Anatomical Relationships and Variations of the Recurrent Laryngeal Nerve in the surgical field of Thyroidectomy

- A Prospective Study of assessment of the topographic relationship between the Recurrent Laryngeal Nerve and the Inferior Thyroid Artery in patients undergoing Total Thyroidectomy at the Otolaryngology Department of the University Hospital of Larissa
- A Systematic Review and Meta-analysis (THESIS)

Gkrinia Eleni

Thesis Committee:
Zibis A., Associate Professor of Anatomy, University of Thessaly: Supervisor
Fiska A., Professor of Anatomy, Democritus University of Thrace
Hajiioannou J., Associate Professor of Otolaryngology, University of Thessaly

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Cover Figure:

Hand drawn using black and red ball-point pens. The “Wandering” nerve is the longest cranial nerve. This sketch shows its course in the neck and thorax.

Jason Glide artscience, https://jasongilde.info/vagus-nerve
Abstract

**Background:** Thyroidectomy is considered to be the preferred treatment modality for many benign and malignant thyroid diseases. Recurrent laryngeal nerve dissection and identification is the gold standard surgical technique, determining the security of nerve function in order to severe postoperative complications to be prevented. The aim of this study is to assess the topographic relationship between the recurrent laryngeal nerve and the adjacent noble structures, and especially the inferior thyroid artery, along with the clinical impact of the presence of anatomical alterations on local complications and hypocalcaemia.

**Methods:** This thesis is constituted of two parts. The first one is a prospective collection of data regarding the relationship between the recurrent laryngeal nerve and the inferior thyroid artery in patients of the Otolaryngology Department of the University Hospital of Larissa, undergoing total thyroidectomy, during a 6-month period. The second part is a systematic review and a meta-analysis of the literature concerning the topographic relation of the recurrent laryngeal nerve and the inferior thyroid artery.

**Results:** As far as the prospective study is concerned, 64 patients (mean age 52 years, range 21-81 years, female 72%), were included in the study. Among the 128 recurrent laryngeal nerve dissections, in 27.3% of the cases, the nerve was identified to traverse the inferior thyroid artery anteriorly, with equal distribution between the two sides. One out of 64 patients (1.6%) presented transient vocal cord palsy unilaterally, while in 21.9% of the participants hypocalcaemia was developed. However, no statistical significance was observed between the postoperative complications and the topographic variation of the recurrent laryngeal nerve. In regard to the meta-analysis, 10 studies were included and 5671 recurrent laryngeal nerves were dissected in total.
The nerve was most frequently identified posteriorly to the inferior thyroid artery, while the possibility of intraoperative recurrent laryngeal nerve injury reached 1%.

**Conclusion:** The inferior thyroid artery constitutes a reliable anatomical entity, which can be used as a landmark for the identification of the recurrent laryngeal nerve during surgery of the thyroid gland. The knowledge of anatomical variations’ presence possibility is of great importance, in order postoperative complications to be prevented.
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As a student of the Master’s Degree Program “Clinical - Surgical Anatomy” of the Democritus University of Thrace, I had the opportunity to obtain specialized knowledge on the remit of Human Anatomy, not only at a theoretical, but also at a practical level, by approaching extensively its implementation in daily clinical practice. This valuable education is an irreplaceable asset for a young doctor, and more specifically, for a resident in the field of Surgery, as it contributes to the smooth transition from the stage of undergraduate studies to the stage of substantial and all-embracing practice of Medical Science. During my two years of involvement in this curriculum, I was given the chance to approach and become familiar with the various surgical techniques, classical and modern, of each anatomical area. I was interested in the area of the head and neck, on the one hand because of its special anatomy, and on the other because of my decision to specialize in Otolaryngology. Thyroidectomy is numbered in the long list of surgeries performed in this anatomical area. Considering the complexity of the anatomy of the neck, as well as the possible presence of its multiple alterations, various questions arose, among which was the clinical significance of the topographic anatomy of the recurrent laryngeal nerve in the surgical field of thyroidectomy. The answer was given through the elaboration of my diploma thesis, thanks to which I welcomed the chance to be introduced to the remit of medical research methodology.

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PART A’

1. Introduction

The thyroid is a sizeable endocrine gland, that in 1656, was named by the English physician and anatomist Thomas Wharton (1614-1673), after the ancient greek word “θυρεοειδής”, which means shield-like, because of its shape. Its development starts at the end of the 3rd week of gestation, as a midline anlage in the pharyngeal floor, which later is transferred to the anterior part of the neck, in order to be placed in its final position.\cite{1,2,3} Its function is associated with the iodine concentration in the human body and it is responsible for the production and retention of thyroid hormones.\cite{1,4,5}

A variety of diseases, both benign and malignant, can affect its normal activity, resulting in the appearance of a long list of symptoms. Among them, hyperthyroidism, hypothyroidism, thyroiditis, thyroid goitre and thyroid cancer stand out. Their treatment varies, depending on the condition, and can be either conservative or surgical.\cite{6}

Thyroidectomy is numbered among of the most frequently performed surgeries worldwide. However, until the beginning of the 20th century, due to the high rates of complications and mortality, it was considered one of the most dangerous surgical operations. The revolution in Thyroid Surgery came when Emil Theodor Kocher, by perfecting the surgical technique, performed more than 5,000 thyroidectomies, and managed to reduce the mortality rate to 0.5%.\cite{7,8}

However, the risk of postoperative complications of thyroidectomy has not been eliminated and this is mainly due to the highly complex anatomy of the anatomical region of the neck. Abundant noble structures are found around the thyroid - among them stands out the recurrent laryngeal nerve.\cite{9,10} Accidental injury of the nerve can lead to even life-threatening situations. Consequently, cautious dissection, in order to
identify it, during thyroidectomy is of utmost importance.[11] For this reason, the excellent knowledge of its anatomy, its anatomical alterations and its topographic relationship with various adjacent structures, which act as guiding points, such as the inferior thyroid artery, is considered an irreplaceable weapon in the quiver of every head and neck surgeon.

The objective of the current thesis is to examine the association of the recurrent laryngeal nerve with the adjacent anatomical entities in the surgical field of thyroidectomy, to appreciate the value of its topographic relationship with the inferior thyroid artery, but also to evaluate the clinical impact of its anatomical localization. This was achieved, on the one hand, through the systematic review and meta-analysis of the relevant literature, in accordance with all the criteria of modern guidelines, and, on the other hand through the analysis of this anatomical entity in patients of the Otolaryngology Clinic of the University General Hospital that underwent total thyroidectomy.
2. Thyroid Gland

2.1. Embryology of the Thyroid Gland

As far as embryology is concerned, the thyroid gland begins to develop on the 17th day of gestation, derived from two different embryonic tissues; primordial pharynx and neural crest. Composed by endodermal cells, it appears as a midline anlage, known as thyroid diverticulum, in the pharyngeal floor, and specifically, in the tongue base. During the next few weeks, the newly formed bilobed diverticulum commences its descending course along an invisible line, from the foramen cecum to the larynx, passing anteriorly to the body of the hyoid bone. (Figure 1)

![Figure 1: The primary thyroid is developed from a thickening of the endoderm that forms a diverticulum in the midline of the ground of the primary pharynx, between the first and second pharyngeal follicle. - Policeni B. A., Anatomy and Embryology of the Thyroid and Parathyroid Glands, Seminars in Ultrasound, CT and MRI, Volume 33, Issue 2, April 2012, Pages 104-114.](image)

The primitive thyroid gland takes its final position just below the level of the thyroid cartilage and it starts augmenting its size. Thyroid’s downward movement forms the thyroglossal duct, which naturally atrophies and closes off till the end of the 6th week of the embryonic life (Figure 2). Nonetheless, any disruptions that may arise...
during thyroid’s repositioning or thyroglossal duct’s closure could provoke the development, on the one hand, of ectopic thyroid tissue either in the tongue base (lingual thyroid), or in the mediastinum, and on the other hand, of thyroglossal duct cysts or fistulas. [3]

**Figure 2:** The primary thyroid gland penetrates the underlying mesenchymal tissue and descends in front of the hyoid bone and the cartilages of the larynx, forming the thyroglossal duct. Ectopic thyroid tissue can be found along the thyroglossal duct. - Policeni B. A., Anatomy and Embryology of the Thyroid and Parathyroid Glands, Seminars in Ultrasound, CT and MRI, Volume 33, Issue 2, April 2012, Pages 104-114 [12]

### 2.2. Anatomy of the Thyroid Gland

The thyroid gland is located in the anterior neck, at the level of C5-T1 vertebrae, hence it is closely related to both respiratory and gastrointestinal system. It consists of two cone-shaped lobes, which are positioned on either lateral side of the trachea and are connected to each other in front of the trachea with a transverse band of thyroid tissue that is widely known as isthmus of the thyroid gland and is usually found in front of the first, second and third trachea ring. [13] It is estimated that it weighs approximately 20-30 gr in adults, while its lobe is circa 5 cm long, 1.5-2 cm wide and 2-4 cm thick. It
is of great importance to mention that thyroid dimensions may be modified depending, on the one hand, on the sex, as thyroid gland appears to be larger in the female population, and, on the other hand, on the possible presence of a thyroid disease. [13]

Occasionally, the presence of a third thyroid lobe, known as pyramidal lobe of the thyroid gland, is observed in about a third of the population. The pyramidal lobe, with mean length 14 mm in the male and 29 mm in the female population, constitutes a remnant of the thyroglossal duct and remains attached to the hyoid bone by connective tissue. (7) Pierre Lalouette (1711-1792), a distinguished French anatomist, was the first to describe pyramidal lobe, hence it is also known as “Lalouette’s Pyramid”. [13] In 2007 Braun et al. reported the detection of the pyramidal lobe in 55% of the cadavers included in their anatomical study. In the majority of them, it was described commencing from the thyroid isthmus, while in statistically less anatomical dissections it was found to begin its course from one of the two lateral thyroid lobes, and most commonly from the left one, resulting to conclusions in compliance with the international literature. [15]

In terms of topographical surveying, each one of the lateral thyroid lobes has three surfaces: the medial surface, the anterior surface and the posterior (lateral) surface. [16] The medial surface of each lobe, which is adjacent to the superior trachea and the cricoid cartilage of the larynx, is concave and extends to the oblique line of the thyroid cartilage. The anterior sub-convex surface is in contact with the sternohyoid muscle, the sternothyroid muscle and the superior belly of the omohyoid muscle, while the posterior (lateral) one is also convex and osculates the carotid sheath that encases common carotid artery, internal jugular vein and vagus nerve. [17]

The thyroid gland is enveloped by a strong fibrous capsule that is comprised of two layers. The inner layer is a thin stratum of fibro-elastic connective tissue (true
capsule), which is adjacent to the thyroid parenchyma and provides it with septae that carry vessels to the interior of the thyroid gland and divides it into microscopic lobules. On the other hand, it is covered superficially by the outer layer (surgical or false capsule), which is a part of the middle layer of the deep cervical fascia. Between these two layers, loose connective tissue, large vessels, as well as parathyroid glands are detected.

2.3. Arterial Supply of the Thyroid Gland

As long as vascularization is concerned, undoubtedly, the thyroid is considered to be one of the most highly vascularized organs in the human body. The arterial supply is mainly provided by two pairs of arteries; the superior and the inferior thyroid arteries. (Figure 3) Firstly, the superior thyroid artery, which constitutes the first branch of the external carotid artery, arising near the bifurcation of the common carotid artery, traverses the external surface of the inferior pharyngeal constrictor muscle, accompanied by the superior laryngeal nerve. After its bifurcation into an anterior and a posterior branch, at the level of the superior pole of the corresponding thyroid lobe, it enters the thyroid gland. However, a division of the superior thyroid artery into more than two branches, before its entrance in the thyroid gland, is not rare to be observed. It is worth mentioning that the terminal branches of the superior thyroid artery anastomose frequently with branches of the inferior thyroid artery, as well as with branches of the contralateral lobe.
The inferior thyroid artery originates from the thyrocervical trunk, which is a branch of the subclavian artery. Initially, it arises moving on the surface of the anterior scalene muscle, till the C7 vertebra level. At this point, it rotates inwards and approaches the carotid sheath and the middle cervical ganglion. Afterwars, it turns abruptly downwards moving on the prevertebral muscles, and after its division into an anterior and a posterior branch, it enters the inferior pole of the thyroid lobe. Except for the vascularization of the thyroid gland, the bifurcated inferior thyroid artery contributes to the arterial blood supply of the parathyroid glands, the trachea and the upper oesophagus. The anatomical relationship of the inferior thyroid artery and the
recurrent laryngeal nerve is highly significant on the field of thyroid surgery and may present multiple alterations that will be discussed further below.\textsuperscript{[13]}

Ofttimes, the thyroidea ima artery, a solitary artery that usually arises from the anonymous artery or, less frequently, from the aortic arch, the subclavian artery and the common carotid artery, may be present.\textsuperscript{[13,21]} Even if it constitutes a rather small vascular branch, it occasionally substitutes the superior thyroid artery, and contributes importantly, in this way, in the arterial blood supply of the thyroid gland. Following an ascending course anteriorly to the thyroid, it provides the middle part of the corresponding thyroid lobe with arterial blood, while the fact that it traverses the thyroid isthmus increases the risk of bleeding during a tracheotomy procedure.\textsuperscript{[13]}

2.4. Venous Drainage of the Thyroid Gland

Venous drainage of the thyroid gland consists of a plexus of vessels that emerge from the thyroid parenchyma through the fibrous capsule septae and form three levels of veins on the thyroid surface bilaterally; the superior thyroid vein, the middle thyroid vein and the inferior thyroid vein. Specifically, the superior thyroid vein either drains exclusively into the common facial vein, or directly into the internal jugular vein. Additionally, sometimes the superior thyroid vein is subdivided into two branches; one of them drains into the common facial artery and the other into the internal jugular vein.\textsuperscript{[19]} Subsequently, the middle thyroid artery either empties into the brachiocephalic vein, or, upon joining the inferior thyroid vein, drain together as a common branch in the innominate vein.\textsuperscript{[22]} Lastly, the inferior thyroid vein either drains directly into the innominate vein, or bifurcates and, as a result, one of its branches empties into the internal jugular vein and the other into the innominate vein, or drains as a common
branch into the innominate vein.\textsuperscript{[22]} It is noteworthy that the thyroid’s venous plexus is the principal cause of bleeding during thyroid surgery.\textsuperscript{[13]}

\section*{2.5. Lymphatic Drainage of the Thyroid Gland}

The lymphatic drainage of the thyroid gland usually follows the venous drainage. Thus, lymphatic vessels of the superior pole run in parallel and in close proximity to the superior thyroid veins, heading to the superior deep cervical lymph nodes, while those that are responsible for the lymph propulsion of the inferior thyroid pole accompany the inferior thyroid vein and reach supraclavicular, pretracheal and paratracheal lymph nodes.\textsuperscript{[13]}

\section*{2.6. Innervation of the Thyroid Gland}

Thyroid gland receives sympathetic nerve supply through afferent nerve fibres, originating from the superior, the middle and the inferior cervical ganglion of the sympathetic trunk, which arrive to the thyroid through the cardiac plexus, as well as the superior and the inferior thyroid plexus that accompany thyroid arteries.\textsuperscript{[23]} On the other hand, parasympathetic nerve supply of the thyroid is achieved through the vagus nerve (10\textsuperscript{th} cranial nerve) and, primarily, the external branch of the superior laryngeal nerve, which is located outside the thyroid capsule. Followed by the superior thyroid artery, the external laryngeal nerve passes along the inferior pharyngeal sphincter and, after it gives rise to a smaller branch, it continues its course inside the thyroid gland, till it enters the cricothyroid muscle.\textsuperscript{[3]}
2.7. Physiology of the Thyroid Gland

Thyroid gland secretes two hormones, thyroxine (T4) and triiodothyronine (T3), which are partially composed from iodine and are responsible for controlling the basal metabolic rate. Through these hormones, the thyroid gland affects almost every human organ. It affects, primarily, normal development of the neonates’ central nervous system, natural growth and maturation of the children’s musculoskeletal system, as well as orderly functioning of adults’ organ systems. Therefore, it is clear that any thyroid gland malfunctioning has a negative impact on human body homeostasis.\[2\]

On histology terms, the thyroid gland is composed of plenty, thickly arranged sphere-shaped adenocytes, known as thyroid follicles. Thyroid follicles consist of an amount of protein-rich material, called colloid, that contains thyroid hormones and thyroglobulin, surrounded by a layer of epithelial follicular cells.\[2\] Follicular cells’ and follicles’ size is determined by thyroid gland activity. Thus, when the gland is in an active phase, follicles are small, follicular cells are cuboidal or cylindrical, while the colloid is scarce. On the contrary, when the thyroid gland enters into an inactive phase, follicles are large, follicular cells are flattened and the colloid is abundant.\[2\] Scattered among thyroid follicles exist parafollicular cells, or else C cells, secreting calcitonin, a hormone that has antagonistic effect to that of parathormone, since it reduces bone remodeling and, in this way, decreases serum calcium levels.\[2\] Specifically, regarding to the production and secretion of thyroid hormones, the primary product of follicular cells is thyroglobulin (Tg) (Figure 4).

Through the dense interweaving capillaries network that encircle follicles, the iodine ion arrives at follicular cells and, after it gets oxidized by thyroperoxidase, enters into the colloid and connects with tyrosyl residues of thyroglobulin in order to form a monooiodotyrosine molecule. Then, monooiodotyrosine becomes oxidized and turns into a diiodotyrosine molecule. Afterwards, through the coupling of a monooiodotyrosine molecule and a diiodotyrosine molecule arises a triiodothyronine molecule ($T_3$).

Both thyroid hormones, after the stimulation of Thyroid-Stimulating Hormone (TSH), pass from the colloid to the follicular cells’ cytoplasm and, consequently, through the cell membrane, enter into the adjacent capillaries. Regarding TSH, it is a pituitary hormone, whose secretion is normally stimulated by Thyrotropin-Releasing Hormone (TRH) that is produced by the hypothalamus. Subsequently, in order the
thyroid hormones’ transportation and equal distribution to the tissues to be easily accomplished, T3 and T4 remain connected to serum proteins, as albumin, transthyretin and thyroxine-binding globulin. Nonetheless, only the free form (unbound) form of thyroid hormones is biologically active and capable to suspend TSH secretion.\cite{25}
3. Recurrent Laryngeal Nerve

3.1. Embryology of the Recurrent Laryngeal Nerve

The recurrent laryngeal nerve is a branch of the vagus nerve that rises from the 6th branchial arch and is correlated to the region of the subsequent newly formed larynx, which is located caudally to the 5th pharyngeal pouch. The primitive vagus nerve appears at the end of the 5th week of gestation, while the presence of the recurrent laryngeal nerve becomes obvious at the end of the next week. In the beginning, the larynx is located below the aortic arch and, in this way, the inferior laryngeal nerve arrives directly to it, after its origination from the vagus nerve. However, as the pharyngeal pouches disappear and the embryo’s neck gets elongated, the aortic arch, accompanied by its rich blood vessels network, remains in the thorax, while the larynx moves upwards, carrying with it the recurrent laryngeal nerve. Hence, the nerve follows a loop-like course that differs, regarding the side. Specifically, on the left side, the recurrent laryngeal nerve passes under the 6th aortic arch, which forms the ductus arteriosus that, after birth, naturally closes and turns into ligamentum arteriosum. On the contrary, on the right side, given that the 6th aortic arch normally atrophies and gets degenerated distally, the recurrent laryngeal nerve hooks under the right subclavian artery, which originates from the right 4th aortic arch. As a consequence, it is evident that the recurrent laryngeal nerves are naturally asymmetric.

It is easy, then, to understand that, the recurrent laryngeal nerve’s course figuration depends significantly on the embryonic development of great vessels and, correspondingly, it is possible that nerve variations may arise due to anatomical alterations of the vessels’ formation. Specifically, the most frequent variation of the recurrent laryngeal nerve, the non-recurrent laryngeal nerve, appears when a part of the forth right aortic arch, between the right common carotid artery and the right subclavian
artery atrophies and disappears. Thus, a dissolution of the primitive arterial ring emerges resulting in the figuration of the aortic arch, with right subclavian artery originating after the point of insertion of the left subclavian artery.[13] Afterwards, the abnormally originated right subclavian artery (arteria lusoria) continues its course to the right side by passing behind the oesophagus. In this way, it is impossible for the right recurrent laryngeal nerve to form the naturally shaped hook under the subclavian artery. On the contrary, after its origination from the vagus nerve, it enters the larynx directly at the level of the superior pole of the thyroid gland.[18,27] As far as the presence of the left non-recurrent laryngeal nerve is concerned, it has been rarely reported and, usually, accompanies other anomalies, like situs inversus totalis.[28] According to Wang et al., the presence of non-recurrent laryngeal nerve that is not associated with abnormalities of the vascular system doesn’t have any evident embryological explanation. Overall, the variation of non-recurrent laryngeal nerve is reported in 0.5-1% of the general population and comprises an important risk factor of injury of the recurrent laryngeal nerve, during surgical operations of the neck, such as thyroidectomy. This happens mostly because there is a high possibility either of mistaking the recurrent laryngeal nerve for the inferior thyroid artery or, less frequently, of damaging it during the ligation of the superior thyroid pole vessels (Figure 5).[18,27]
Figure 5: (A) Normal Right Recurrent Laryngeal Nerve (B) and right non-recurrent laryngeal nerve in the presence of an aberrant subclavian artery. Henry, B.M. et al., The Non-Recurrent Laryngeal Nerve: a meta-analysis and clinical considerations. Peer J. 2017 [27]

Another alteration of the recurrent laryngeal nerves that arises due to the abnormal development of the great vessels is their reversed asymmetry. In this case, instead of a normally left-side shaped aortic arch, a right-side shaped aortic arch is formed, accompanied by a ligamentum arteriosum that is, respectively, turned towards the right side. Consequently, the right recurrent laryngeal nerve is the one that follows a loop-like course under the arterial arch and, on the contrary, the left one hooks under the left subclavian artery and, then, continues its ascending course to the neck. Under these circumstances, it is scarce, but not impossible, a left non-recurrent laryngeal nerve to be reported, while the left subclavian artery is found to form a retroesophageal course.[29]
3.2. Anatomy of the Recurrent Laryngeal Nerve

The recurrent laryngeal nerve, as a branch of the vagus nerve, was described for the first time by Galen of Pergamon (129-210 A.D.). In the 16th and 17th century, Vesalius and Willis described larynx and recurrent laryngeal nerve as they are currently mentioned in the modern textbooks of human anatomy. Later, in 1923 Lahey highlighted the importance of recurrent laryngeal nerve and described the dissection technique in order the recurrent laryngeal nerve to be identified during thyroidectomy.

As it has been mentioned above, recurrent laryngeal nerves are not symmetrical. On the right side, the vagus nerve ramifies at the level of the subclavian artery and the recurrent laryngeal nerve branch hooks under the subclavian artery. Subsequently, it ascends to the neck behind the common carotid artery, till it meets the tracheoesophageal groove, accompanied by the inferior thyroid vessels. On the opposite side, the recurrent laryngeal nerve originates from the vagus nerve at the level of the aortic branch, and after it forms a loop-like course under it, it moves upwards in the tracheoesophageal groove. As a consequence, the length of the right laryngeal nerve from the level of the right subclavian artery to its entrance in the larynx is approximately 5 - 6 cm, while the respective size of the left one, from the level of the aortic arch, reaches a length of 12 cm.

During its ascending course, the recurrent laryngeal nerve, both on the right and the left side, is covered by a thin layer of fascia, in which trachea and inferior thyroid artery are, also, included. Usually, the connective tissue surrounding the recurrent laryngeal nerve is found to be mildly thicker on the right. The nerve, on each side, traverses the tracheoesophageal groove with a slight incline to the middle
line, till its course becomes parallel and closely related to the trachea. It is useful to mention that, at the lowest part of its ascending course, the left recurrent laryngeal nerve approaches trachea more than the right one.\cite{33,34}

However, the relationship of the recurrent laryngeal nerve to the tracheoesophageal groove may vary. According to Hunt et al., in 65% of the general population, the nerve lies in the groove on the right side, while on the left side the rate reaches 77%. Furthermore, the nerve is located on the lateral side of the trachea in 33% on the right side and 22% on the left side. Less frequently, the nerve is positioned posteriorly to the tracheoesophageal groove, or even on the front surface of the trachea, which is an extremely dangerous location for a nerve injury during operations on the specific field (Figure 6).\cite{35,36}

Arriving at the level of cricothyroid joint, the recurrent laryngeal nerve passes behind it and enters the larynx by penetrating inferior pharyngeal constrictor muscle at its point of contact with the lateral surface of cricoid cartilage. At the same time, it innervates cricopharyngeal muscle.\cite{37} After its entrance to larynx, the nerve bifurcates into a motor and a sensory branch. The motor branch is composed by nerve fibres originated from the cranial root of accessory nerve, by cell bodies located in the nucleus ambiguous. It innervates the muscles of the larynx; firstly, the posterior cricoarytenoid, then the lateral cricoarytenoid and the transverse part of the arytenoid muscle, and, finally, the thyroarytenoid muscle.\cite{17,37} Exception to the innervation provided by the motor branch of the recurrent laryngeal nerve is cricothyroid muscle, which is the only muscle of the larynx innervated by the superior laryngeal nerve.\cite{18} Additionally, the sensory branch innervates the laryngeal mucosa and it carries afferent nerve fibres from the larynx sensory receptors, as well.\cite{17} Moreover, an ascending part of the sensory branch anastomizes with the superior laryngeal nerve, forming the entirely sensory Galen’s anastomosis, known as Galen loop.\cite{17,18} As far as its function is concerned, it is worth mentioning that while the recurrent laryngeal nerve hooks under the right subclavian artery on the right and under the aortic arch on the left side, it provides the deep cardiac plexus with nerve fibres. It, also, innervates the mucosa and the muscular sheath of oesophagus and trachea.\cite{17,18}

Nevertheless, multiple studies report that the main branch of the recurrent laryngeal nerve may possibly present an extralaryngeal branching, which means that it may be divided into more than two branches before it enters the larynx. Cernea et al. studied on the whole 2154 recurrent laryngeal nerves of patients that underwent thyroidectomy between 1983 and 2008, and came to the conclusion that 64.5% of the nerves presented extralaryngeal branching. Among them, 87.9% were bifurcated into 2
branches, 11.9% were divided into 3 branches and only 0.2% into 4 branches.[38] Furthermore, in the most recent relevant meta-analysis, in which there were 28,387 nerves under study, Henry et al. mention that an extralaryngeal nerve branching is observed in 60.0% (95% CI 52.0–67.7) of the cases. Forty-seven out of 69 studies that were included in the meta-analysis, with a total number of 16,618 nerves, reported data about the type of extralaryngeal branching. Bifurcation into 2 branches was the prevailing one, as its rate was 51.1% (95% CI=35.7–55.3) of the devided nerves. Nerve division into 3 branches reached 4.7% (95% CI=1.0–9.2), and, finally, nerve division into more than 3 branches was the rarest one with 2.2% (95% CI=0–5.9) (Figure7). [39]

![Figure 7: Types of extralaryngeal branching of the recurrent laryngeal nerve. - Henry, B.M. et al., Extralaryngeal branching of the recurrent laryngeal nerve: a meta-analysis of 28,387 nerves. Langenbecks Arch Surg., 2016][39]

During its ascending course, the recurrent laryngeal nerve comes into contact with multiple anatomical structures of the neck and the, till it enters the larynx, and the relationship between them may present many variations. The inferior thyroid artery, the
Zuckerkandl’s tubercle and the Berry ligament are the anatomical structures with the highest clinical significance.

3.3. The anatomical relationship of the recurrent laryngeal nerve and the inferior thyroid artery

The relationship between the inferior thyroid artery and the recurrent laryngeal nerve is highly variable, and because of that, it has been meticulously studied during the last century. Undoubtedly, the inferior thyroid artery constitutes a stable landmark for the identification of the recurrent laryngeal nerve, especially during procedures that require an anterior surgical approach of the neck, like thyroidectomy, since the point of their confluence is immensely vulnerable for iatrogenic nerve injuries, because of the abundant anatomical variations of the recurrent laryngeal nerve.

In the modern anatomical textbooks, the recurrent laryngeal nerve is predominately described crossing the inferior thyroid artery by passing behind it.\cite{23,41} However, due to the numerous alterations that may be present in this specific area, a wide number of classification systems has been developed. Among them, this of Reed et al., where 28 subtypes are described (Figure 8), and that of Freschi et al., that includes the description of 8 subtypes, as well as the common classification system of three subtypes.\cite{40,42} The three subtypes’ classification system, where the recurrent laryngeal nerve is described to cross the inferior thyroid artery by passing behind it, in front of it or among its branches, is the system mainly used by the modern anatomists. Additionally, it is the one that is utilized in the most recent original studies and meta-analyses that outline the relationship between the nerve and the artery (Figure 9).\cite{43,44,45,46}
Figure 8: Possible relationships of the recurrent laryngeal nerve and the inferior thyroid artery and its branches. - Reed, A.F. The relations of the inferior laryngeal nerve to the inferior thyroid artery. The Anatomical Record. 1943, 85(1), 17–23 [40]

It would be purposive to be mentioned that Ardito et al. in their study, that identified 2646 recurrent laryngeal nerves intraoperatively, on the right side observed the nerve posterior to the artery in 61% of the cases, while only 12% of the right nerves were found anterior to the artery and 27% of them among the artery branches. On the opposite side, the left recurrent laryngeal nerve was observed posteriorly to the artery
in 77.4% of the cases, while only 1.9% of the identified nerves were found anteriorly to the artery and 20.5% among the artery branches.[9] Furthermore, in the most recent relevant meta-analysis that is encountered in the literature, in which 14,269 recurrent laryngeal nerves were identified, Henry et al. reported that the predominant nerve position is the one posteriorly to the artery with its rate reaching 50.7% (95% CI = 45.2–53.5). The nerve position anteriorly to the artery was less frequent with a rate of 27.6% (95% CI 5 23.2–30.6), followed, finally, by the nerve position among the artery branches with a rate of 21.7% (95% CI 5 17.8–24.6).[39,43]

Figure 9: The three main subtypes of the anatomical relationship between the recurrent laryngeal nerve and the inferior thyroid artery. - Henry, B.M., et al. Variable relationship of the recurrent laryngeal nerve to the inferior thyroid artery: A meta-analysis and surgical implications: A meta-analysis and surgical implications. HEAD & NECK. 2016, 00: 000–000, 2016.[43]

3.4. The anatomical relationship of the recurrent laryngeal nerve and the Zuckerkandl’s tubercle

The Zuckerkandl’s tubercle, that was named after the Hungarian anatomist Emil Zuckerkandl in 1902, but, firstly, described by the German physician and
surgeon Otto Wilhelm Madelung in 1867, is an extension of normal thyroid tissue on the posterolateral surface of each thyroid lobe that extends to the tracheoesophageal groove.\textsuperscript{[47,48,49]} As far as its embryological aspect is concerned, it arises from the coalescence of the fifth and the forth pharyngeal pouch. This could account for the fact that the Zuckerkandl’s tubercle is closely related to the superior parathyroid glands, but, also, for the increased amount of parafollicular cells in this anatomical region of the thyroid gland that could justified the statistically more frequent development of myeloid carcinoma in this specific part of the gland.\textsuperscript{[50]} The Zuckerkandl’s tubercle is present in about 75-80\% of the general population and it is encountered more often on the right thyroid lobe (Figure 10).\textsuperscript{[50]}


The clinical significance of the Zuckerkandl’s tubercle identification is based on the fact that it indicates the anatomical position of the recurrent laryngeal nerve and, for this reason, it constitutes an important landmark in the field of surgery of the thyroid gland.
gland. The relationship between them was mentioned for the first time by Gilmour in 1938, when he noticed that the recurrent laryngeal nerve is usually found posteriorly, less often laterally and rarely anteriorly to the Zuckerkandl’s tubercle (Figure 11).\textsuperscript{[49]}

In the most recent relevant meta-analysis that is encountered in the literature, Henry et al. report that the recurrent laryngeal nerve is located behind the Zuckerkandl tubercle in 82.7\% (95%CI: 53.6–95.4) of the identified tubercles (n=1005), laterally in 8.7\% (95%CI: 0.0–24.4) and in front of it in 8.6\% (95%CI: 0.0–24.2) of the cases. Thus, it becomes apparent that when the nerve is located either laterally or anteriorly to the Zuckerkandl’s tubercle, there is a high risk of a nerve injury. On the contrary, when it lies posteriorly to the Zuckerkandl’s tubercle, the tubercle protects the nerve and, in this way any possible iatrogenic nerve damage can be prevented.\textsuperscript{[51]}

\textbf{Figure 11}: Variation in anatomic relationships of the recurrent laryngeal nerve and the tuberculum Zuckerkandl.- Mohebati, A. and Shaha, A. R. Anatomy of Thyroid and Parathyroid Glands and Neurovascular Relations. Clinical Anatomy. 25:19–31 (2012), 2012. \textsuperscript{[13]}
3.5. The anatomical relationship of the recurrent laryngeal nerve and the Berry Ligament

The Berry ligament, also known as suspensory ligament of thyroid gland, that was named after Sir James Berry in 1988, constitutes a thickening of the pretracheal fascia, which connects the thyroid gland with the cricoid cartilage and the first rings of trachea. In this way, the thyroid gland is attached to the laryngeal skeleton. Berry’s ligament length is approximately between 8 and 14mm, while its width ranges from 2 to 7mm. It consists of two layers and usually a small amount of thyroid tissue is located between them. Typically, the recurrent laryngeal nerve traverses the outer surface of the Berry ligament (anteriorly to the ligament). Therefore, it is clear that, when total thyroidectomy is executed, the recurrent laryngeal nerve must be carefully detached from the ligament of Berry, as well as it is of great importance the ligament to be cautiously transected, in order every part of the thyroid gland to be adequately dissected and extracted. As a result, the point of nerve and ligament confluence is considered to be extremely dangerous to dissect, due to the increased amount of nerve injuries that are reported at this specific area during thyroidectomy.

Nonetheless, apart from the common relationship between the recurrent laryngeal nerve and the ligament of Berry, there are plenty anatomical alterations. Pradeep et al. in 2012 studied 584 recurrent laryngeal nerves and noticed that 61.81% of them were located anteriorly to the Berry ligament, while only 7.02% was found posteriorly to the ligament. A great amount of recurrent laryngeal nerves was observed to perforate Berry ligament, since 31.16% of the identified nerves was reported to follow this specific course through the ligament (49). These results, concerning the prevailing relationship of the recurrent laryngeal nerve and the ligament of Berry, are similar to those of the latest relevant meta-analysis, where 16 studies were included,
with a total number of 2470 recurrent laryngeal nerves. Henry et al. deduced that 78.2% (95% CI=51.5–90.8) of the identified nerves were located anteriorly to the Berry ligament, in 14.8% (95% CI=0–33.0) of the cases the nerve was found posteriorly to it, while 7.0% (95% CI: 0–19.6) of the nerves were observed to perforate the ligament (Figure 12).[35]

4. Thyroidectomy

4.1. History – Surgical Approach

Thyroidectomy, a word that is used to describe every procedure in the field of surgery of the thyroid gland, constitutes one of the most frequent surgical operations, with a total number of over 100,000 procedures per year in the United States of America. Due to its high complications and mortality rate, thyroidectomy was considered to be one of the most dangerous surgical attempts and, as a result, its execution was forbidden by the French Academy of Medicine till 1850.\textsuperscript{[7]} Emil Theodore Kocher (1841-1917) was a Swiss surgeon and medical researcher that is reputed to be the “father” of surgery of the thyroid gland. In 1909 Kocher received a Nobel Prize for his accomplishments regarding thyroidectomy, since he performed more than 5000 thyroidectomies with a mortality rate about 0.5%, that was a phenomenal number by the standards of the day. Furthermore, in 1898 Kocher established the tranverse cervical incision, that eventually was named after him and is used widely to this day (\textbf{Figure 13}).\textsuperscript{[7,8]} Nowadays, a major progress has been acheived in regard to the diagnosis and management of both benign and malignant thyroid diseases, since new histopathologic and cytologic diagnostic criteria, molecular detection tests have been invented, new operative techniques has been developed and the older ones have been optimised.

Goitre of the thyroid gland is the principal thyroid disease that requires to be surgically treated. Main indications of thyroidectomy due to goitre are: presence or suspicion of malignancy, tracheal or oesophageal compression, retrosternal expansion, but, also, failure of medical treatment.\textsuperscript{[6]} According to the recent american and european guidelines regarding management of thyroid, total thyroidectomy is
considered to be the gold standard for the surgical treatment of any kind of goitres, due to the low relapse rate.\textsuperscript{[6,56]} However, except for total thyroidectomy, other types of thyroidectomies have been used, but are different regarding their extent and their post-surgical complication rate, such as hyperparathyroidism and recurrent laryngeal nerve injury. Currently utilized are lobectomy, subtotal thyroidectomy and near total thyroidectomy, while, on the other hand, techniques like enucleation of nodules or subtotal unilateral lobectomy have been abandoned lately.\textsuperscript{[57]}

Figure 13: Kocher’s Incision. - Townsend, CM. (2010), Atlas of General Surgical Techniques, 1st Edition, Saunders, Elsevier, Philadelphia, USA\textsuperscript{[58]}

Specifically, the surgical procedure of total thyroidectomy is being held with the patient lying in supine position, combined with cervical hyperextension. A transverse cervical incision (Kocher’s incision) is performed about 2cm above suprasternal notch, that is extended laterally till the internal edge of sternocleidomastoid muscle on each side. Subsequently, subcutaneous tissue and platysma muscle are
transected and subplatysmal flaps are elevated both upwards and downwards, till the laryngeal prominence and the suprasternal notch, respectively. Afterwards, strap muscles are separated in the midline and they get detached from the surgical thyroid capsule. Consequently, thyroid isthmus is dissected, ligated and transected.\textsuperscript{[6,59]} Thyroid excision usually begins from the lobe, where malignancy is found, or from the most affected lobe, in the case of multinodular goitre.

According to the American Head and Neck Society, there are four possible surgical approaches regarding recurrent laryngeal nerve identification and management; the lateral, the inferior, the superior and the medial approach. Each one of them is used depending on circumstances and surgeon’s preference.

4.2. The lateral approach

The lateral approach is the one utilized more often in thyroid gland surgery and starts with the mobilization of the superior and inferior pole of the thyroid lobe.\textsuperscript{[60]} Firstly, the thyroid lobe is pulled upwards, so that the middle thyroid vein is identified and ligated; in this way the lobe gets easily mobilized.\textsuperscript{[59]} Afterwards, the superior pole is revealed and carefully dissected, in order the superior laryngeal nerve not to get injured, by dissecting the superior thyroid vessels. At this point, superior laryngeal nerve injury is rather frequent, since it is reported at 58% of thyroid surgical procedures.\textsuperscript{[60]} The safest way of superior laryngeal nerve management is, on one hand, nervemonitoring utilization and, on the other, cautious identification of each one of the superior thyroid vessels and their ligation as close as possible to the thyroid tissue. Subsequently, the inferior pole is dissected, the inferior thyroid artery is identified and carefully ligated, since, as has been mentioned above, its relationship with the recurrent
laryngeal nerve may vary and, as a result, there is a big risk of nerve damaging at this specific point. Furthermore, the inferior thyroid artery is closely related to parathyroid glands, both superior and inferior, whose protection and preservation is crucial.\textsuperscript{[61]} Consequently, after the superior and inferior poles get disengaged by the surrounding tissues, the thyroid lobe is pooled to the middle line and over the trachea. The recurrent laryngeal nerve is usually encountered at the middle of the thyroid lobe, closely related to the inferior parathyroid gland. Gradually, the nerve is dissected and repelled. The presence of the Zuckerkandl’s tubercle and thick connective tissue at the point where the gland is attached to the trachea may render the lateral approach sorely laborious.

4.3. The inferior approach

By choosing the inferior approach, the surgeon encounters the recurrent laryngeal nerve at the superior thoracic aperture and follows it cephalad by dissecting it all along its length. Ofttimes, on the right side the nerve is located more laterally, in comparison to the left one, and, therefore it traverses the tracheoesophageal groove diagonally or more vertically than on the left side, where its course is almost parallel to the groove.\textsuperscript{[33,34,60]} This method is considered notably useful in revision surgery, since thick connective scar tissue enables nerve dissection particularly difficult, whereas under normal conditions it is rather easier. The recurrent laryngeal nerve is found under the level of a contingent extralaryngeal branching. However, one of the major disadvantages of the lateral approach is the fact that there is a high risk of nerve injury and, also, inferior parathyroid gland devascularization.\textsuperscript{[60]}
4.4. The superior approach

The superior approach starts with superior thyroid pole mobilization. At this point, the inferior pharyngeal constrictor muscle acts as a landmark, since the recurrent laryngeal nerve enters the larynx by penetrating this muscle and can be easily identified at the muscle’s inferior edge. The ligament of Berry transection, at an early stage during the procedure, facilitates thyroid gland detachment from the trachea, thus it enables thyroid mobilization and, in this way, it reduces the risk of nerve damage due to excessive traction. Through this technique, the recurrent laryngeal nerve is identified between the larynx and the superior thyroid pole, which is laterally located. The superior approach is considered appropriate for large goitres and, especially, those with retrosternal expansion, when lateral and inferior approaches are not considerably efficient. Furthermore, it is indicated in situations where encountering recurrent laryngeal at its proximal part has failed, but, also, in remote access thyroidectomy surgical approaches (e.g., facelift thyroidectomy, retroauricular thyroidectomy).[60]

4.5. The medial approach

The medial approach starts with thyroid isthmus ligation, followed by lateral mobilization of the thyroid lobe. At that point, dissection of the central part of the thyroid lobe begins from the middle line and continues through the avascular space between the thyroid lobe and the trachea, heading towards the lateral part of the lobe. Subsequently, the inferior edge of the cricothyroid muscle is identified, by dissecting the avascular space between the superior thyroid pole and the cricothyroid muscle fascia. This method is considered quite safe for the recurrent laryngeal nerve preservation, since the nerve is located right below this specific area, deep under the
inferior pharyngeal sphincter muscle. Dissection continues cephalad, till the superior thyroid pole is clearly identified and the superior thyroid vessels are cautiously ligated, by preserving the superior parathyroid gland, at the same time. Consequently, the Berry ligament is carefully transected, ensued by the inferior thyroid pole dissection, using the same technique. After the adequate mobilization of both superior and inferior poles of the thyroid lobe, the Zuckerkandl tubercle remains the sole point of thyroid attachment to the trachea, that is cautiously dissected. The recurrent laryngeal nerve is usually encountered right posteriorly to the tubercle. This method is indicated for procedures where a small incision is chosen or when the goitre is of large dimensions, since through this method, the thyroid lobe, after its appropriate dissection can be shifted out of the paratracheal space.\[60\]

Regardless of the approach chosen by the surgeon, after the recurrent laryngeal nerve identification, the superior thyroid vessels ligation and the Berry ligament transection, the thyroid lobe is detached from its attachment to the trachea and finally gets extracted from the surgical field. The exact same process is applied to the other lobe. Afterwards, meticulous haemostasis is ensured, usually by bipolar coagulation diathermy, strap muscles are reapproximated in the middle line.\[59\] Ultimately, subcutaneous tissue suturing is performed, followed by an intradermal suture, in order to achieve the best possible aesthetic result.

**4.6. Minimally Invasive Techniques**

As has been mentioned above, classic thyroidectomy is performed through a transverse cervical incision and presents quite low mortality and morbidity rates. However, the scar that is developed after the incision’s healing may dissatisfy the majority of the
patients, that for the most part is consisted by females, due to the unsightly aesthetic result.\textsuperscript{[62]}

During the 1990s, because of the general tendency of minimally invasive surgical techniques development, endoscopic surgery started to be applied in thyroid procedures. This method was finally established by Miccoli et al. in 1999 in Pisa, Italy, when minimally invasive thyroidectomy technique was applied by utilizing a video-endoscope (Minimally Invasive Video-Assisted Thyroidectomy - MIVAT) in 12 patients, resulting in rather satisfying outcomes.\textsuperscript{[63]} The objective of minimally invasive techniques was and continues to be the reduction of tissues’ damage and post-operative pain, in combination with the best aesthetic result, the shorthest operation time leading to the lowest possible hospitalisation cost, but also, the least possible intra-operative and post-operative complications. Specifically, endoscopic thyroidectomy offers the potential of 20-25 times magnification of the surgical field and, as a result, every anatomical structure, and especially parathyroid glands and the recurrent laryngeal nerve, is better visualized, resulting in fewer relevant complications.\textsuperscript{[62]}

Therefore, the phrase “endoscopic thyroidectomy” is used to describe the execution of the thyroidectomy procedure completely, from the beginning to the end, by using an endoscope. It consists of three stages; the access to the thyroid gland and the dissection of the surgical field through a small skin incision, the detachment of the thyroid lobes from the trachea after the recurrent laryngeal nerve and parathyroid glands’ identification and preservation on both sides and, finally, the thyroid lobes extraction and the wound closure. Depending on the chosen technique of access, the duration of these three stages may vary.\textsuperscript{[64,65]} Endoscopic approach indications include the benign thyroid disease of small dimensions, such as a solitary thyroid nodule less than 3 cm or a multinodular goitre with total thyroid gland volume less than 30 cc.\textsuperscript{[62]}

\textit{Σελίδα 41 από 80}  
Gkrinia Eleni
Grave’s disease constitutes a relative contraindication for the endoscopic technique, due to the higher risk of intra-operative or post-operative bleeding. Among absolute contraindications of the endoscopic enhanced thyroidectomy are goitres of large dimensions, preceded neck radiotherapy or surgical procedures of the neck region, invasive thyroid carcinoma or lymph nodes metastasis. Nevertheless, surgical treatment of well differentiated thyroid carcinomas entirely through the endoscopic approach is rather controversial.[66]

The endoscopic approaches of the thyroid gland are divided into cervical (medial, lateral, retro-cervical approach) and extra-cervical approaches, that include the anterior chest wall approach, the breast approach, the axillary approach, the vestibular (or retro-auricular) approach and the transoral approach.[65,67,68,69] Among the most widespread and broadly utilized methods stand the cervical ones, the axillary and the breast approach.[62] The vestibular approach, because of the comparatively higher complications rate that is related to swallowing disorders, and the longer operation time that is usually demanded, is still fairly experimental.[70] Ultimately, the transoral endoscopic thyroid gland approach is becoming more and more popular, since it provides the best possible aesthetic result by using the principles of surgery through natural body openings, provided that it prevails over the rest remote approaches with regard to the distance from the thyroid gland.[71] Undoubtedly, it is evident that there is abundant room for improvement and progress in the field of minimally invasive techniques and, especially, in endoscopic thyroidectomy, thus impressive development and evolution is expected in the near future.
5. Intra-operative neuromonitoring of the recurrent laryngeal nerve

Injury of the recurrent laryngeal nerve during thyroid gland surgery lies among the commonest post-operative complications, leading to severe consequences that affect patients’ quality of life perceptibly.[72] On the one hand, paresis and, on the other hand, paralysis of the recurrent laryngeal nerve emerge in 0.4-12% and 5-6% of thyroidectomy procedures, respectively, influencing in a great manner patients’ everyday life.[73] Thus, in order vocal hoarseness, dysphonia, dysphagia or even dyspnoea to be avoided, recurrent laryngeal nerve recognition and cautious dissection is of enormous importance for the surgeon. Nerve injury incidence depends on multiple factors. The type of thyroid disease – since malignancies augment the risk of nerve damage – thyroidectomy type (total or subtotal), revision surgeries, in addition to clinical and surgical education, as well as surgeon’s experience are encountered among the most significant ones.[74]

To date, visual identification of the recurrent laryngeal nerve is considered to be the safest method of recognition and nerve injury elusion. Notwithstanding, intraoperative nerve monitoring (IONM) gains popularity, not only as an nerve identification too, but also, as a mean of post-operative vocal chords’ functionality prediction. Besides, nerve injury mechanism clarification is of great importance.[75] Nowadays, intraoperative nerve monitoring is increasingly utilized from both general surgeons and otolaryngologists, with its preference rate approaching 40-45%.

The technique of neuromonitoring is based on the nerve stimulation by using a monopolar electrode, as well as the consequent nerve’s response, whose electric potential is converted into an audio signal that is recorded.[76] Specifically, the nerve monitoring system utilizes recording electrodes, which are attached on the intubation
tube surface (Figure 14). During intubation, the anesthesiologist inserts the tube in this way, so that the electrodes osculate the vocal chords (Figure 15). Furthermore, recording electrodes are placed on the patients’ sternum and shoulders. Both simulation electrode and recording electrodes are connected to a detection system, including a screen where the neurography waveform is projected. During thyroidectomy, the thyroid lobe is pulled anteriorly and towards the middle line, in order superior thyroid vessels to be revealed and, afterwards, ligated. Subsequently, the recurrent laryngeal nerve is identified, dissected and stimulated using a monopolar electrode, through intermittent nerve stimulation (electric current of 1mA, frequency 4 Hz, duration 100ms).[^76] Nerve stimulation provokes vocal cord contraction, which is recorded through the intubation tube’s electrodes and interpreted in electromyographic signals. The response signal waveform is evaluated on the basis of its amplitude, the signal threshold and latent response time. By virtue of this system, it is possible to distinguish a true response signal from a false one. Additionally, an audio warning system alerts the surgeon for potential abnormalities in signal quality and, in combination with the waveform assessment, the nerve and its branches’ identification, as well as the nerve injury possibility is achieved in real time; hence, vocal cords postoperative functionality can be estimated.[^76]
Figure 14: Nerve integrity monitoring endotracheal tube for electromyography signals of a patient's laryngeal muscles (drawn by Silvia Marola) - Cirocchi, R., et al., Intraoperative neuromonitoring versus visual nerve identification for prevention of recurrent laryngeal nerve injury in adults undergoing thyroid surgery (Review). Cochrane Database of Systematic Reviews. Issue 1 [74]
Moreover, except for the intermittent intraoperative recurrent laryngeal nerve stimulation, Zuckerkandl continuous nerve-monitoring is a useful asset for Head and Neck surgeons. This technique is based on a clip-electrode attachment to the vagus nerve, that stimulates the nerve periodically, allowing only short interruptions. Continuous nerve-monitoring facilitates the detection of any nerve functionality alteration during the procedure, and in this way, it warns the surgical team for an imminent nerve damage.\textsuperscript{[77]}

**Figure 15**: Monitoring endotracheal tube in position positioned at the patient's vocal folds (drawn by Silvia Marola - Cirocchi, R., et al. Intraoperative neuromonitoring versus visual nerve identification for prevention of recurrent laryngeal nerve injury in adults undergoing thyroid surgery (Review). Cochrane Database of Systematic Reviews. Issue 1 \textsuperscript{[76]}**
Ultimately, it would be an oversight not to mention that, even if intraoperative nerve-monitoring constitutes a safe process and, in parallel, a very helpful tool in thyroid gland surgery, it presents some confinements. Specifically, it is usually difficult to discern whether a signal loss is false or true and what it is caused by; a nerve injury or a detachment of the recording electrodes from the vocal cords. In addition, it is worthmentioning that the signal intensity can be possibly affected by anaesthesia, as well as by intraoperative handling of the trachea.\[77\]
PART B’

6. Introduction

Total thyroidectomy numbers among the most frequently performed procedures in the anatomic area of the neck, since it is indicated for the treatment of thyroid malignancies and most of the benign thyroid diseases. Among the greatest postoperative complications of thyroidectomy, palsy of recurrent laryngeal nerve and hypocalcaemia have been reported in all current guidelines, given that both conditions can be life-threatening, potentially. Hence, an excellent knowledge of the anatomy of the neck and its anatomical variations is necessary for total thyroidectomy in order to achieve the best clinical outcome.

Despite the fact that over the previous decades, head and neck surgeons used to avoid surgical dissection close to the recurrent laryngeal nerve, in order to prevent the potential of a nerve injury, nowadays, recurrent laryngeal nerve identification is the gold-standard technique, determining the security of nerve function. Iatrogenic injury of the recurrent laryngeal nerve may lead to temporary nerve palsy, which usually recovers spontaneously within 6 months. Nevertheless, any malfunction exceeding this period is considered permanent and, apart from the vocal, swallowing and breathing difficulties, it may affect patient’s psychology and social life. Therefore, recurrent laryngeal nerve dissection is of great importance, regarding the visualization of the location of the nerve and its anatomical relations with the adjacent structures; especially the inferior thyroid artery and its branches.

Over the last twenty years, multiple studies have been conducted regarding the relationship of the recurrent laryngeal nerve and the inferior thyroid artery. The objective of the present study is to assess substantially this anatomic relationship by
combining a systematic review and meta-analysis of the existing literature with a prospective study of reporting and evaluating this entity in patients undergoing total thyroidectomy at the Otolaryngology Department of the University Hospital of Larissa.

7. Methods and Materials

7.1 Prospective study

7.1.1 Study Population

A prospective anatomic study was performed in patients of the Otolaryngology Department of the University Hospital of Larissa, over a 6-month period, from October 2019 to March 2020. All patients that underwent total thyroidectomy for both malignant and benign thyroid diseases were considered eligible. The study was approved by the Institutional Review Board. All patients signed an informed consent prior to thyroid surgery. Patients who had hemithyroidectomies or had undergone previous thyroid operation were excluded from this study.

7.1.2. Surgical approach technique

Thyroidectomies were performed through Kocher’s incision under general anaesthesia by three experienced ENT surgeons (I.B., C.S., J.H.). Intraoperative nerve monitoring was implemented in every patient, and, consequently, an endotracheal tube equipped with surface electrodes that recorded the response signal was utilized [NIM® EMG Tubes - Medtronic, Internal Diameter (ID) = 6.5 mm for females and ID = 7.5 mm for males]. The procedure’s steps were performed in the same order in all patients, by using the lateral approach of the thyroid lobe dissection and extraction. After skin, subcutaneous tissue and the platysma muscle were transected, superior and
inferior flaps were undermined between the platysma and strap muscles. Afterwards, the middle line was recognized and strap muscles were separated, and detached from the thyroid capsule. After the thyroid gland exposure, isthmectomy was performed. Subsequently, starting from the lobe where malignancy was encountered, or from the most affected lobe due to multinodular goitre, the lateral surface of each lobe was dissected, accompanied by the ligation of the middle thyroid vein. Then, dissection of the superior pole with cautious ligation of the superior thyroid vessels ensued, after the superior laryngeal nerve was recognized. In addition, dissection of the inferior pole was performed. Consequently, the recurrent laryngeal nerve was identified, near the middle part of the thyroid lobe and approaching the inferior parathyroid gland, using surgical loupes, as well as by utilizing the nerve stimulation electrode of the electro-myographic digital recording system NIM-Response® 3.0 – Medtronic. Afterwards, the recurrent laryngeal nerve was dissected progressivelly, till its entrance to the larynx, at the level of the cricoid cartilage. Ultimately, after dissecting the ligament of Berry, each thyroid lobe was extracted. The same process was followed on the other side. Great caution was excercised in the identification of the recurrent laryngeal nevre, its relationship with the inferior thyroid artery, but also, the careful dissection of parathyroid glands, on both sides. Before subcutaneous tissue and skin closure, a negative-pressure drainage was placed and strap muscles were pulled towards the middle line.

7.1.3. Data surveillance

A database was established to prospectively document patients’ characteristics, regarding demographics, surgery date, diagnosis, preoperative and postoperative blood tests (serum calcium fluctuation), anatomic variations and postoperative complications. Furthermore, in order postoperative recurrent laryngeal nerve malfunction to be
correctly assessed, vocal cords’ functionality was evaluated before surgery by an experienced ENT surgeon (I.B., C.S., J.H.), using a 70-degree rigid endoscope. Postoperatively, laryngoscopy was repeated (by the same ENT surgeon) for the purpose of detecting any RLN injury. In addition, serum calcium was measured before surgery and on the first postoperative day. Blood sampling was held without using a tourniquet, in order falsely incorrect serum calcium values to be avoided, and every sample was analysed by the Microbiology Laboratory of the University Hospital of Larissa. Every corrected serum calcium measurement over 8.5 mg/dl was considered normal (Corrected serum calcium = [0.8 x (normal albumin - patient's albumin)] + patient’s serum calcium level, normal calcium levels: 8.5 – 10.5 mg/dL).

7.1.4. Postoperative management and follow-up of the patients

The majority of the patients was discharged from the Otolaryngology Department on the second postoperative day, after being given the adequate advice in regard to wound care and precautionary calcium supplement administration, regardless of whether they presented hypocalcaemia or not. On the 7th postoperative day, blood test was repeated, and with the assent of the treating endocrinologist, tapering of the administered calcium was accomplished. On the 12th postoperative day, every patient came back to the clinic for the suture removal. Additionally, all patients underwent a second laryngoscopy, in order the proper function of the vocal cords to be confirmed. Laryngoscopy was, also, repeated one month postoperatively.

In case of symptomatic hypocalcaemia during their hospitalization, patients that presented oral, perioral, acral paraesthesias, positive Chvostek or Trousseau sign, were examined by specialized doctors of the Endocrinology Department of the University Hospital of Larissa, and calcium gluconate was administrated intravenously in addition
to the precautionary calcium and vitamin-D₃ supplements administration’ hence, they were hospitalized until normal serum calcium measurements were achieved and patients remained asymptomatic. On the contrary, patients that presented non-symptomatic hypocalcaemia during their first or second postoperative day, continued with the precautionary calcium and vitamin-D₃ supplements administration. As a result, normal serum calcium values were achieved on the 3rd or 4th postoperative day, leading to their discharge from hospital without any problems.

Moreover, patients that were diagnosed with vocal cords malfunction were acceded to a program of frequent ENT evaluation for the next six months. During the first trimester postoperatively, they underwent laryngoscopy every 15 days, while for the next three months, only once every month. Laryngoscopy after the six months postoperatively was not needed, since every dysfunction was restored within this period.

Furthermore, patients that were diagnosed with thyroid carcinoma, according to the histopathological examination, were committed to their treating endocrinologist, in order to decide whether a postoperative treatment with radioactive iodine would follow. Till today, no patient diagnosed with thyroid carcinoma needed to be reoperated.

7.1.5. Statistical analysis

Continuous data were reported as a mean ± standard deviation. Categorical data were expressed as absolute numbers and percentage of prevalence (%) in the study cohort. In the statistical analysis for continuous variables the independent t-test for normally distributed data and the Mann-Whitney U test for nonparametric data were used. The Pearson’s chi square test was used for categorical variables. P value was
considered significant when it was <0.05. Statistical analysis was performed by SPSS 22.0 for Windows software (IBM Corp, Armonk, NY).

7.2. Meta-analysis

7.2.1. Methodology - Eligibility criteria

Meta-analysis and systematic review’s objectives and methodology, as well as the eligibility criteria were predetermined before the start of the study. No patient informed consent or ethics committee approval was required due to the nature of the current study, which was based on published records. This meta-analysis was conducted in accordance to the Preferred Reporting Items for Systematic Review and Meta-analysis Protocol (PRISMA).[82] Data extraction was performed by two independent reviewers (Ε.Γ., Π.Ν.), while any dissidences were solved by advisory discussion with a third one (Α.Ζ.). Studies’ eligibility criteria were: 1. Studies with reporting the relationship between the recurrent laryngeal nerve and the inferior thyroid artery, 2. Studies including patients that underwent thyroidectomy. Exclusion criteria were: 1. Non-related studies, 2. Studies not including quantified data, 3. Studies in other languages except for english, 4. Letters to the editor, 5. Other systematic reviews and meta-analyses 6. Conferences presentations 7. Studies with less than 5 participants, 8. Experimental studies, 9. Non-human studies, 10. Cadaveric studies, 11. Studies related to surgical procedures apart from thyroidectomy.

7.2.2. Search Strategy

An electronic literature search of the English medical literature was performed by two reviewers (Ε.Γ., Π.Ν.) separately, using Pubmed/Medline (U.S. National Library of Medicine, Bethesda MD - USA) and Scopus (Elsevier, Amsterdam –
Netherlands) databases to identify relevant studies. There was no specific search starting date, while June 30th was the last day of literature search. The P.I.C.O. (patient; intervention; comparison; outcome) model was used to define the clinical questions and select relevant articles (Table 1). The following search terms including Expanded Medical Subject Headings (MeSH) were used in various combinations: “recurrent laryngeal nerve”, “inferior thyroid artery”, “thyroidectomy”. The primary selection was based on title and abstract. A secondary scrutiny was performed according to the full text of publications.

<table>
<thead>
<tr>
<th>Frame</th>
<th>Mesh terms</th>
<th>Search</th>
<th>Inclusion criteria</th>
<th>Exclusion Criteria</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P</strong> (patients, participants, population)</td>
<td># 1. “Patients undergoing thyroidectomy”</td>
<td>“recurrent laryngeal nerve” AND “inferior thyroid artery” AND “thyroidectomy”</td>
<td>Articles focusing on the RLN variations and the relationship of RLN regarding to ITA</td>
<td>Irrelevant title or abstract, Irrelevant full-text, Non-English, Editorial, reviews, meta-analyses, Studies with less than 5 subjects, Experimental/nonhuman/cadaver studies, Interventions other than thyroid surgery, Total number of patient sample not obvious,</td>
<td>Databases: Pubmed/Medline (U.S. National Library of Medicine, Bethesda MD - USA), Scopus (Elsevier, Amsterdam – Netherlands)</td>
</tr>
<tr>
<td><strong>I</strong> (intervention)</td>
<td>The anatomical relationship of #2. recurrent laryngeal nerve (RLN)”</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>C</strong> (reference test)</td>
<td>Regarding #3 “inferior thyroid artery (ITA)”</td>
<td></td>
<td></td>
<td>Reference list: p.71</td>
<td></td>
</tr>
<tr>
<td><strong>O</strong> (outcome)</td>
<td>Anatomical relationship of RLN regarding inferior ITA, variations of this relationship, RLN variations, RLN injury during thyroidectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>Search period: not specific - June 2020 Last search: 30/06/2020</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 1**: P.I.C.O.(T.) model (patient; intervention; comparison; outcome; time)
7.2.3. Data extraction

A Microsoft Excel file was created in order data to be extracted. Data was encountered either in the text or in the tables included in the articles. Firstly, general information such as author name and year of publication was detected. Moreover, further clinical data was collected: patients’ demographics (age, gender), thyroid disease requiring thyroidectomy, topographic relationship of the recurrent laryngeal nerve to the inferior thyroid artery, recurrent laryngeal nerve’s anatomical variations, the presence or absence of the non-recurrent laryngeal nerve, intraoperative recurrent laryngeal nerve’s injury, postoperative vocal cords’ palsy.

7.2.4. Quality Assessment

Study quality assessment was achieved by using the quality assessment tool for case series of the Joanna Briggs Institute (The Joanna Briggs Institute, Faculty of Health Sciences of the University of Adelaide, Australia). By utilizing a list of 10 questions, the Joanna Briggs Institute tool evaluates case series according to the answers; “yes” corresponds to high risk of bias, “no” to low risk of bias and “unclear” to uncertain risk of bias. The questions focus on the following characteristics: articulate patients’ eligibility criteria, use of reliable methods for the identification of the wanted object under research to all participants, continuous and complete integration of participants in the series of events, clear reporting of the participants’ demographics, clear reporting of the results and their subsequent monitoring, but also the use appropriate means of statistical analysis.
7.2.5. Statistical Analysis

The statistical analysis of the topographic relationship of the recurrent laryngeal nerve regarding to the inferior thyroid artery, in addition to the presence of anatomic variations and postoperative complications was conducted through a meta-analysis of the data. The outcomes of continuous measurements were pooled in mean differences and their 95% CI, whereas the outcomes of count measures were summarized in odds ratio along with their 95% confidence intervals (CI), through a paired meta-analysis. The inter-study heterogeneity was evaluated using the significance of the Cochran’s Q-metric (pQ) and quantified by the Higgins I² statistics. Significance was set at p<0.05. The pooled estimate was assessed using the random-effects model in the presence of inter-study heterogeneity (I²>50%), or else with the fixed-effects model. Publication bias was eyeballed by funnel plots and assessed using the fail-safe N analysis, also known as file-drawer analysis. All statistical analyses were executed using the Jamovi project for the R-statistical environment.[85,86]

8. Results

8.1. Prospective Study

Sixty-four patients, were included in the current study; 46 (71.9%) were females and 18 (28.1%) were males. The mean age was estimated at 51.7 (range 21-81 years. The majority of patients (70.3%) were treated for benign pathologies. Pre-operative diagnoses for all patients are presented in Table 2. In all cases, diagnosis was confirmed by histological examination of the extracted gland.
Table 1: Pre-operative diagnosis, confirmed by histological examination.

Regarding the topography of the recurrent laryngeal nerve to the inferior thyroid artery; in total 35 cases, among 128 recurrent laryngeal nerve dissections (27.3%), the recurrent laryngeal nerve was located anteriorly to the inferior thyroid artery [17 cases (13.3%) at the right side and 18 (14.1%) at the left] (Table 3) (Figure 16). The classical retro-vascular course of the recurrent laryngeal nerve was identified in 72.6% of the nerves dissected.

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=18 / 64)</td>
<td>(n=46 / 64)</td>
<td>(n=64 / 64)</td>
</tr>
<tr>
<td></td>
<td>(28.1%)</td>
<td>(71.9%)</td>
<td>(100.0%)</td>
</tr>
<tr>
<td>Multinodular Goitre</td>
<td>9 / 18 (50.0%)</td>
<td>27 / 46 (58.7%)</td>
<td>36 / 64 (56.3%)</td>
</tr>
<tr>
<td>Retrosternal</td>
<td>2 / 18 (11.1%)</td>
<td>4 / 46 (8.7%)</td>
<td>6 / 64 (9.4%)</td>
</tr>
<tr>
<td>Multinodular Goitre</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid Cancer</td>
<td>7 / 18 (38.9%)</td>
<td>12 / 46 (26.1%)</td>
<td>19 / 64 (29.7%)</td>
</tr>
<tr>
<td>Grave’s Disease</td>
<td>0 / 18 (0.0%)</td>
<td>3 / 46 (6.5%)</td>
<td>3 / 64 (4.7%)</td>
</tr>
</tbody>
</table>

Table 2: Position of the recurrent laryngeal nerve (RLN) in relation to the inferior thyroid artery (ITA) /

<table>
<thead>
<tr>
<th></th>
<th>Right RLN</th>
<th>Left RLN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Anterior to the ITA</td>
<td>17</td>
<td>26.6%</td>
</tr>
<tr>
<td>Posterior to the ITA</td>
<td>47</td>
<td>73.4%</td>
</tr>
<tr>
<td>Total</td>
<td>64</td>
<td>100</td>
</tr>
</tbody>
</table>
In terms of sex and recurrent laryngeal nerve distribution, the analysis has demonstrated that any unilateral or bilateral topographic alterations were more common in female patients; 69.2% and 63.6%, respectively [p=0.812 (in unilateral alteration), p=0.504 (in bilateral alteration)]. In 22.2% of males a unilateral alteration was recorded while a bilateral one was described among 22.2% of them, as well (Table 4 and 5). No statistical significance was noticed in the association of topographic alterations and sex (unilateral, p=0.8; bilateral, p=0.5).
Table 3: Distribution of presence or absence of alteration in relation to sex. (n = number)

<table>
<thead>
<tr>
<th></th>
<th>Unilateral alteration</th>
<th>Bilateral alteration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=13</td>
<td>n=11</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Male</td>
<td>4 / 13</td>
<td>30.8%</td>
</tr>
<tr>
<td>Female</td>
<td>9 / 13</td>
<td>69.2%</td>
</tr>
<tr>
<td>Total</td>
<td>13 / 13</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 4: Distribution of unilateral and bilateral alteration regarding to sex. (n = number)

Concerning other anatomic alterations, overall, two cases of bifurcation of the recurrent laryngeal nerve were observed (Figure 17) both were encountered on the left side. On the contrary, no case of trifurcation was recorded. Apart from these, a right recurrent laryngeal nerve was found to lead a retro-tracheal course. Furthermore, no case of non-recurrent laryngeal nerve was recorded.
As far as postoperative complications are concerned, one case of vocal hoarseness (1.6%) due to transient right recurrent laryngeal nerve palsy was observed in recovered within 6 months. Regarding the post-operative serum calcium measurements, three cases of symptomatic hypocalcaemia were noted, but none of them in patients with unilateral or bilateral alteration. The symptoms observed were oral or perioral (3.1%) and acral paraesthesias (1.6%). On the contrary, no case of tetany, laryngospasm or electrocardiographic changes was noticed. Furthermore, 17.2% (11/64) of the patients presented non-symptomatic hypocalcaemia. In 4 out of 11 patients presenting with non-symptomatic hypocalcaemia a recurrent laryngeal nerve alteration was identified; in two of the cases the recurrent laryngeal nerve was encountered posteriorly to the inferior thyroid artery bilaterally, while in the other two cases this happened only unilaterally (Table 6). However, the presence of RLN topographic variation was not associated to low serum calcium measurements (p=0.52).

In conclusion, no other local complication, including hematoma, seroma, wound infection, aerodigestive perforation, pneumothorax or chyle leak was noticed.
<table>
<thead>
<tr>
<th></th>
<th>Symptomatic Hypocalcaemia</th>
<th>Asymptomatic Hypocalcaemia</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>RLN alteration</td>
<td>0/3</td>
<td>0%</td>
<td>4/11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 unilateral</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 bilateral</td>
</tr>
<tr>
<td>No RLN alteration</td>
<td>3/3</td>
<td>100%</td>
<td>7/11</td>
</tr>
<tr>
<td>Total</td>
<td>3/3</td>
<td>100%</td>
<td>11/11</td>
</tr>
</tbody>
</table>

Table 5: Hypocalcaemia in relation to RLN alteration presence. (RLN: recurrent laryngeal nerve, n: number)

8.2. Meta-analysis

Totally, 271 articles were identified through database searching- one extra article was encountered from other sources (Chart 1). Subsequently, 21 articles were excluded because of duplication. Afterwards, 60 more were excluded due to language restrictions (only studies composed in English language were considered eligible). Then, 174 studies were excluded, based on their title or abstract. After full text assessment, 7 more articles were excluded as ineligible. Finally, 10 studies were considered eligible and were included in both the quality assessment and the quantitative synthesis (Table 7).
<table>
<thead>
<tr>
<th>Study Number</th>
<th>Author (year)</th>
<th>Study design</th>
<th>Country of Origin</th>
<th>Number of participants</th>
<th>Number of RLN studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Sturniolo G. et al. (1999) [87]</td>
<td>case series</td>
<td>Italy</td>
<td>192</td>
<td>280</td>
</tr>
<tr>
<td>2.</td>
<td>Hisham A.N. et al. (2002) [81]</td>
<td>case series</td>
<td>Malaysia</td>
<td>325</td>
<td>491</td>
</tr>
<tr>
<td>6.</td>
<td>Pradeep P.V. et al. (2012) [55]</td>
<td>case series</td>
<td>India</td>
<td>404</td>
<td>584</td>
</tr>
<tr>
<td>7.</td>
<td>Zada B. et al. (2014) [88]</td>
<td>case series</td>
<td>Pakistan</td>
<td>271</td>
<td>398</td>
</tr>
</tbody>
</table>

**Table 7:** Eligible studies included in the meta-analysis. (RLN: Recurrent Laryngeal Nerve)
Overall, 3374 patients were included in the meta-analysis and 5671 recurrent laryngeal nerves were studied. The most frequent anatomic position of the nerve was posterior to the inferior thyroid artery (57% [95% CI = 45% - 69%, I²=98.0%, p<0.001]). The second most common relation of the nerve to the artery was anterior to it (28% [95% CI = 18% - 38%, I²=98.7%, p<0.001]), while the nerve was observed.

**Chart 1:** PRISMA Flow Diagram for the systematic review and meta-analysis of the literature.
among inferior thyroid artery’s branches in 13% of the cases [95% CI = 7% - 19%, \( I^2=98.0\% \), \( p<0.001 \)]. The left recurrent laryngeal nerve was found to be posterior to the artery more frequently than the right one. On the contrary, the right recurrent laryngeal nerve was encountered anterior to the inferior thyroid artery or among its branches more often than the left one.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>k</th>
<th>Confidence interval (CI)</th>
<th>( I^2 )</th>
<th>Publication bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>RLN anteriorly to ITA</td>
<td>10</td>
<td>0.28 [95% CI = 0.18 - 0.38]</td>
<td>98.7%</td>
<td>0.120</td>
</tr>
<tr>
<td>Right RLN anteriorly to ITA</td>
<td>8</td>
<td>0.65 [95% CI = 0.50 - 0.80]</td>
<td>95.8%</td>
<td>0.174</td>
</tr>
<tr>
<td>Left RLN anteriorly to ITA</td>
<td>8</td>
<td>0.40 [95% CI = 0.26 - 0.53]</td>
<td>94.5%</td>
<td>0.461</td>
</tr>
<tr>
<td>RLN posteriorly to ITA</td>
<td>10</td>
<td>0.57 [95% CI = 0.45 - 0.69]</td>
<td>98.8%</td>
<td>0.427</td>
</tr>
<tr>
<td>Right RLN posteriorly to ITA</td>
<td>8</td>
<td>0.43 [95% CI = 0.37 - 0.49]</td>
<td>81.9%</td>
<td>0.756</td>
</tr>
<tr>
<td>Left RLN posteriorly to ITA</td>
<td>8</td>
<td>0.57 [95% CI = 0.51 - 0.63]</td>
<td>81.9%</td>
<td>0.756</td>
</tr>
<tr>
<td>RLN among ITA branches</td>
<td>8</td>
<td>0.13 [95% CI = 0.07 - 0.19]</td>
<td>98.0%</td>
<td>0.035</td>
</tr>
<tr>
<td>Right RLN among ITA branches</td>
<td>7</td>
<td>0.70 [95% CI = 0.59 - 0.82]</td>
<td>80.0%</td>
<td>0.418</td>
</tr>
<tr>
<td>Left RLN among ITA branches</td>
<td>7</td>
<td>0.36 [95% CI = 0.24 - 0.48]</td>
<td>79.6%</td>
<td>0.731</td>
</tr>
<tr>
<td>RLN divided</td>
<td>8</td>
<td>0.38 [95% CI = 0.16 - 0.60]</td>
<td>99.7%</td>
<td>0.002</td>
</tr>
<tr>
<td>Right RLN divided</td>
<td>6</td>
<td>0.16 [95% CI = 0.05 - 0.27]</td>
<td>99.4%</td>
<td>0.678</td>
</tr>
<tr>
<td>Left RLN divided</td>
<td>6</td>
<td>0.12 [95% CI = 0.02 - 0.22]</td>
<td>99.3%</td>
<td>0.852</td>
</tr>
<tr>
<td>Non-RLN</td>
<td>8</td>
<td>0.002 [95% CI = 0.001 - 0.003]</td>
<td>0.0%</td>
<td>0.604</td>
</tr>
<tr>
<td>Right Non-RLN</td>
<td>8</td>
<td>0.82 [95% CI = 0.65 - 1.00]</td>
<td>0.0%</td>
<td>0.114</td>
</tr>
<tr>
<td>Left Non-RLN</td>
<td>8</td>
<td>0.18 [95% CI = 0.00 - 0.35]</td>
<td>0.0%</td>
<td>0.114</td>
</tr>
<tr>
<td>RLN Injury</td>
<td>6</td>
<td>0.01 [95% CI = 0.00 - 0.02]</td>
<td>93.4%</td>
<td>0.006</td>
</tr>
<tr>
<td>Monolateral RLN Injury</td>
<td>6</td>
<td>0.02 [95% CI = 0.00 - 0.04]</td>
<td>93.9%</td>
<td>0.012</td>
</tr>
<tr>
<td>Bilateral RLN Injury</td>
<td>6</td>
<td>0.00 [95% CI = 0.00 - 0.00]</td>
<td>0.0%</td>
<td>0.084</td>
</tr>
<tr>
<td>Permanent RLN Injury</td>
<td>6</td>
<td>0.004 [95% CI = 0.00 - 0.01]</td>
<td>30.3%</td>
<td>0.658</td>
</tr>
</tbody>
</table>

Table 8: Summary of Evidence (RLN: Recurrent Laryngeal nerve, ITA: Inferior Thyroid Artery)

Eight out of ten studies that were included in the meta-analysis referred to the presence of extralaryngeal branching of the recurrent laryngeal nerve, but also to the presence or absence of non-recurrent laryngeal nerve. The possibility of extralaryngeal branching reaches 38% [95% CI = 16% - 60%, \( I^2=99.7\% \), \( p<0.001 \)], while the non-
The recurrent laryngeal nerve is present only in 0.2% [95% CI = 0.1% - 0.3%, $I^2=0.0\%$, $p=0.003$]. Moreover, according to data encountered in 6 out of 10 studies, recurrent laryngeal nerve injury during thyroidectomy is possible to emerge in 1% [95% CI = 0%-2%, $I^2=93.4\%$, $p=0.032$] and permanent recurrent laryngeal nerve paralysis is estimated in only 0.4% [95% CI = 0% - 1%, $I^2=30.3\%$, $p=0.026$] (Table 8).

Quality assessment of the studies showed a “low” risk of bias in total. However, in some studies “unclear” or “high” risk of bias was observed, regarding the recurrent laryngeal nerve identification method (since in most of the studies the utilization or not of intraoperative nerve monitoring was not mentioned), the patients’ thyroid disease and demographics, patients’ follow-up, as well as the statistical analysis (Table 7) (Chart 2).

![Table 7](image)

**Table 7:** Quality assessment of case series studies according to quality assessment tool of Joanna Briggs Institute. [84]
9. Discussion

As has been mentioned above, during the 6th week of gestation the recurrent laryngeal nerve follows the ascending course of the primitive larynx to its final position, from the thorax to the neck. As far as their anatomical location is concerned, the recurrent laryngeal nerves are not symmetrical, since the right nerve forms a hook under the right subclavian artery, while the left one follows a similar course under the aortic arch before it continues cephalad. Apart from this normally observed asymmetry between the two nerves, a wide variety of anatomical alterations has been elaborately described, regarding the recurrent laryngeal nerve, but also its relationship with other
anatomical landmarks, such as the Berry ligament, the Zuckerkancl tubercle and the inferior thyroid artery.\textsuperscript{[9]}

Historically, surgery of the thyroid gland was considered one of the most dangerous procedures, due to the high mortality rate. This theory was abandoned at the end of 19\textsuperscript{th} century, when Emil Theodor Kocher, known as the “Father of Thyroidectomy” contributed irreplaceably to this surgical field by executing more than 5000 thyroidectomies, with a total mortality rate of 0.5%. His recommendations about more cautious extracapsular dissection of the thyroid gland and more meticulous haemostasis, formed the basis of the fundamental principles of the modern thyroid surgery.\textsuperscript{[7,8]}

Undoubtedly, the thorough knowledge of the thyroid gland anatomy and its anatomical variations is essential for the identification and preservation of vital structures, like recurrent laryngeal nerve, in order to avoid ruinous complications, such as recurrent laryngeal nerve palsy. The presence of a recurrent laryngeal nerve alteration may be due for accidental recurrent laryngeal nerve injury (stretching, cauterization, cross-section), given that the nerve is not located in the ordinary position. Thus, even if the surgeon is aware of the recurrent laryngeal nerve variation possibility, its recognition usually demands a more laborious dissection, leading to damaging RLN and other noble structures, like trachea, oesophagus, vagus nerve or carotid artery and its branches.\textsuperscript{1} However, in this prospective study, the recurrent laryngeal nerve topographic variation was not associated to post-thyroidectomy complications.

Over the last two decades, a plethora of studies has been conducted, regarding the anatomical relations of the recurrent laryngeal nerve with substantial entities of the thyroid surgical field, like inferior thyroid artery.\textsuperscript{[20,55,89,90]} However, the majority of
them have been carried out in cadavers. Besides, pertinent studies have been conducted including Asian, African or European population, but to our knowledge, there is no relevant study in the local literature to underline this anatomical detail.

Even though multiple positions of the recurrent laryngeal nerve regarding to inferior thyroid artery have been reported, the ordinary position of the recurrent laryngeal nerve is considered to be posteriorly to the inferior thyroid artery. In the present prospective study, the nerve was identified to be running superiorly to the inferior thyroid artery in 27.3% of the cases. Additionally, this topographic alteration was shown to be more frequent in females. Furthermore, in the meta-analysis that was conducted, the nerve was observed anteriorly to the inferior thyroid artery in 28% of the recurrent laryngeal nerves that were identified. These results are similar to those of a recent relevant meta-analysis, which included 79 studies on both cadaveric and human patients and more than 14000 recurrent laryngeal nerve dissections in total, and reported a pooled prevalence of 50.7% for the recurrent laryngeal nerve position posteriorly to inferior thyroid artery. Henry, et al. observed that there was no significant difference between sexes, but, on the contrary, a statistically significant difference existed between the right [(37.1% (95% CI 30.7–41.5)) and left side [(17.2% (95% CI 13.3–20.6)]. (p<0.001). It is worth mentioning that in the current prospective study the pooled prevalence of the recurrent laryngeal nerve variation was observed bilaterally in the 79.7%’ the corresponding rate in Henry et al.’s study was only 36.6%. Additionally, the frequency of extra-laryngeal branching of the recurrent laryngeal nerve RLN was remarkably lower than that reported in the literature.[10,39,87]

While, nowadays, thyroidectomy is considered to be a non-hazardous operation, among its most frequent complications lie, both, palsy of the recurrent laryngeal nerve and hypocalcaemia.[6,78] Hoarseness may manifest postoperatively as the first symptom
of unilateral or bilateral recurrent laryngeal nerve damage, because of complete cross section, trauma, thermal injury or stretching. Specifically, bilateral vocal cord dysfunction, presented with more severe symptoms such as stridor and breathlessness, can be a life-threatening situation, leading to re-intubation or tracheotomy.\cite{6,92} In the present prospective study, only one patient, whose right recurrent laryngeal nerve crossed over the right inferior thyroid artery, developed hoarseness, that recovered spontaneously within 6 months. Moreover, in the current meta-analysis it is reported that the possibility of monolateral or bilateral intraoperative injury of the nerve reaches 1%. It needs to be highlighted that, provided that no improvement in the vocal cord function is noted in the first six months postoperatively, recurrent laryngeal nerve paralysis is assumed to be permanent.\cite{92}

Hypocalcaemia, is one of the most frequent complications of thyroid surgery, and especially total thyroidectomy, with an incidence ranging between 13 and 49\%.\cite{78} A serum calcium level reduction is usually recorded 24 to 48 hours postoperatively and is associated to symptoms like paresthesia, perioral or acral numbness, and tetany arise. Thus, hypocalcaemia can possibly turn into a hazardous condition, provoking laryngospasm, cardiac arrhythmias, coma or even death.\cite{78,93,94} In order to minimize this risk, routine oral calcium and vitamin D supplementation may be beneficial.\cite{78,95} According to this suggestion, in this study every patient participating was administered oral calcium and vitamin D supplements. Nonetheless, 21.9\% of the patients presented hypocalcaemia, while in 3 of them symptoms such as oral, perioral and acral numbness were observed. Overall, topographic alteration of the recurrent laryngeal nerve was noticed in 28.6\% of the patients with low serum calcium value.
10. Conclusion

Total thyroidectomy is numbered among the most frequently performed surgical procedures worldwide, that requires extensive and thorough knowledge of the anatomy of the neck, as well as of the anatomical variations that it may present, in order injury of the noble structures of this specific area to be avoided and, consequently, adverse complications, such as palsy of the recurrent laryngeal nerve and hypocalcaemia, to be prevented. In accordance with the data retrieved from the international literature, the present prospective study of the recurrent laryngeal nerve anatomical position indicated that in the majority of the cases the nerve is located posteriorly to the inferior thyroid artery, regardless of the sex and the side. Additionally, the meta-analysis that was conducted resulted in adequate outcomes, with the recurrent laryngeal nerve positioned more often posterior to the inferior thyroid artery and the possibility of intraoperative nerve injury rising to 1%.

In conclusion, the inferior thyroid artery constitutes a reliable anatomical entity of great importance, which can be used as a landmark for the identification of the recurrent laryngeal nerve during thyroidectomy. Nonetheless, it is crucial that more studies need to be conducted, in order a potential relation between the presence of recurrent laryngeal nerve variations and the emerging of postoperative complications of thyroidectomy to be clarified.
11. References


