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SURGERY OF INTRATHORACIC GOITER

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Contents

SURGERY OF INTRATHORACIC GOITER

1. Abstract

Aim: we describe intrathoracic goiter (IG) background, epidemiology, clinical features and surgery outcomes of a series of 50 patients intervened by the Endocrine Surgery Unit of Hospital Universitario Marqués de Valdecilla within a period of 4 years.

Methods: we present a surgical series of 50 primary IG, all of them amenable to total thyroidectomy through cervicotomy.

Results: in our series, surgical risk factors were involved in 80% of the patients; bulky cervical mass was present at diagnosis in 70%, and dyspnea, in 60%, being associated with dysphagia in 30% and dysphonia in 10% of the cases. Benign goiter was the main cause of IG (92%) and the main postoperative complication was short-term hoarseness (8%).

Conclusions: IG has a preference for mean aged women (84%). Surgery is a safe procedure for those patients with respiratory complaints, even in the presence of surgical risk factors. Permanent sequelae from the surgery, such as hypoparathyroidism and recurrent laryngeal nerve (RLN) palsy are rarely seen, with a rate, respectively, of 4% and 2%.

Resumen

Objetivos: describimos en este trabajo las generalidades, epidemiología, características clínicas y los resultados de una serie de 50 pacientes operados en el Servicio de Cirugía Endocrina del Hospital Universitario Marqués de Valdecilla en un periodo de 4 años.

Métodos: presentamos una serie quirúrgica de 50 pacientes aquejados de bocio intratorácico primario, operados en su totalidad a través de cervicotomía y en quienes se practicó tiroidectomía total.

Resultados: 80% de los pacientes presentaban factores de riesgo quirúrgicos. La principal manifestación al diagnóstico fue la masa cervical (70%), seguida de disnea (60%), que se asoció a disfagia en un 30% de los pacientes y a disfonía en un 10%. Un 92% de los bocios operados fueron benignos, y la principal complicación postoperatoria fue la ronquera transitoria (8%).

Conclusión: el bocio intratorácico aparece preferentemente en mujeres de mediana edad (84%). La cirugía es un procedimiento seguro, a realizar en aquellos pacientes con clínica de dificultad respiratoria, incluso en presencia de factores de riesgo quirúrgicos. Es infrecuente encontrar secuelas permanentes derivadas de la cirugía, tales como el hipoparatiroidismo (4%) y la parálisis recurrencial (2%).

Keywords: Intrathoracic goiter; Substernal goiter; Mediastinal mass; Thyroidectomy; Cervicotomy.

2. Aim of the study

IG entails additional complexity when compared with simple, cervical goiter. Its clinical manifestations can be similar, but greater severity of the symptoms concurs in IG; therefore, surgical treatment is of choice in the vast majority of the patients. The complications secondary to this surgery are usually more frequent and severe, primarily due to a greater distortion of the normal anatomy, by the goiter itself and by the surgical approach as well.

The scarcity of literature focusing on this particular subject is remarkable. Hence, a review of the textbooks, articles and surgical series is presented in this paper to achieve a better understanding of this entity, along with the presentation of our own surgical series.

3. Introduction

3.1. Prevalence

Intrathoracic goiter is estimated to account for 5.8% of all mediastinal masses. Up to 40% are incidentally diagnosed in asymptomatic patients, while the remaining 60% will most likely present obstructive respiratory symptomatology. Primary IG is rather a rare entity, accounting for only 0.2-1% of all the intrathoracic goiters, which is more prevalent in females, with a male-female ratio of 1:3 to 1:4.[1]

3.2. Embryology and anatomy

The thyroid gland is the result of the adaptation to an iodine-deficient land environment of organisms from an iodine-rich sea environment. It emerges, in mammals, from a diverticulum of the primitive pharynx. Two distinct cell types of different embryological origins compose the gland: the epithelial or follicular cells, derived from the endoderm, and the parafollicular or C cells, scattered within the interfollicular space, derived from the neural crest, bilaterally to the fourth pharyngeal pouches, to become located in the ultimobranchial bodies.

Follicular cells, which are the most abundant cells in the thyroid, phylogenetically derive from the primitive iodide-concentrating gastroenteric cells of the endostyle, which migrated and evolved to specialize in iodine uptake and storage.

The thyroid is the first endocrine structure that becomes recognizable in humans, as a thickening in the ventral wall of the primitive pharynx floor, from which follicular cells develop. This anlage or primordium is located in the midline of the embryonic mouth cavity, in its posterior part, between the first and second branchial arches, and can be seen on days 20-22 of human embryogenesis. This

specification process continues with the expansion of the thickening and the outpouching of the thyroid bud from the endoderm adjacent to the heart primordium. It has been proposed that the signals required for the specification of thyroid cells, as well as liver, pancreas and other endoderm-derived estructures, are released by the differentiating myocardium; nonetheless, the mechanism is still unknown and further research is needed to elucidate the physiology of the thyroid differentiation.

The thyroid bud continues growing while remaining attached to the pharyngeal floor by the thyroglossal duct, a tubular structure that degenerates in days 30-40 of embryogenesis. The foramen cecum at the base of the tongue constitutes the remnant of the anlage.

The thyroid anlage migrates caudally, to reach the anterior aspect of the tracheae while growing laterally from the isthmus, the thyroglossal duct disappears, and the migration is completed at days 45-50. The migration mechanism remains unknown, but it has been proposed that is due to both an active process of the thyroid precursor itself and to a mechanical traction exerted by the heart during its descent. The ultimobranchial bodies migrate and merge with the thyroid anlage by day 60 of human embryogenesis, completing the formation of the primitive thyroid gland.

Thyroid cell proliferation and gland expansion takes place when the gland reaches its definitive position, and is not dependent on TSH signalling, since the receptor is not expressed at this point of thyroid's development. Its mechanism is still to be fully understood.

Folliculogenesis starts on day 70, under circumstances not well known and may be related to signalling from neighboring tissues. Full differentiation of the gland takes place when follicles are formed, with the expression of a series of proteins essential for thyroid hormone production. It has been suggested that complete migration needs to be achieved within the correct timing for the onset of the thyroid function. However, ectopic thyroid tissue can be functional as well, and thyroglobulin has been detected in humans at fifth gestational week, when thyroid morphogenesis is still taking place. Moreover, iodine uptake and T4 synthesis occur by the tenth to the fourteenth week, corresponding to the final stages of the folliculogenesis[2].

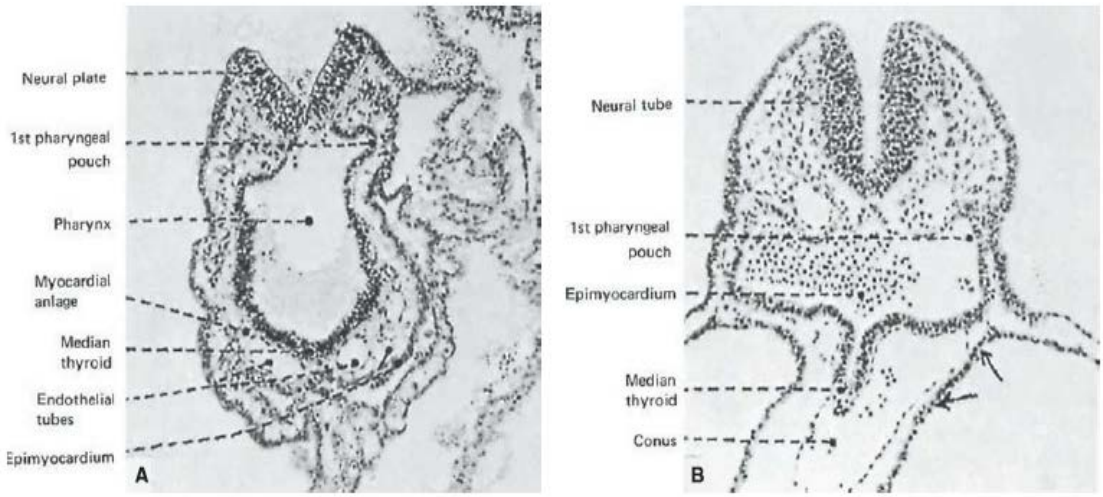
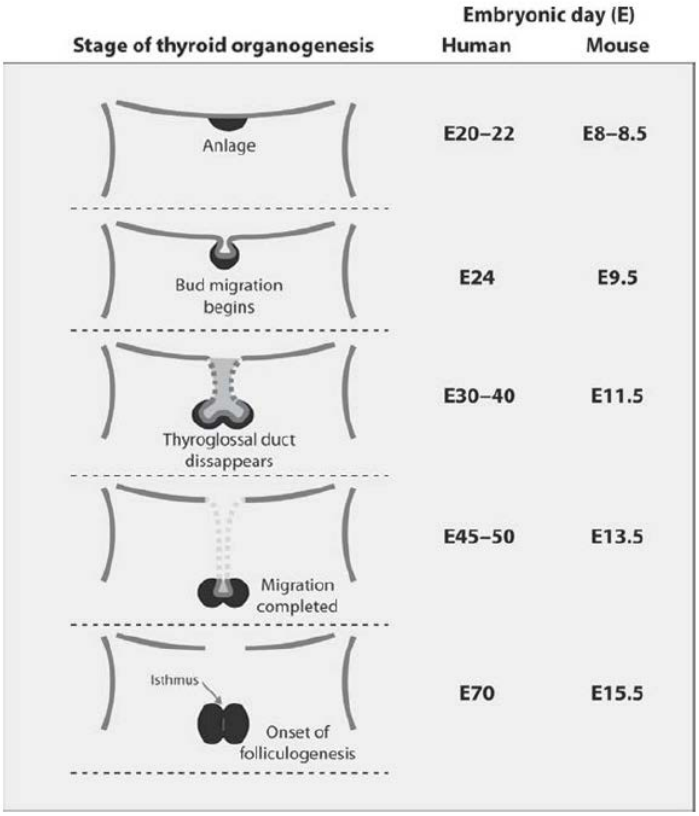


FIGURE 2.4 Sections of human embryos showing thyroid development. A: Section through a 2-somite embryo (x150). B: Section through the thyroid anlage of a 10-somite embryo (x150).

Taken, with permission, from Werner & Ingbar's The thyroid: A fundamental and clinical text. 10th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins Health; 2012.



Taken, with permission, from Werner & Ingbar's The thyroid: A fundamental and clinical text. 10th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins Health; 2012.

3.3. Physiology

Thyrotropin (TSH, thyroid stimulating hormone) binds to its receptor, TSHR, a seven-transmembrane receptor that couples to G proteins, to trigger the process of thyroid hormone synthesis at the follicles.

Iodide is uptaken into follicular cells through the basolateral membrane by the sodium iodide symporter, and then transported into the lumen by pendrins. Thyroperoxidase, located in the apical membrane, oxidizes iodide using H_2O_2 generated by the dual oxidase. Then, thyroglobulin is iodinated and stored as colloid until requirement. For triiodothyronine (T_3) and thyroxine (T_4) synthesis, thyroglobulin is endocytosed and digested by lysosomes. The results of the proteolysis are mono- and diiodotyrosine (MIT and DIT), which are deiodinated by a dehalogenase to reuse its iodide for hormone synthesis, and T_3 and T_4, which are secreted into the blood stream by monocarboxilate 8, a specific transporter recently identified.

The main carriers for thyroid hormones are thyroxine-binding globulin, transthyretin and albumin, but a number of minor carriers, such as lipoproteins (VLDL, LDL and HDL), α1-acid glycoprotein, immunoglobulins and sterol hormone-binding proteins exists. Membrane transporters are necessary for the thyroid hormones to enter the intracellular environment.

Thyroxine (T_4), the main product of the gland, is a prohormone that requires to be locally deiodinated, thus converted to triiodothyronine (T_3), the active hormone, which can be bound by the thyroid hormone nuclear receptors with high affinity. This process is catalyzed by deiodinases type 1 and 2, generating approximately 80% of the T_3 daily produced each day and becoming a tissue-specific regulator of both intracellular and serum T_3 homeostasis. This is likely due to evolutionary pressure, since triiodothyronine half-life is 1 day and great requirements of iodine would be needed to maintain T_3 serum concentrations. Thyroxine half-life is 7 days, so, instead, a T_4 pool is available to quickly regulate T_3 blood levels. Deiodinase type 3 inactivates T_4 to form reverse T_3[2].

3.4. Pathogenesis

In primary IG formation, defective ontogenesis of the thyroid takes place when part or all of the thyroid blastoma leaves primordial pharinx through the thyroglossal duct and is pulled by the descending heart and great vessels into the thorax, with the possibility of separated ectopic thyroid fragments residing anywhere along this embryologic pathway, in the midline, from the root of the tongue to the diaphragm. This thyroid tissue is, in most cases, independent from the cervical thyroid gland. Hence, its vascularization depends on intrathoracic arteries.

Secondary IG arises from the lower pole of one or both lobes, or from the isthmus, preserving its inferior thyroid artery blood supply, and growing through the

thoracic inlet aided by mechanical forces, such as swallowing, gravity and thoracic negative pressure, to the lowest resistance position inside the chest cavity. First, the anterior superior mediastinal (restrosternal) space is occupied by the mass. At this point several structures restrain the goiter and redirect its growth: thymus (or remnants), brachiocephalic veins, superior vena cava, and the aortic arch and its branches. The goiter will most likely deflect to the right posterior mediastinum, rather than the left, due to its lower resistance.

Up to 20% of IG grow from recurrent goiters after partial thyroidectomy, lead by the remnant scar tissue developed after the surgery, which prevents lateral and medial extension and prompts intrathoracic growth at the expense of the inferior aspect of the gland[3].

Most of the IG are prevascular, located in the anterior compartment of the mediastinum; only few of them are retrovascular, growing behind the great mediastinal vessels, retrotracheally or in the posterior mediastinum, behind the esophagus[1].

The characteristics described above, along with the clinical and complementary examination of the patient is relevant to decide the therapeutic approach and to perform the preoperative assessment in case surgery is required.

3.5. Definition of intrathoracic goiter

Intrathoracic goiter is a term submitted to continuous discussion. Multiple definitions of IG have been introduced since Haller's first anatomical description of this entity in 1749. Their overlap, the lack of consensus and the criteria variability difficults the estimation of its real prevalence and the comparison of surgical series[4].

While Huins, et al., over the necessity of a standard definition of IG, propound a 3-grade classification system based on goiter's relation to the aortic arch and right atrium[5], Rios, et al. consider the use of 2 currently existing definitions to properly assess IG: the clinical definition, and Katlic's definition[4].

The clinical definition of IG comprises a thyroid gland that has a portion that remains permanently retroesternal on neck examination without hyperextension. The advantages of the use of this definition are that complementary examinations are not required and the sensitivity is the same as other definitions' in assessing airway compromise, since the degree of extent of the goiter beyond the manubrium does not change the potential risk of complication inherent to any substernal goiter[4].

Katlic's definition consists on a retroesternal component of at least 50%. This definition can predict the need for sternotomy[4], especially in case of thyroid carcinomas, large or recurrent goiter, previous cardiac surgery, subcarinal or retroesophageal extension, left posterior goiters that extend to right pleural cavity, and acute respiratory distress[3].

Clinical definition	A portion of the goiter that remains permanently retroesternal on neck examination without hyperextension.
Katlic	Retroesternal component of at least 50%.
Hsu	A thyroid gland (clinically or radiologically) below the sternal manubrium.
Kocher	A thyroid gland in which some portion remains permanently retro-sternal.
Torre	Goiter with its lower position permanently remaining below the sternal notch with the neck in hyperextension.
Lahey	Goiter which needs exeresis to be performed in the upper mediastinum.
Eschapase	Goiter totally or partially located in the mediastinum that, in operating position, has its edge at least 3 cm below the sternal manubrium.
Lindskog	Thyroid growth up to the level of the fourth thoracic vertebra on x-ray examination.
Crile	Thyroid growth up to the aortic arch.
Subcarinal goiter	Goiter with thyroid growth that reaches the carina tracheae[3].

Huins classification sorts patients according to the extent of their goiters in 3 grades, each of them with different degree of particular complications and therefore, different approach. Thereby, in grade 1 IG, those retroesternal goiters above T4 (and above the aortic arch), a cervical approach should be sufficient; grade 2 IG, those extending from the aortic arch to the pericardium, should undergo manubriotomy; and in grade 3, those expanding beyond the right atrium, full sternotomy, rather than lateral thoracotomy[5].

3.6. Clinical presentation

The most common manifestations of intrathoracic goiters are due to compression or displacement of adjacent viscerae or neurovascular estructures, hyperfuctioning autonomous nodules, or seldom malignant infiltration. However, the perception of a bulk or mass usually leads the patient to seeking medical attention[6].

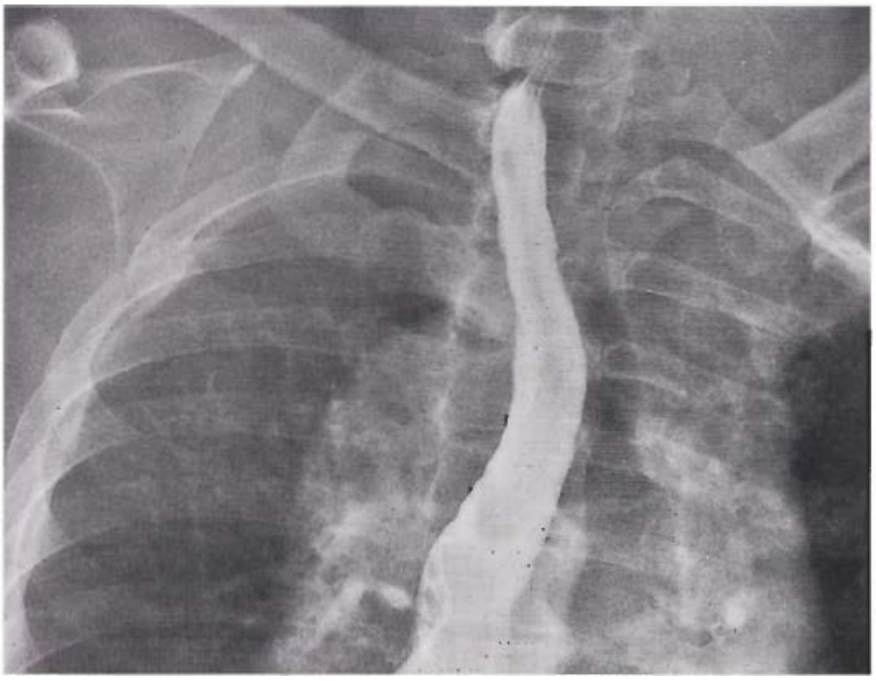
Cervical mass in one of our patients. Note the distended neck veins and telangiectasias. Courtesy of Dr. Dieter Morales, Professor and Endocrine Surgeon at Hospital Universitario Marqués de Valdecilla.

3.6.1. Compressive symptoms

Upper airway compression symptoms, related to tracheal obstruction caused by entrapment of an expanding goiter between bony structures, comprise isolated dyspnea, or dyspnea associated with cyanosis, suffocation, and ultimately, choking that requires immediate resuscitation. Dyspnea and cough can be worsened by lying flat or on one side. The approach must always be surgical when emergency care is needed. It is important to differentiate upper airway symptomatology from dyspnea due to lung disease, by performing lung function tests. Radioactive iodine, which has proven to be an ineffective means of hyperthyroidism control in MNG, can cause radiation thyroiditis and trigger an emergency situation in patients with airway obstruction[7].

Hoarseness can be caused by laryngeal anatomy distortion or by entrapment, ischemia, compression, stretching, surgical trauma or malignant infiltration of the RLN.

Lateral and posterior displacement of the esophagus can induce mild dysphagia.



Barium swallow, showing displacement of the esophagus. Taken with permission from Shah JP, Patel SG, Morel AA. Head and neck surgery and oncology. 3rd ed. United Kingdom: Mosby; 2003

An overt superior vena cava syndrome can be present, or it can take place subclinically. In this case, it becomes manifest by performing Marañón's maneuver, which consists on asking the patient to raise the chin, or Pemberton's maneuver, in which the patient must rise the arms instead. Facial pletora and cyanosis, and dilation of superficial facial and neck veins and collateral venous circulation would appear when executing this maneuvers. Upper esophagus collateraral circulation is rarely developed, but can lead to upper gastrointestinal haemorrhage.

Abscesses, Horner's syndrome, chylothorax after thoracic duct occlusion, transient ischemic attacks caused by a thyroid steal syndrome and axillosubclavian vein thrombosis after compression of the innominate vein are unusual but severe clinical presentations. In addition, anterior angulation of the trachea by a posterior intrathoracic goiter can lead to the damage of the membranous portion of the trachea while attempting intubation for general anesthesia[6], [7].

COMPRESSED ESTRUCTURE	ASSOCIATED SYMPTOM
UPPER AIRWAY	Dyspnea
	Cyanosis
	Cough
	Suffocation
	Asphyxiation
LARYNX/RLN	Hoarseness
ESOPHAGUS	Dysphagia
SUPERIOR VENA CAVA	Superior vena cava syndrome
	Gastrointestinal Bleeding
THORACIC DUCT	Chylothorax
INNOMINATE VEIN	Axillosubclavian vein thrombosis
SUPERIOR CERVICAL GANGLION	Horner's Syndrome[7]

3.6.2. Thyrotoxicosis

Thyrotoxicosis syndrome comprises hypermetabolism and hyperactivity that results from high free serum concentrations of T_3, T_4 or both, due to hyperthyroidism or other causes of excess hormone release such as thyroiditis.

The symptoms characteristically include fatigue, weakness, tremor, palpitations, nervousness and hyperactivity, heat intolerance, increased perspiration and appetite, menstrual disturbances and weight loss[7].

Systolic hypertension and tachycardia are common findings in patients with thyrotoxicosis, as well as warm, moist skin, stare and eyelid retraction and hyperreflexia associated to muscle weakness[2].

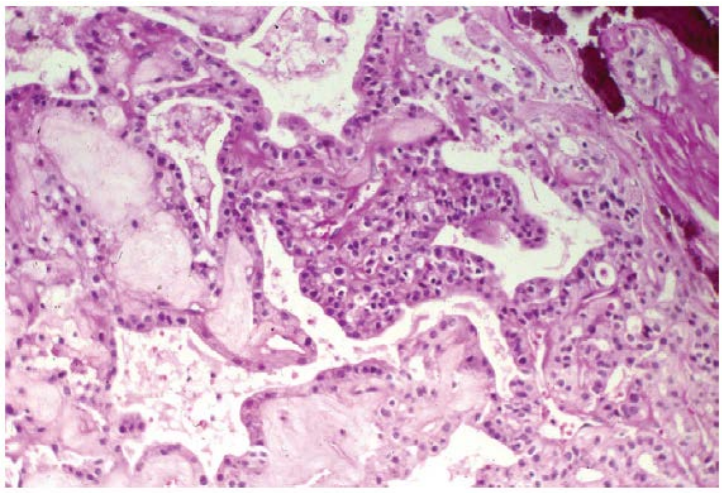
Long-standing multinodular goiters tend to develop autonomous nodules that can cause hyperthyroidism, particularly in elder patients in which the complications, such as congestive heart failure, arrhythmias and aggravation of ischemic heart disease, can be lethal. Therefore, definitive treatment should be administered.

Thyrotoxicosis can be also triggered by the administration of iodinated contrast media, or adjuvant T_4[7].

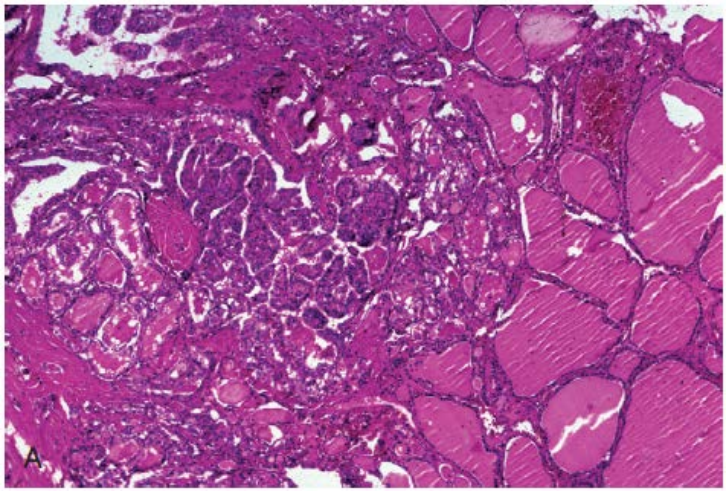
3.6.3. Malignancy

Infiltrative and compressive symptoms aside, the patient can present constitutional syndrome at the moment of the diagnosis, even as the first clinical

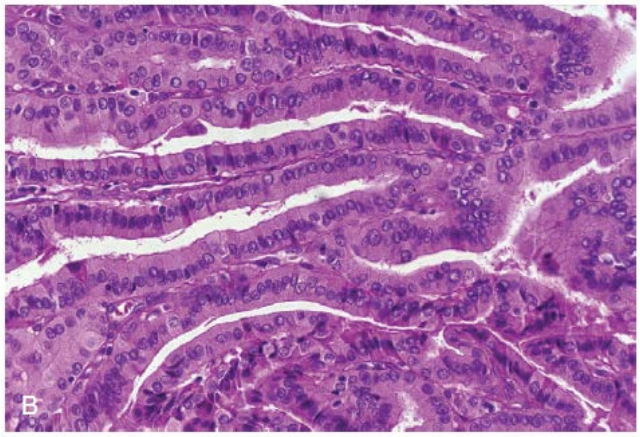
manifestation. Malignancy is usually derived from thyroid tissue, but is not infrequent to find a lymphoma settled in the thyroid gland[7, 10]. Some studies have shown dysphonia to be strongly suggestive of malignancy[8].



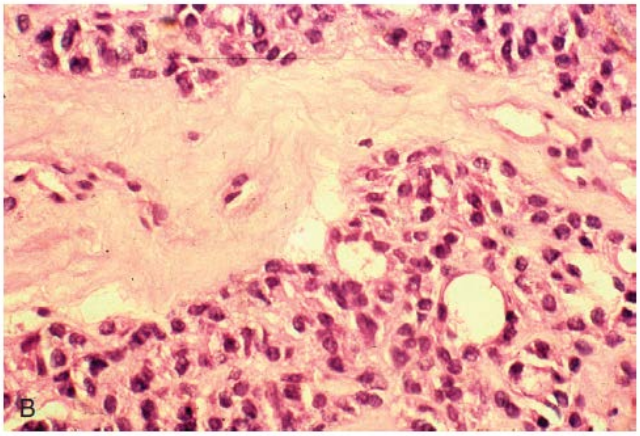
Anaplastic carcinoma of the thyroid in a thyroid mass (H&E Stain, x200). Taken with permission from Townsend CM. Sabiston textbook of surgery international edition. 19th ed. United States: Elsevier; 2012



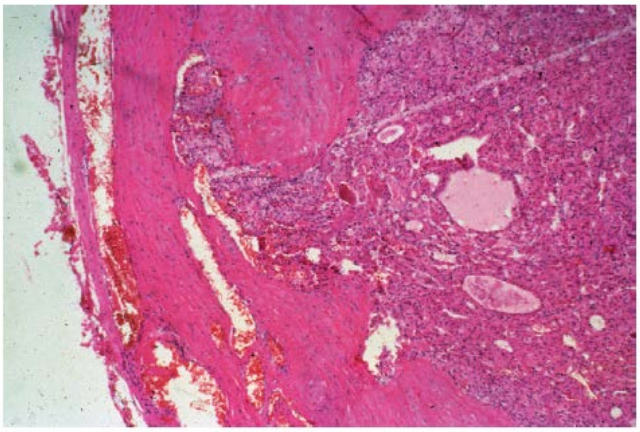
Papillary projections consistent with papillary carcinoma in a thyroid mass (H&E Stain, x100). Taken with permission from Townsend CM. Sabiston textbook of surgery international edition. 19th ed. United States: Elsevier; 2012



Tall cell variant of papillary carcinoma, associated with poorer prognosis than well-differentiated papillary cancer (H&E Stain, x400). Taken with permission from Townsend CM. Sabiston textbook of surgery international edition. 19th ed. United States: Elsevier; 2012



Medullary carcinoma with amyloid infiltrate. (H&E Stain, x400). Taken with permission from Townsend CM. Sabiston textbook of surgery international edition. 19th ed. United States: Elsevier; 2012



Follicular lesion with capsular invasion (H&E Stain, x100). Taken with permission from Townsend CM. Sabiston textbook of surgery international edition. 19th ed. United States: Elsevier; 2012

3.7. Preoperative assessment

3.7.1. Laboratory tests

Thyroid function tests must be run in order to detect associated hypo- or hyperthyroidism that could cause intraoperative metabolic complications. Hyperthyroid patients should receive antithyroid drugs before surgery, and, according to some authors, associate steroids to prevent worsening of an existing compartmental syndrome of the neck secondary to thyroid inflammation[7]. TSH should be measured to evaluate dysfunction, and T_4 and T_3, in patients with suppressed TSH. In the event of suspected autoimmune disease, antibodies to the TSH receptor, thyroid peroxidase and thyroglobulin can be measured. Chronic thyroiditis, which can present as an hyperthyroidism, can complicate the delivery of a substernal goiter, in particular, and its surgery in general[9].

3.7.2. Imaging methods

Imaging techniques are mandatory to classify the goiter and evaluate its anatomy. While some asymptomatic IG are incidentally detected in chest x-ray, CT scans or MRI, radiographic assessment is usually performed in symptomatic patients to confirm the clinician's suspicion, and a thorough physical examination should always precede the complementary tests [3], [7].

Chest x-ray detects mediastinal enlargement as well as tracheal lateral and anterior deviation and compression, in both posteroanterior and lateral films respectively. Occasionally, lung metastasis from a thyroid carcinoma can be found[1].

Ultrasonography is limited to the differentiation between solid and cystic masses only in the cervical portion of the goiter, to detect the presence of cervical lymphadenopathy, and to guide fine needle aspiration biopsies, which entail greater difficulty in IG, thus lesser usefulness to rule out malignancy[10].

CT scan must be performed to evaluate the volume, compression, extension and limits of the IG, the continuity between cervical and intrathoracic components, its anatomical relations and its characteristics, such as areas of calcification and the degree of heterogeneity/cystification, as well as tracheal involvement[7].

MRI can be useful for those cases entailing greater anatomical complexity, since it provides sharper images of the tissue limits, specially regarding the involvement of the great mediastinal vessels, and adds the possibility of coronal and sagital tomographic cuts, as well as demonstrating associated parathyroid abnormalities[11].

Sagital-oblique CT scan of a 95 year old woman, showing a prevascular IG exerting severe compression of the supraaortic trunks and aorta itself. Courtesy of the Radiology Service of Hospital Universitario Marqués de Valdecilla.

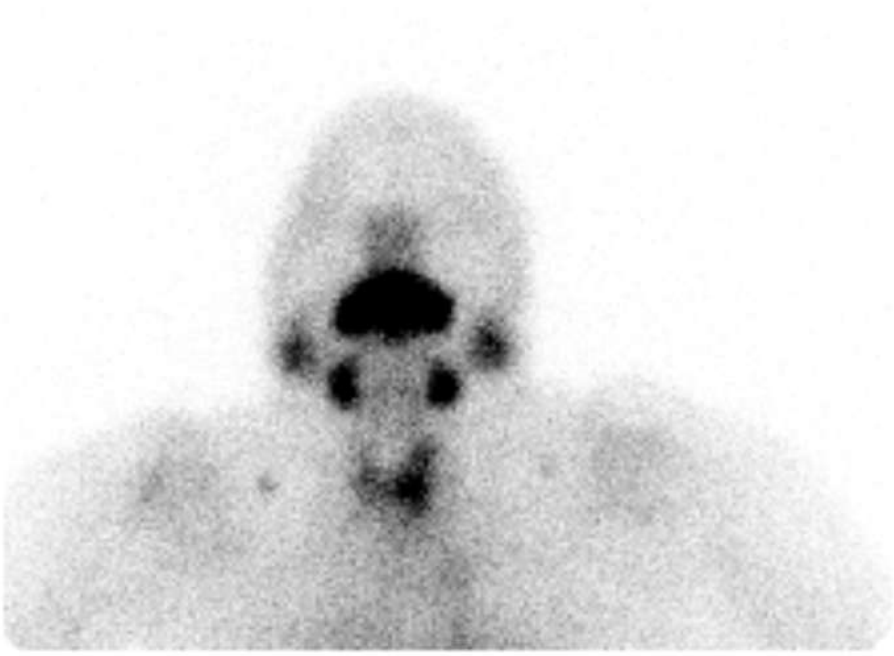
Thyroid scintigraphy is indicated in patients whose CT scan show isolated mediastinal masses, discontinuity of both cervical and mediastinal masses, and in the presence of subclinical or overt hyperthyroidism and nodularity[7, 10]. Iodine-131 scintigraphy should precede CT scan, since iodine uptake may be blocked by the intravenous contrast administered for the CT scan vascular enhancement. Technetium-99m is not dependent on the iodine uptake but being less thyroid-specific and having a poor sensitivity for IG, its results might be complex to evaluate[7].

Radioiodinated compounds, such as ^{123}I, ^{124}I and ^{131}I show both uptake and organification of iodine, while technetium-99m pertechnectate is not organified. For this and the higher thyroid accumulation and gamma emission, radioiodine is preferred over pertechnectate for confirmation of ectopic thyroid tissue, except in those cases in which the intrathoracic component might not uptake iodine. ^{131}I, which is cheaper and has a better availability than ^{123}I, has a longer half-life and too high gamma emission, resulting in higher radiation to the patient and poorer image quality. Therefore, ^{123}I scintigraphy is recommended by some authors for the initial nuclear medicine imaging[12].

Thyroid scintigraphy might be used to measure the probability of response to radioiodine therapy. Lower and heterogeneous iodine uptake is related to less responsive goiters and might require higher activities of the radiotracer[10].

^{18}F-FDG PET/CT is used to detect malignant nature of many mediastinal masses, but benign lesions such as benign IG, non-invasive thymoma and teratoma can show increased FDG uptake as well[12].

Nuclear Image of an IG enhanced with Tc-99m. Courtesy of Dr. Ignacio Banzo, head of Nuclear Medicine and Molecular Imaging Service of Hospital Universitario Marqués de Valdecilla.



Nuclear Image of an IG enhanced with I-131. Courtesy of Dr. Ignacio Banzo, head of Nuclear Medicine and Molecular Imaging Service of Hospital Universitario Marqués de Valdecilla.

3.7.3. Lung function tests

Lung function tests, including a flow volume-loop spirogram and measurement of the response to bronchodilators in peak airflow and forced expiratory volume, will differentiate dyspnea secondary to lung disease from an obstruction caused by a bulky goiter, and determine the degree and location of the airway obstruction. Measurement of peak expiratory flow can be useful to determine the functional impact of the IG and its improvement after surgery[7].

3.7.4. Laryngoscopy

In those patients who present with hoarseness or dysphonia, or have undergone prior neck surgery, laringoscopy must be performed in order to detect compression induced palsy of the vocal cord[7].

3.7.5. Preanesthetic assessment

Foremost, a pre-anesthetic and cardiac function evaluation must be carried out. General and specific clinical examination along with electrocardiography and echography are mandatory[7].

3.8. Surgical Treatment

While expectant management with periodic follow up by TSH measurement and US assessment can be reasonable in nontoxic, asymptomatic benign goiters, the anatomical difficulty of the IG to rule out thyroid malignancy makes this approach less frequently indicated[7].

3.8.1. Surgical approach

Surgery is often preferred, since it is the only definitive treatment, alternative radioactive iodine based treatment can precipitate a respiratory emergency in the elderly, malfunction and local complications are most likely to occur within time if left untreated, undetected malignancies are not exceptional and most IG can be resected by cervical approach[7], [13].

IG surgery involves a higher risk for complications than cervical goiter. There is a lack of consensus whether asymptomatic patients must undergo surgery or not, therefore thorough assessment of individual benefits and risks must be accomplished[3]. Some authors consider absence of symptoms does not seem to influence the outcome of the surgery, and since the natural history of

asymptomatic retrosternal goiter is unknown, surgery in these patients, in the absence of suspected cancer, seems not to be mandatory[14].

Total thyroidectomy is the technique of choice, except from benign unilateral goiters which can be amenable to partial resection to avoid further parathyroid glands or nerve injury[3].

En bloc thyroidectomy is the gold standard technique, since it prevents an incomplete removal in case of independent IG, an event known as “forgotten goiter” [1].

3.8.1.1. Cervical approach

With the patient in a semisitting Kocher position with hyperextension of the neck, venous pressure in the upper trunk is reduced, allowing to prevent haemorrhage.

Standard collar incision is usually sufficient for the complete resection of an IG; up to 10 % require additional mediastinal access. Division of the sternal head of the sternomastoid and the strap muscles helps relieve pressure on the neck and allows for a wider exposure, to achieve better vein management, better access to the upper pedicles, more space to handle the thyroid and therefore identify structures to be preserved, such as RLN[7],[15].

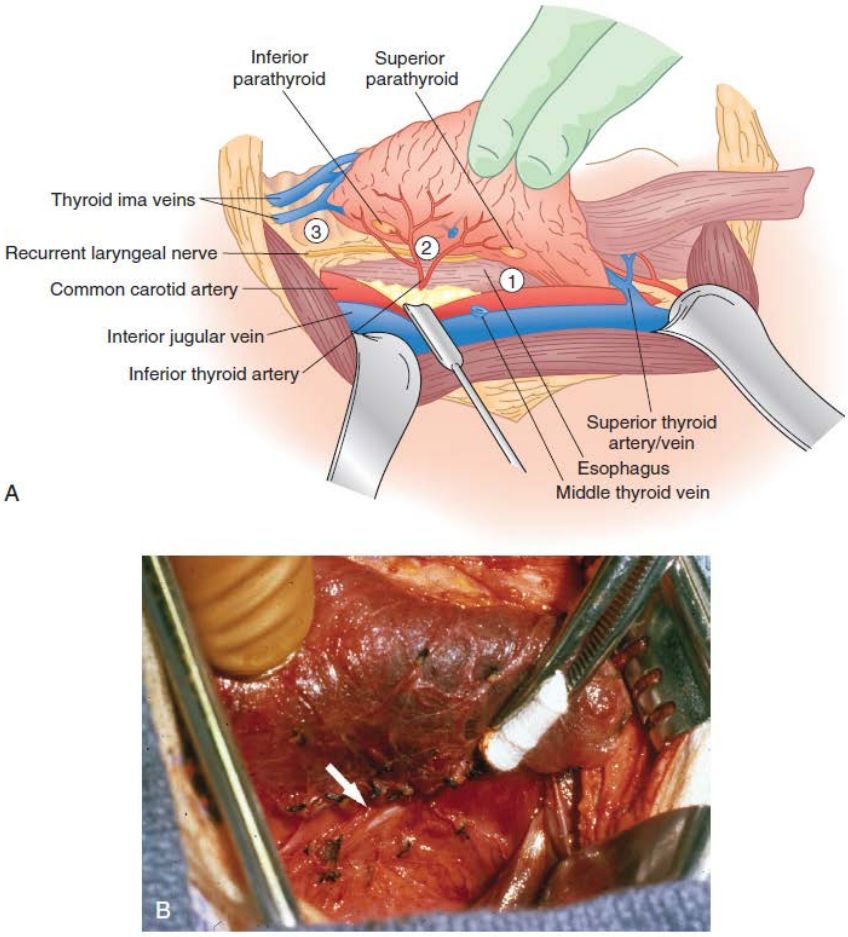
After the cricothyroid space is exposed, upper thyroid vessels of both sides and then lateral middle veins are ligated, reducing blood flow to the thyroid and relieving neck pressure[7].

The smaller lobe is shifted medially in order to identify the inferior thyroid artery and any subcapsular parathyroid glands, located at the posterolateral surface of the lower pole, that may need autotransplantation[7]. Searching for the RLN in this area is aided by the use of an electrode that stimulates the nerve, and a motor response detection device built within the endotracheal tube at the level of the vocal cords, intraoperative *NIM* nerve monitoring system (NIM). This information is then displayed on a screen and along with the emission of specific sounds, allows the surgeon to confirm the presence and integrity of the RLN.

The lobe is detached from the trachea to the greatest extent allowed. The inferior hilum is identified and dissected, and the lobe excised. In order to access the inferior hilum it might be necessary to deliver the intrathoracic portion to the neck first, by gently pulling it up while performing digital dissection of the adhesions of the mediastinal process [15].

Digital dissection can be replaced by the use of a spoon, which reaches further and is thinner than the surgeon’s finger, by performing “morcellation”, or intracapsular fragmentation of the thyroid, as suggested by Lahey, or by the use of a metal suction device through small capsular incisions, as Allo and Thompson described. After this maneuvers, identification and dissection of RLN and parathyroid glands can be carried out in the standard manner described before[7].

After the small lobe is completely separated from the trachea, and its neurovascular structures and parathyroid glands detached, the same procedure is performed on the other lobe[15].



Intraoperative identification of RLN. The main spots where RLN can result damaged are, as follows: 1. Ligament of Berry; 2. Inferior thyroid artery; 3. Thoracic inlet. Taken with permission from Townsend CM. Sabiston textbook of surgery international edition. 19th ed. United States: Elsevier; 2012, adapted from Kahky MP, Weber RS. Complications of surgery of the thyroid and parathyroid glands. Surgical Clinics of North America. 1993;73(2):307-321.

IG delivered through cervical incision. Courtesy of Dr. Dieter Morales, Professor and Endocrine Surgeon at Hospital Universitario Marqués de Valdecilla

3.8.1.2. Combined cervicomediastinal approach

Recurrent goiters have an added difficulty in identifying RLN due to the scar tissue developed from anterior interventions. Setting aside recurrent goiters and superior vena cava syndrome, which are both indication for performing early sternotomy along with the collar incision, the preferred approach consists on an initial cervical management and a posteriorly, sternotomy as a last resort. The sternotomy, either way, must be considered and scheduled after the demonstration by imaging techniques of bulky, low-lying solid goiters with complex anatomical relations[15], [17].

Retroesophageal or carinal extension, demonstrated invasive carcinoma, acute respiratory distress as well as goiters of large discrepancy of size with regard to the thoracic inlet and superior vena cava syndrome as mentioned before, should electively undergo the combined approach, rather than cervical approach at the expense of thyroid mass fragmentation (and, according to some authors, of higher risk of RLN injury). These indications will require sternotomy in 30-40% of cases[3], [16]. Sternotomy is more frequently necessary when managing retrovascular, rather than prevascular IG[1].

Sternotomy can be complete or partial (manubrium). The latter can be performed under the same collar incision made for a cervical approach, sparing an additional vertical presternal wound, but the complete sternotomy is usually preferred. Sternal suture dehiscence must be prevented, particularly in elder women with osteoporotic frail bones. [3]

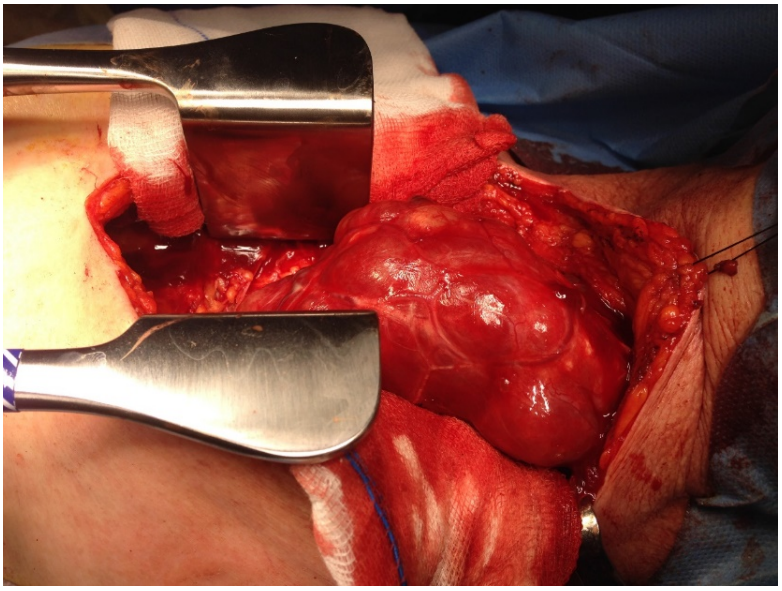
The sternal split may be necessary if the patient has a recurrent substernal goiter or a previous thoracic surgery (mainly cardiac surgery) since scarring or adherence to adjacent structures is more likely to occur; suspicion of malignancy

might as well be an indicator for this approach[16], [17]. However, even the largest goiters can be easily retrieved via cervicotomy alone[18].

3.8.1.3. Thoracotomy

Although posterior IG are safely removed by the methods described above, and there is no current indication for this approach, posterolateral thoracotomy might be executed in the event of primary, independent ectopic thyroid tissue, misdiagnosed of posterior mediastinal tumour, to achieve vascular control of the mass[1] and invasive IG. In this context, it is important to keep in mind that the risk for RLN injury is higher[16].

In some situations, retroesophageal goiters can reach the right pleural cavity, and an added left anterolateral thoracotomy can be required to free the goiter and deliver it to the sternotomy. This technique should be exerted with care to not damage the phrenic nerve and the superior vena cava[3].



Sternotomy performed for a massive IG not amenable to resection through cervicotomy. Courtesy of Dr. Daniel Casanova, section chief of the Endocrine Surgery Unit of Hospital Universitario Marqués de Valdecilla.

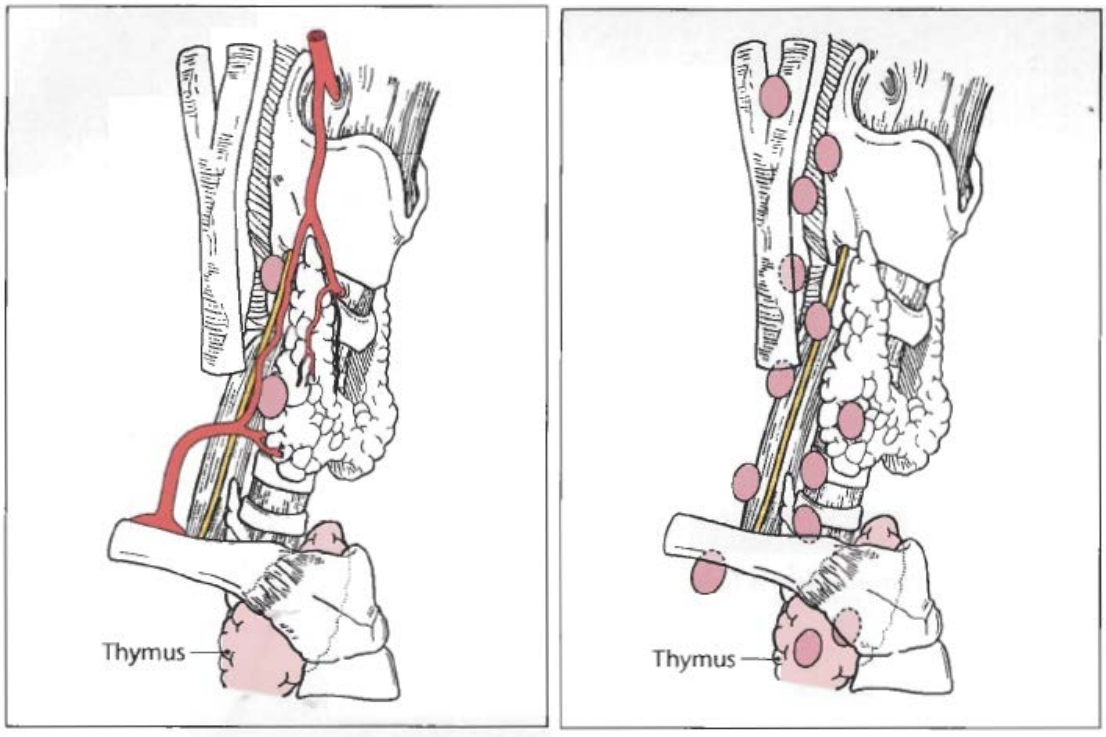
3.8.2. Complications

Highest morbidity rates occur in patients with thyroid malignancies and in which a combined cervicomediastinal approach is carried out[7]. Also, bulkier goiters entail greater difficulty at identifying estructures, therefore higher risk of complications, such as haemorrhage[3].

RISK FACTORS ASSOCIATED WITH GREATER MORBIDITY
Female sex: some studies pointed out higher risk for hypoparathyroidism
Hyperthyroidism: tendency to richer vascularization and parathyroid adherence
Evolution: long history correlates with gland malignization and thyrotoxicosis
Recurrent IG: scarring causes tissue retraction and distortion of the anatomy
Surgical approach: greater resections entail greater morbidity
Intraoperatory identification of structures: prevents hypoparathyroidism and RLN damage
Surgeon's experience: individual over health centre experience
Volume of interventions performed by the Endocrine Surgery Unit

3.8.2.1. Hypoparathyroidism

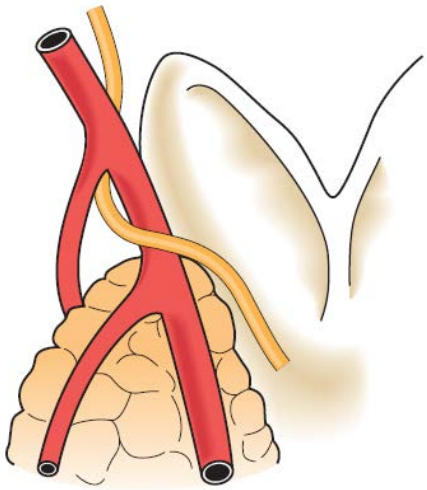
Permanent hypoparathyroidism is unusual when surgery is performed by experienced surgeons[7]. With an overall incidence of 5%, 80% resolves within a year. Prevention is made by thoroughly assessing the parathyroid vascularization intraoperatively, and in case of devascularization, by performing immediate autotransplantation of 1 mm fragments of saline-chilled tissue into sternocleidomastoid or brachioradialis muscle[10].



Depiction of blood supply and usual (left) and ectopic (right) locations of the parathyroid glands. Taken with permission from Shah JP, Patel SG, Morel AA. Head and neck surgery and oncology. 3rd ed. United Kingdom: Mosby; 2003

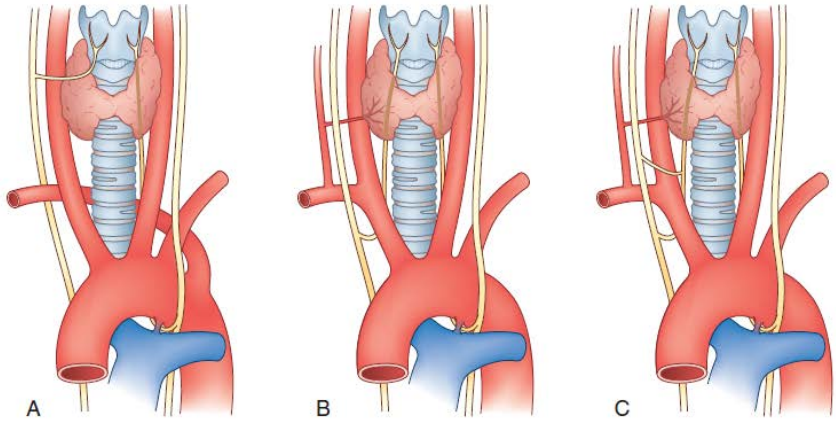
3.8.2.2. Nerve injury

Superior laryngeal nerve (SLN): its internal branch carries sensory fibers to the supraglotic mucosae and upper aspect of the vocal cord, while the external branch carries motor fibers to cricothyroid muscle and vocal cords. Dissection of the superior thyroid artery, which runs closely along the nerve, must be performed carefully to avoid nerve damage, which would lead to failure to tense the vocal cord, and cause voice changes, fatigue, huskiness, and reduction of voice range[3].



Relationship between the external branch of the SLN, depicted in yellow, and the superior thyroid artery. Adaptation of Clark OH, Sipperstein A, Duh QY, editors. Textbook of Endocrine Surgery. 1st ed. Philadelphia: W.B Saunders Company; 1997, taken with permission from Townsend CM. Sabiston textbook of surgery international edition. 19th ed. United States: Elsevier; 2012

Recurrent laryngeal nerve: a mixed motor, sensory and autonomous nerve arising from the vagus, which inervates every laryngeal muscle except cricothyroids, and carries the sensitive fibers to the infraglotic mucosae and inferior aspect of the vocal cord. Unilateral injury is characterized by a paralyzed vocal cord in a midline position, with a temporary or permanent voice change, and difficulty to swallow due to the injury of posterior cricoarithenoid muscle. Bilateral injury can lead to asphyxia. If the nerve is not transsected, vocal cord paralysis is often temporary[7].



Variations in the course of the right RLN, showing a non-recurrent laryngeal nerve, arising from the vagus, in the setting of an aberrant origin of the right subclavian artery (left); the normal course of the RLN (mid); and the coexistence of both normal RLN and non-recurrent laryngeal nerve, joining into a common nerve. Taken with permission from Townsend CM. Sabiston textbook of surgery international edition. 19th ed. United States: Elsevier; 2012

3.8.2.3. Haemorrhage

Bleeding, mainly from the inferior thyroid veins can occur inadvertent. Hence ligation is needed. Drainage, mostly used for larger goiters, are placed for approximately 48 hours, and the patient must remain under observation in case airway obstruction or hematoma appears[18].

Prevention of this complication can be achieved as well by performing careful haemostasis at closing the incision, with a 1% incidence. Suspicion of bleeding must be investigated by immediate reexploration in the operating room, unless airway compromise is present[2].

Harmonic scalp is an instrument of great utility to accelerate the procedure and ensure a great degree of haemostasis[15].

3.8.2.4. Airway Obstruction

Manipulation of the airways by intubation or by surgery itself can cause laryngotracheal edema, trauma, and less frequently tracheomalacia, all of these entities being reversible within hours after the intervention. Tracheomalacia is usually managed by performing tracheostomy, rather than prosthetics[7].

If significant tracheomalacia with residual narrowing or kinking of the lumen exists following goiter removal, the tracheal airway may be improved by using traction sutures placed around cartilaginous rings (tracheopexy). The sutures then are secured to strap muscles or are brought out through the skin tied over a button[9].

4. Objectives

To describe the most frequent characteristics found in our series of patients, diagnosed with IG, and operated by the Endocrine Surgery Unit at the Hospital Universitario Marqués de Valdecilla within a period of 4 years. We describe demographics, surgical risk factors, clinical manifestations, complementary tests performed, surgery times, preventive techniques, outcomes and complications, and finally, the proportion of benign histopathology in the resected glands.

5. Patients and methods

We performed a retrospective, descriptive study based on a surgical series of 50 patients who underwent complete thyroid excision for an intrathoracic, multinodular goiter within a period of 4 years, in the Endocrine Surgery Unit of Hospital Universitario Marqués de Valdecilla.

Our study population consisted on 42 women (84%) and 8 men (16%). Mean age was 53,7+ 10,2, widely ranging from 19 to 62. Recurrent goiters were not included in this surgical series.

6. Results

Of our 50 patients, 15 (30%) had a familiar history of goiter. 40 patients (80%) presented preoperative surgical risk factors. The variables analyzed were: arterial hypertension, present in 22 patients (44%); diabetes mellitus type II, present in 4 patients (8%); chronic treatment with acetylsalicylic acid, present in 10 (20%), and chronic treatment with acenocoumarin, present in 5 (10%).

As for the debut of the disease, 35 patients (70%) related cervical mass, and 30 (60%), compressive symptoms, such as: dyspnea (60%, 30 patients); dysphagia (30%, 15 patients); dysphonia (10%, 5 patients), and a group of inespecific, miscellaneous manifestations (10%, 5 patients).

PERSONAL HISTORY		%	*n*
Sex	Female	84	42
	Male	16	8
Mean age		53,7 ± 10,2 yo.	
Familiar history		30	15

Preoperatory risk factors	Arterial Hypertension	44	22
	Diabetes Mellitus	8	4
	Acetylsalicylic Acid Intake	20	10
	Acenocoumarin	10	5
Debut	Cervical Mass	70	35
	Compression	60	30

During the preoperative assessment, measurement of the thyroid function, ultrasound, CT scan, laryngoscopy and ASA classification were carried out. 20 patients (40%) had associated thyroid hyperfunction, another 20 (40%) were euthyroid, and 10 (20%) had either clinical or subclinical hypothyroidism. Cervical ultrasound was performed in all patients, and 40 (80%) underwent an additional cervicothoracic CT scan. Also, laryngoscopy was undertaken in 26 patients (52%). ASA II was the main physical status score in our series, accounting for 40 patients (80%), followed by III (6 patients, 12%) and I (4 patients, 8%).

PREOPERATORY EVALUATION		%	*n*
Thyroid function			
	Hyperthyroidism	40	20
	Euthyroidism	40	20
	Hypothyroidism	20	10
Ultrasound		100	50
Cat scan		80	40
Laryngoscopy		52	26
ASA			
	I	8	4
	II	80	40
	III	12	6
	IV	-	-
	V	-	-

Cervical approach was the elective procedure in 100% cases, not requiring sternotomy in any of the surgeries performed. Mean surgery time was 107,87 +_ 15,3 minutes, ranging from 60 to 300 minutes. RLN was identified in 100% of the patients, aided by neuromonitoring of the RNL in 22 cases (44%).

Autotransplantation of one or more parathyroid glands was necessary in 8 patients (16%). Harmonic scalpel was used in 25 cases (50%). In 34 surgeries (68%), drainage placement was needed. 5 intraoperative biopsies (10% of the patients) were performed in our surgical series.

SURGICAL PROCEEDING	%	*n*
Mean surgery time		107,87 ± 15,3 minutes
Mean hospitalization time		2,4 ± 2,1 days
Cervical approach	100	50
RLN Neuromonitoring	44	22
Parathyroid autotransplantation	16	8
Intraoperatory biopsy	10	5
Harmonic scalpel	50	25
Drainage placement	68	34

Within the first 24 hours, hoarseness was the most common complication, present in 9 patients (18%), and dysphonia, in 4 (8%). Temporary RNL palsy was detected in 3 patients (6%), of whom 1 (2%) turned permanent. At discharge, one month-long prophylactic treatment with oral calcium supplements was prescripted in 14 patients (28%), and oral calcium with additional vitamin D in 11 (22%) patients. On the other hand, permanent hypoparathyroidism occurred in 2 patients (4%). 2 patients (4%) had their wound infected by Staphylococcus Aureus, one of them (2%) requiring hospitalization and surgical drainage and debridement. Only one wound developed an hematoma, solving spontaneously and not requiring any surgical intervention. Mean hospitalization time was 2,4 + 2,1 days, ranging from 1 to 4 days.

COMPLICATIONS	%	*n*
Dysphonia	18	9
Hoarseness	8	4

Temporary RLN palsy	6	3
Permanent RLN palsy	2	1
Permanent hypoparathyroidism	4	2
Wound hematoma	2	1
Wound infection	4	2

Definitive pathological analysis of the excised goiters showed 46 benign goiters (92%), the vast majority of them corresponding to nodular hyperplasia (43 goiters, 86%), and 3 of them (6%) to follicular adenoma. Malignancy was demonstrated in 4 cases (8%), corresponding to 2 papillary carcinomas (4%) and 2 microcarcinomas (4%). Mean weight of the resected thyroid was 112 ± 20 grams, ranging from 40 to 521 grams.

HISTOPATHOLOGY		%	*n*
Mean thyroid weight		112 ± 20 gr (40 – 521)	
Benign	Multinodular Hyperplasia	86	43
	Follicular Adenoma	6	3
Malign	Papillary Carcinoma	4	2
	Microcarcinoma	4	2

7. Discussion

Our series shows a mean age of 53,7 ± 10,2, widely ranging from 19 to 62 years. In a retrospective study including data collected from 1957 to 1996, of secondary, recurrent IG operated at Royal North Shore Hospital, Sydney, Hsu, et al. estimated the mean age of the patients to be 60,1 years, ranging from 23 to 88[19]. Polistena, et al. showed in a restrospective analysis of 28 years that total thyroidectomy via a cervical approach is a safe procedure for patients over 80 years of age; nonetheless, every IG in their study belonged to the group of patients under 80 years of age. Further research is needed to assess the safety of the procedure for IG in the elderly[20].

In our series, a cervical mass could be evidenced in 35 patients (70%). 30 patients (60%) in our series referred compressive symptoms. Dyspnea was the most frequent clinical manifestation, present in all 30 patients; dysphagia was related by 15 patients (30%), and dysphonia by 5 (10%).

In the surgical series presented by Di Crescenzo, et al. over a population of 97 patients admitted in Thoracic Surgery Unit of AOU Second University of Naples within a period of 15 years and in Thoracic Surgery Unit of AOU “San Giovanni di Dio & Ruggi D’Aragona” of Salerno, within a period of 3 years, compressive symptoms were present in 57% of the patients, being dyspnea the most common finding (52%); in addition, cough was present in 23% and an asthma-like syndrome in 7,6%. Dysphagia was related by 23% of the population, and dysphonia by 9,2%. Superior vena cava syndrome was present in 6.1% and asymptomatic patients in their series accounted for 13,8% of the patients[1].

20 of our patients (40%) had associated thyroid hyperfunction, and the same amount were euthyroid. However, hypofunction can also be present, as 10 patients in our series (20%) had either clinical or subclinical hypothyroidism. Di Crescenzo, et al. reported an incidence of hyperthyroidism of 18,5%. Tachycardia was present in all of them, anxiety was associated in 9,2%, weight loss in 6,1%, hyperhidrosis in 4,6% and tremors in 4,6%. No hypothyroid patients were reported in their series[1].

Cervical ultrasound was performed in 100% of the patients in our series. 40 patients (80%) in our series had undergone a cervicothoracic CT scan. Laryngoscopy was undertaken in 26 patients in our series (52%).

Surgical risk factors are highly prevalent in our context, but surgery is still preferred over medical or radioiodide therapy. In our series, 80% of the population (40 patients) had surgical risk factors, such as hypertension (22 patients, 44%), diabetes (4 patients, 8%), and acetylsalicylic acid (10 patients, 20%) and acenocoumarin (5 patients, 10%) regular intake.

In our series, the average surgery length was 107,87 ± 15,3 minutes, ranging from 60 to 300. All the excisions were performed through a cervical approach, and thoracotomy or sternotomy were not needed. Di Crescenzo, et al. performed cervicotomy alone in 77,32% of the patients; sternotomy, in 22,68% (sternal split was the technique of choice in half of their sternotomies, over 12,37%). In their series, sternotomy was related to higher rates of complications, reporting 16% of the patients developing complications over cervicotomy alone, increased to 30,7% in patients in whom sternotomy was undertaken, and mortality rates of 2% for cervicotomy alone, and 15,3% for sternotomy[1].

In our series, the average length of postoperative stay was 2,4 ± 2,1 days, ranging from 1 to 4 days. Di Crescenzo, et al. reported a mean hospitalization length of 7,7 days[1].

Rios, et al. in a review of the literature on IG, reported great variability of the complication rates between different surgical series, depending on the criteria used for the definition of temporary hypoparathyroidism, the inclusion of wound related complications, the percentage of recurrent and toxic goiters included, the assessment of the RLN through preoperative laryngoscopy and the surgical approach of choice[3].

Wound related complications, such as infection and seroma, range, according to Rios, et al. from 0,9 to 2,4%, and 0,1 to 2,3%, respectively, in primary

interventions, and from 0,5 to 3,5% both, in reinterventions. In our series, only 2 wound infections occurred (4%), both caused by *Staphylococcus Aureus*, one of them requiring hospitalization for surgical debridement[3].

25 of our patients (50%) were prescripted a one month-long prophylactic supplementation treatment at discharge, 14 of them (28%) consisting on oral calcium and 11 (22%), calcium in combination with vitamin D, although none met criteria for transient hypoparathyroidism. Di Crescenzo, et al. reported a transient hypoparathyroidism rate of 10%[1]. Rios, et al. obtained great variation of the incidence of this event in an analysis of multiple series, ranging from 0,22 to 50% in primary IG surgery, and from 3 to 75% in reintervention[3]. Our unit performed parathyroid glands autotransplantation in 8 procedures (16%), either single or multiple parathyroid gland.

Permanent hypoparathyroidism was estimated by Rios, et al. within a range from 0,1 to 3,5% in first surgeries and from 0,2 to 5% in recurrent goiter surgery. In our series, the occurrence was 4% (2 patients). They also estimated the rate of hypothyroidism in partial resections in 3 to 45% in primary surgery[3]. Our series does not include partial thyroid resections.

Postoperative palsy of the superior laryngeal nerve was not found in our series. Rios, et al. estimate its occurrence within 0,5 to 3% in primary surgery and 0,7 to 5% in recurrence surgery[3].

Di Crescenzo, et al. reported an incidence of 8% of postoperative dysphonia[1]. In our series, 18% of the patients (9 patients) developed hoarseness and 8% (4 patients), dysphonia, within 24 hours postsurgery. Transient RLN Palsy occurred in 3 patients (6%), of whom only one turned permanent. Rios, et al. estimate the incidence in 0,7 to 7,8% for transient palsy for first surgeries, and in 3,5 to 20% for reinterventions. Permanent palsy was estimated in 0 to 3,1% for first surgeries and in 1,3 to 17% for reinterventions[3].

In our series, RLN were identified in all the procedures, 22 (44%) of which were performed through NIM.

Rios, et al. estimated the incidence of haemorrhage and haematomas in 0,8 to 3% for primary resections and in 1,5 to 4% in reinterventions[3]. Di Crescenzo, et al. reported a rate of haemorrhage of 4%[1]. In our series, none of our patients developed suffocating haematoma, and only 1 patient (2%) developed a wound haematoma, which resolved spontaneously. Drainage placement was required in 34 patients (68%). Harmonic scalp is an instrument of great utility to accelerate the surgical procedure and ensures a great degree of haemostasis. It was used in 25 of the procedures of our surgical series (50%).

Rios, et al. estimate the incidence of postoperatory sudden dyspnea in 0,5 to 1% for primary interventions, and in 0,9 to 3,1% for reinterventions; need of tracheotomy in 0,4 to 2,1% and 0,8 to 3%, respectively, and tracheomalacia in 0,001 to 1,5% for both primary and recurrent interventions[3]. Di Crescenzo, et al. reported an incidence of respiratory failure of 10%[1].

Intraoperatory biopsy was performed in 5 (10%) of our patients. The definitive histopathological analysis showed a 92% prevalence of benign goiters (46 cases), being 43 (86%) nodular hyperplasia, and 3 (6%) follicular adenoma, a finding that correlates with those described on the literature[8]. Malignancy was detected in 4 cases (8%), resulting in 2 (4%) papillary carcinomas and 2 (4%) microcarcinomas. Di Crescenzo, et al. reported in their series 8 carcinomas (7,7%)[1]. Rios, et al., in an analysis of the risk factors for malignancy in multinodular goiters, found a negative correlation between intrathoracic extension of a multinodular goiter and risk of thyroid carcinoma[21].

8. Conclusions

1. Since our sample size is limited the interpretation of the results should be made with caution, taking into account the value of the absolute numbers rather than the rates.

2. Our results depict the predominant female distribution of IG, with a preference for median age. Surgery can entail greater complexity due to a high concurrence of surgical risk factors in the general population, with special regard to anti clot and anticoagulant drugs in the context of a surgery demanding thorough haemorrhage control. Despite concomitant treatment with these drugs, none of the patients in our series developed suffocating haemorrhage.

3. Hyperthyroidism, bulky masses, isolated mediastinal remnants and recurrent IG can be challenging in the operating room as well, especially when there is a long history of goiter. Vascularization of the gland turns richer over time, and greater adherence to adjacent structures, such as the trachea, difficults resection and can cause a life-threatening degeneration. However, tracheomalacia was not found in any of our patients.

4. In our context, large and long-standing goiters are rarely seen, probably due to the availability of health care and high socioeconomic status of our population. Our study did not include any recurrent goiter surgery, nor isolated mediastinal masses.

5. Instruments such as NIM and harmonic scalp have become useful tools in prevention of RLN damage and haemorrhage respectively, and in the decrease in surgery length. Nonetheless, its availability in a public health system is not always ensured.

6. Although the vast majority of IG is found to be benign, histopathology does not necessarily correlate with its clinical manifestations. Reduced space in the neck and thoracic inlet entail a greater probability of developing respiratory difficulty, which indicates indicates the need for surgery, and other compressive symptoms of importance, ultimately superior vena cava syndrome, which was not found in our study population.

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