present in 6 out of 86 patients at 1 month, 4 out of 81 patients at 3 months, 5 out of 68 patients at 6 months (after totalization) and 3 out of 58 patients at 12 months.

In patients without post-operative immobility, we present results obtained for voice evaluation, LS functional changes (either insufficiency or squeezing) and thyroid volume.

Symptoms

Dysphonia reported by patients increased dramatically in the first post-operative month and then steadily reduced to a level less than pre-operative baseline condition at 12 months (table 1).

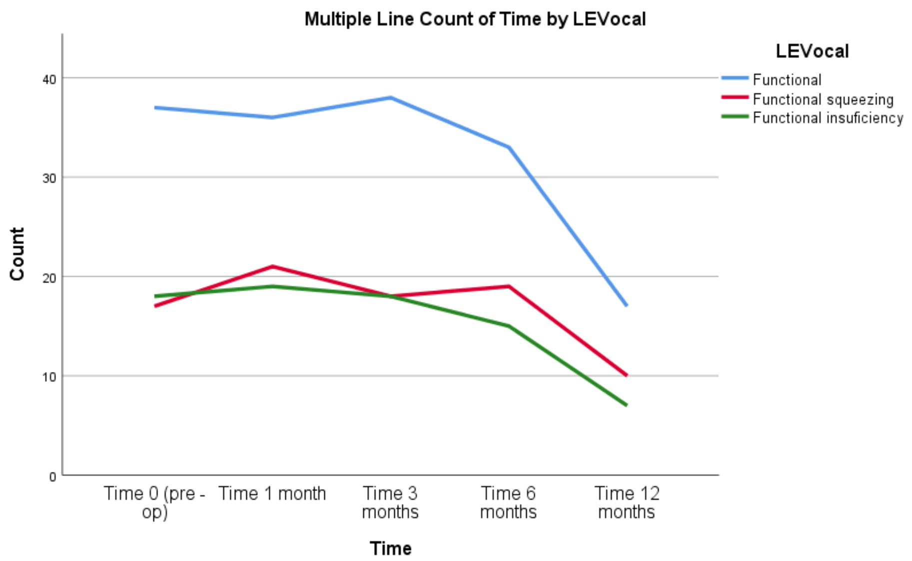
Table 1 – Dysphonia frequency and percent in patients without post-operative vocal fold immobility

	Pre-operative (n=90)	1 month (n=80)	3 months (n=77)	6 months (n=63)	12 months (n=55)
Frequency	53	62	58	49	41
Percent	25%	53%	41%	31%	17%

LS examination

Functional changes were analyzed for either squeezing or insufficiency. Global functional changes decreased at 1 month, slightly increased at 3 months, followed by an eventual decrease below the pre-operative condition at 6 months, and then revealed a dramatic decrease at 12 months to a functional status much better than pre-operative condition (graphic 3).

Graphic 3 – Functional changes in LS examination over time



Voice evaluation

We analyzed G grade from the GRBAS scale, Fi subscore from the VHI questionnaire, MPT, f0/a/ and HPf0/i/.

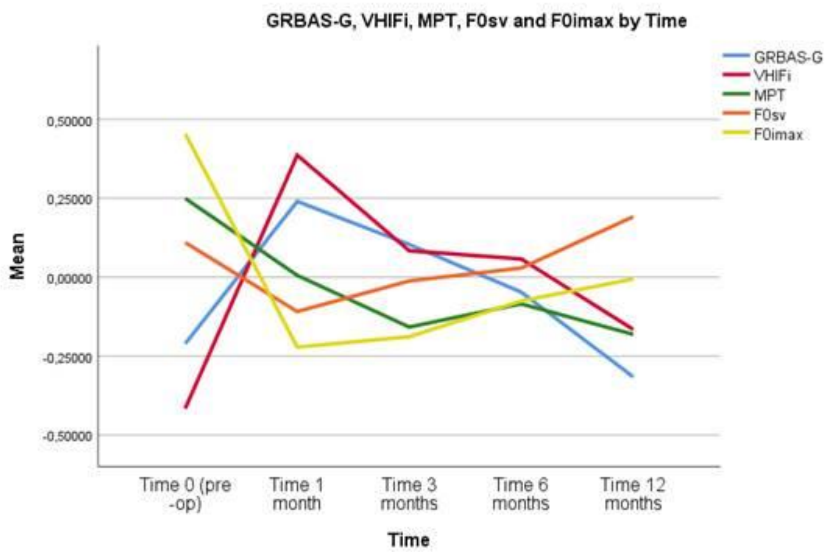
Analyzing GRBAS-G grade of dysphonia results, the number of patients with dysphonia almost doubled at 1 month, followed by a sharp decrease at 3 and 6 months. There was a more steady but continuous descent at 12 months to a lower incidence of dysphonia at 12 months compared to pre-operative evaluation.

Subscore Fi from the VHI index relates to physical effort in vocal production self-perceived by the patient. Its behavior post-operatively, even though its score was within normal value, parallels that of GRBAS G grade with a sharp self-perceived increased effort in the first post-operative month followed by a steady decrease to a better Fi mean subscore compared to pre-operative mean value.

Regarding MPT /a/, its variation over time did not reveal significant changes. Variable f0/a/ did not show variation over time as well. Conversely, when analyzing HPf0/i/, there was a sharp decrease in its value in the first post-operative month in line with patients' complaints of dysphonia, GRBAS G grade and physical effort revealed by Fi subscore of VHI. Afterwards, its value slowly and steadily increases but it does not recover to the pre-operative value, maintaining a decrease of 60 Hz in its mean value.

Multiple line graphic 4 clearly demonstrates intra and inter-variable changes of these factors over time.

Graphic 4 – Multiple line graphic of GRBAS -G, VHI-Fi, f0/a/, HP f0/i/ over time



Correlation essay in the subpopulation without post-operative vocal fold immobility

Pearson correlation coefficient was determined to identify possible correlations of VHIFi, GRBAS-G grade higher than 1, MPT, F0 /a/ (F0sv) and HPf0/i/ with self-perceived dysphonia over the first year, and total pre-operative echographic thyroid volume. Correlations are detailed in table 2.

VHIFi, as a score for physical effort perceived by the patient in voice production, had a low/moderate correlation with total echographic volume and self-perceived dysphonia, more evident from the pre-operative evaluation up to the 6th month evaluation.

Dysphonia confirmed by a GRBAS G score than 1, had a low correlation with weight and total echographic volume.

MPT as an aerodynamic variable of voice, had a low/moderate correlation with self-perceived dysphonia from the first up to the sixth post-operative month and a low correlation with weight and total echographic volume.

F0 /a/ (F0sv) had a high degree of correlation (significance level 0.01) with self-perceived dysphonia in the 12th month. F0 /a/ (F0sv) in the first post-operative month had a moderate degree of correlation (significance level 0.01) with total weight and echographic volume.

HP f 0 /i/ had a low/moderate degree of correlation with self-perceived dysphonia after the third month and this correlation was high in the 12th post-operative month (significance level 0.05). HP f 0 /i/ in the 12th month also had a moderate degree correlation with surgery (significance level 0.01).

		Thyroid disease	Symptomology 0	Symptomology 1	Symptomology 3	Symptomology 6	Symptomology 12	Surgery	Total Weight	Total Eco
VHIFi	VHIFi0	**-0,265***	-0,263	0,078	0,236	0,053	0,215	0,095	-0,002	0,118
	VHIFi1	-0,112	-0,158	0,178	0,041	-0,323	-0,077	**-,287***	0,247	0,202
	VHIFi3	-0,141	-0,227	0,176	0,185	-0,153	-0,265	-0,173	0,218	0,155
	VHIFi6	-0,236	-0,18	0,248	0,219	-0,147	-0,023	-0,18	0,18	0,076
	VHIFi12	-0,195	-0,172	0,163	0,42	0,215	-0,136	b	0,128	0,08
GRBASG	GRBASG0	-0,234	-0,028	0,143	0,121	-0,018	0,034	-0,158	-0,13	-0,171
	GRBASG1	-0,139	0,116	0,142	0,256	0,133	-0,028	**-,374****	0,195	-0,022
	GRBASG3	-0,244	0,07	0,005	0,346	0,126	-0,135	-0,246	0,119	-0,105
	GRBASG6	-0,248	0,199	-0,108	,417*	0,172	-0,115	-0,121	0,124	-0,106
	GRBASG12	-0,202	0,081	-0,203	0,387	0,087	0,149	-0,117	0,242	-0,027
MPT	MPT0	0,142	0,155	0,164	-0,153	0,07	-0,328	0,143	0,128	0,206
	MPT1	-0,077	0,061	0,195	-0,228	-0,155	-0,436	0,181	0,207	0,196
	MPT3	0,015	0,049	0,153	-0,274	-0,174	-0,45	0,186	0,137	0,165
	MPT6	0,019	0,123	0,063	-0,388	-0,212	-0,485	0,209	0,026	0,094
	MPT12	-0,076	0,13	0,149	-0,232	-0,006	-0,699	0,208	0,239	0,292
F0sv	F0sv0	0,108	0,014	-0,135	0,11	-0,093	0,256	0,067	-0,182	-0,263
	F0sv1	0,095	0,099	-0,173	0,044	-0,009	0,513	0,112	**-,317***	**-,321***
	F0sv3	0,13	0,137	-0,193	-0,209	-0,116	**,892****	0,059	-0,186	-0,225
	F0sv6	0,059	0,045	-0,286	0,072	-0,017	**,834****	-0,041	-0,208	-0,301
	F0sv12	0,096	0,094	-0,203	0,568	-0,316	**,810***	-0,276	-0,076	-0,15
F0imax	F0imax0	0,102	0,111	-0,13	-0,116	0,087	0,461	-0,074	0,025	0,005
	F0imax1	0,11	0,019	-0,107	-0,139	-0,162	**,637***	0,152	-0,238	-0,274
	F0imax3	0,002	0,143	-0,004	-0,337	-0,295	0,509	0,044	0,026	-0,178
	F0imax6	0,209	-0,15	-0,076	-0,231	-0,095	0,525	0,094	-0,254	-0,147
	F0imax12	0,198	0,003	0,169	**-,512***	-0,391	0,606	**-,314***	0	0,059

Table 2 – Pearson correlation test results. Pearson correlation coefficient (R2 value) intervals: [0.1-0.29] - low degree correlation (light gray); [0.3-0.49] - moderate degree correlation (medium gray); [0.5-1] - high degree correlation (dark gray); *correlation is significant at the 0.01 level (2-tailed); ** correlation is significant at the 0.05 level (2-tailed).

DISCUSSION

When analyzing patients without post-operative vocal fold immobility, variable correlations are concordant with our hypothesis of weight and echographic volume playing a role in dysphonia. VHIFi and GRBAS G grade both revealed a low/moderate correlation with weight and total echographic volume. F0 /a/ (F0sv) is an objective measure of voice and correlated with self-perceived dysphonia in all study patients without immobility. Interestingly this correlation was stronger at the 12th post-operative month. These results strongly suggest F0 /a/ (F0sv) plays a role in the dysphonia perceived by these patients and it is a confirmation that the symptom is effectively related to a change in voice quality.

HP f 0 /i/ was included as a measure of vocal behavior in the falsetto range. Anatomic change induced by surgery in the pre-laryngeal muscles with resultant fibrous deposition (promoting reduced elasticity) and superior laryngeal nerve lesion are two possible reasons for cricothyroid muscle function compromise. It would be reasonable to assume that HP f 0 /i/, a measure of voice in the high pitch range, may be compromised after thyroid surgery because vocal extension for high pitch production derives both from cricothyroid muscle function and the superior laryngeal nerve´s innervation of this muscle. Effectively, in patients without post-operative vocal fold immobility, HP f 0 /i/ had a low/moderate correlation with self-perceived dysphonia after the 3rd month with a high degree of correlation showing a significance level 0.05

in the 12th month. HP f 0 /i/ in the 12th month also has a moderate correlation with surgery with 0.01 significance.

These results of our study demonstrate a compromise in voice throughout the first post thyroidectomy year in patients without vocal fold immobility. Patients perceive dysphonia and the symptom is confirmed by self-perceived scores of effort in voice production and objective perceptive analysis of voice.

According to the results of our study, dysphonia in patients without vocal fold immobility is related to weight of the surgical specimen and echographic thyroid volume. It is related to F0 /a/ change and HP f 0 /i/ reduction (mean 60Hz). HP f 0 /i/ change may be a reason for singing limitations perceived by patients in the long-term. Based on the results of this study in patients without vocal fold immobility, we propose echographic thyroid volume as a new pre-operative prognostic factor for post-operative dysphonia relating to F0 /a/ change and HP f 0 /i/ reduction in the first post-operative year.

Further research is needed to assess the criteria for thyroid volume significance in voice compromise without vocal fold immobility. Multivariate analysis for the significance of echographic volume in this subpopulation would be beneficial to determine whether or not it could be considered an independent risk factor. Further study is also needed to assess whether increased echographic thyroid volume may also be an independent risk factor for post-operative vocal compromise in patients with post-operative vocal fold immobility. This would help to stratify the risk of muscular and nervous structures damage in patients with increased thyroid volume prior to surgery.

CONCLUSIONS

Vocal compromise in the first year after thyroid surgery is present in patients without vocal fold immobility. Voice changes in these patients involve F0/a/ change and HP f 0 /i/ reduction (mean 60Hz). These voice changes are related to thyroid volume and weight which, in turn, are correlated to pre-operative echographic thyroid volume. Increased echographic thyroid volume should be considered a pre-operative prognostic factor for vocal compromise after thyroid surgery in patients without post-operative vocal fold immobility.

VI. Conclusions

This study wanted to quantify pre-operative and post-operative long term voice changes in thyroidectomy patients without VF immobility and to confirm the hypothesis of increased thyroid volume being a risk factor for post-operative voice changes.

The clinical practice improvement pretended with this investigation was the need to stratify risk factors more finely in statement 2b from 2010 American Academy of Otolaryngology – Head and Neck Society published guideline "Best Practice Guidelines for Voice Preservation in Thyroid Surgery"[2], establishing whether goiter surgery should be included in the conditions to refer for pre-operative laryngeal assessment.

If bigger thyroid volume in goiter relates to increased risk for voice change post-operatively, then early referral to voice clinics of patients with increased volume thyroids submitted to surgery should be promoted, permitting timely intervention for better voice results.

The more relevant conclusions were the following:

1. There are relevant voice and laryngeal changes pre-operatively in patients proposed for thyroidectomy.
2. Most patients who seek medical advice related to voice changes post-operatively don´t have vocal fold mobility impairment.
3. Patients without thyroid cancer have more voice changes pre and post-operatively than patients with thyroid cancer. This factor should prompt a revision of statement 2b, including non-malignant thyroid disease in peri-operative voice evaluation in thyroidectomy.
4. In patients without post-operative VF immobility, dysphonia in the first post-operative year is more frequent in the first three months.
5. In patients with dysphonia but without post-operative VF immobility, the voice improves to a level better than the pre-operative voice condition 6 months after surgery. Follow up and intervention for these patients is probably cost-effective in the first 3 post-operative months because, 6 months after surgery, voice improves in every patient without post-operative VF immobility comparing to the first 3 post-operative months.
6. Post-operative dysphonia in thyroidectomy patients without VF immobility is characterized by reduced f0/a/ and reduced HPf0/i/ comparative to pre-operative results. This factor confirms that dysphonia perceived by patients without VF immobility is objectively caused by a quantifiable change in objective voice analysis parameters.
7. Mean HPf0/i/ reduction post-operatively in patients without VF immobility is 60Hz. Reduced HPf0/i/ post-operatively is certainly one of the factors causing reduced singing ability perceived by the patients when high pitch tones are required.
8. In patients without post operative VF immobility, both dysphonia, reduced f0/a/ and HPf0/i/ correlate to bigger thyroid volumes
9. Thyroid volume (cc) and weight (gram) is correlated to thyroid echography volume determination (cc) and both measures directly correlate to dysphonia, reduced f0/a/ and HPf0/i/ post-operatively.

10. This finding provides justification for considering increased echography thyroid volume as a risk factor for voice compromise in thyroidectomy patients. Increased thyroid volume pre-operatively should prompt early referral for voice clinics in the peri-operative period aiming at early and tailored voice re-habilitation when proven necessary, promoting a better voice related quality of life (QoL) in thyroidectomy patients.
11. Statement 2b in Best Practice Guidelines for Voice Preservation in Thyroid Surgery should include patients with increased volume goiter in peri-operative laryngeal evaluation.
12. Even without LOS in intra-operative NIM of recurrent nerve in thyroidectomy, patients with goiter should be referred for voice and laryngeal evaluation post-operatively

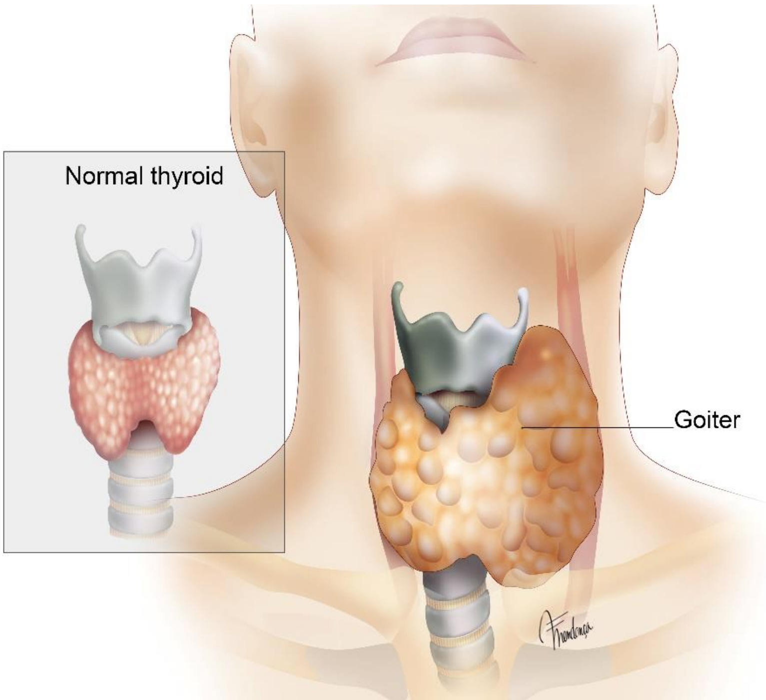


Figure 4 – Conceptual image of goiter induced anatomical changes in laryngotracheal anatomy (original)

VII. Final comments and future research

When we assumed for the first time our willingness to start this research, we asked Steven Zeitels and Robert Hillman from the Voice Center in Harvard, Boston, if they considered it a valid and clinically significant research in voice. We still remember Steven Zeitels remark when he complimented us for the idea, but in his usual and very practical straightforward way, told us it would be impossible to gather in general surgeons for the research, because we would be uncovering their surgical complications so they would, presumptively, refuse to cooperate.

It was therefore with great satisfaction that we were able, not only to include general surgeons in the study, but also to convince them that voice in thyroid surgery is much more than just a recurrent nerve issue. We were invited to participate in courses on thyroid surgery organized by general surgeons and we are regularly participating in courses on intra-operative neuromonitoring of the recurrent laryngeal nerve in thyroid surgery with Portuguese and Spanish thyroid surgeons.

Our research opened a broad basis for future research concerning the mechanisms involved in voice change in thyroid surgery. Our database includes information concerning pulmonary function tests because we believe that subglottic pressure may play a role in patients' subjective feeling of dysphonia when mechanical distortion by big thyroids is removed. We therefore engaged in a multicentric research with Instituto Superior Técnico in Lisbon "Evaluation of the impact of thyroidectomy in the subglottic aerial flux and phonation using a model of dynamic fluids". This research is underway and obtained Hospital da Luz Ethical approval CES/40/2019/ME.

Another line of research is the influence of thyroid hormone level in the voice of patients with thyroid disease. Our colleagues in the endocrinology department invited us to participate in research concerning voice changes in patients with Graves' disease, a condition known for its hyperthyroid status pre-operatively with a dramatic reduction to a hypothyroid status post-operatively. The results were presented at the Congresso Português de Endocrinologia 2020 -71ª reunião anual da SPEDM as a poster "Avaliação do impacto da terapêutica da doença de Graves na voz".

The work involved in this thesis research was extremely rewarding. As a clinically active researcher, it is with great satisfaction that we have assisted to a subtle but steady trend of non-ENT thyroid surgeons towards a multi-disciplinary voice preservation protocol in thyroid surgery.

The original broad objective of this research - changing thyroid surgeons resistance to engage in a multidisciplinary approach of thyroidectomy patients with laryngologists and SLP - is underway. Reliable interdisciplinary cooperation is possible even when laryngologists deal with thyroid surgeons' complications. Trust, cooperation and objective results are fundamental to change our clinical practice towards the common objective of improving our patients' voice quality.

This thesis is research centered in voice, sound and acoustics. We believe it would be most useful for our readers to engage in an experience - listening to an example of the difference between a pre and a post-operative voice in a patient who had thyroidectomy for goiter. No pre or post-operative laryngeal changes were registered in this patient. Please refer to the QR code below for animation and assessment of the reductions in the perceptual (objectively demonstrated) reduction of voice strain.

One case is not a scientific proof but sometimes it is this case that triggers the question for research.

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IX. Tables and Figures

➢ Tables

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X. Abbreviations and acronyms

AAO-HNS : American Academy of Otolaryngology, Head and Neck Surgery

APT : Averaged phonation airflow

CAPE – V : Consensus Auditory- Perceptual Voice Evaluation

CT : Computed Tomography

DSI : Dysphonia Severity Index

ELS : European Laryngological Society

EGG : Electroglottography

EMG : Electromyography

EMG LOS : EMG loss of signal

ENG : Electroneurography

ENT : Otolaryngologists (ear nose and throat)

F0 : Fundamental frequency of vibration

F0 /a/ (F0sv) : Fundamental frequency (f 0) for sustained vowel /a/

F0/i/max : Fundamental frequency for the high pitch sustained /i/

FEES : Functional endoscopic assessment of swallowing

FNA : Fine needle aspiration biopsy

GRBAS : Perceptive voice evaluation scale. GRBAS rates G-grade, R-roughness, B-breathiness, A-asthenicity and S-strain

GRBAS-T : GRBAS total score

HNR : Harmonics to noise ratio

HP f 0 /i/) : Fundamental frequency for the high pitch sustained /i/ (HP f 0 /i/ or F0/i/max)

Hz : Hertz

LE or LS : Laryngostroboscopy

LOS : Loss of signal (EMG)

MPT : Maximum phonation time

NIM : Intraoperative neuromonitoring

NSI : Nonspecific laryngeal inflammation

PQ : Phonation quotient

PROM : Patient reported outcome measure

PPV : Positive predictive value

QoL : Quality of Life

RLN : Recurrent laryngeal nerve

SLN : Superior Laryngeal Nerve

SLP : Speech Language Pathologist

T3 : Triiodothyronine

T4 : Thyroxine

TSH : Thyroid stimulating hormone

VC : Vital capacity

VER : Vocal extension in reading

VF : Vocal fold

VFP : Vocal fold paralysis

VHI : Voice Handicap Index

VHI – E : VHI subscore E (emotional)

VHI- F : VHI subscore F (functional)

VHI- Fi : VHI subscore Fi (physical effort)

VHI-T : VHI total score

VNL : Videonasolaringoscope