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Evaluation of Secondary Retrosternal Goiter and Challenges in Management: A review

Constantinos Avgoustou[1*], Dimitrios Jannussis[2], Eirini Avgoustou[3]

[1]Director of Surgery, Department of Surgery, General Hospital of Nea Ionia "Constantopouleion-Patission-Aghia Olga", Athens, Greece. https://orcid.org/0000-0001-6976-6678
[2]General Surgeon - Consultant, "Hellenic National Emergency Aid Center'', Athens, Greece, e-mail: jannusi@gmail.com
[3]Internist, Consultant in 2nd Department of Internal Medicine & Infectious Diseases, Hygeia Hospital, Athens, Greece, https://orcid.org/ 0009-0009-8010-2288

[*]**Corresponding author:** Constantinos Avgoustou, MD, General Surgeon, Director of Surgery. General Hospital of Nea Ionia "Constantopoulion-Aghia Olga", Athens, Greece. Tel: +30 6977218339; E-mail: avgoustouk@yahoo.gr

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Abstract

This article aims at reviewing the challenges in the diagnosis and management of the secondary retrosternal goiter (SRG). We have searched relative current literature and discussed principle issues of debate and controversy.

The definition of SRG meaning a goiter descending to the thoracic inlet is not universally accepted, and this leads not only to variability in given incidence rates, but also to difficulty in recommendation of surgical indication, as well as to comparison of results. SRGs are initially asymptomatic, occasionally impalpable, and may incidentally be diagnosed. When symptoms occur, they are severe and related to the progressive compression and dislocation of the aerodigestive tract (most commonly) and of the adjacent vascular or nervous structures. The diagnosis should be clinically oriented, but imagistic studies are necessary, as is a various laboratory work-up, for definitive confirmation. Computed tomography scan is very useful for evaluating the tracheal intubation and planning surgery. Another issue of concern is the potential malignant risk of a long-standing SRG, ranging variably. Issue of debate is the use of medical treatments. Surgical removal of the SRG represents a challenge to the skilled surgeon in high-volume centers, and is widely considered as the gold standard management in all symptomatic and most of the asymptomatic cases, even if it involves a higher risk of complications compared to cervical goiters. Several studies have indicated improved breathing and swallowing outcomes after thyroidectomy. Debate exists with the use of novel surgeries.

Keywords: *retrosternal goiter, substernal goiter, mediastinal goiter, intrathoracic goiter, diagnosis, thyroidectomy.*

Introduction

One of the most accepted definitions of the secondary retrosternal goiter (SRG) is "*the thyroid gland enlargement in which any part extends below the thoracic inlet*" [1-6]. The progressive growth of an SRG can lead to symptoms and signs from compression of the trachea and esophagus, and, more rarely, of the great vessels and nervous structures [1,5,7-11]. Medical management with thyroxine or radioactive iodine (^{131}I) is very rarely sufficient [4,12,13]. Open surgical removal is generally indicated for all symptomatic and most of the asymptomatic cases, before dangerous compressive symptoms appear [1,4,6,9,11-15]. Recently, novel minimally invasive methods, technically demanding, have also been introduced [13,16,17].

Controversies and the significant variability found in the literature regarding the incidence, the clinical presentation and the treatment options of SRG can, at least in part, be explained by the various definitions encountered [2,6,9,13,18]. Principle issues to highlight are to make a correct diagnosis and have a timely indication for surgery, and to organize the collaboration of specialists in a multidisciplinary team, prepare the patient, follow a meticulous surgical technique, and manage anaesthesiological problems at intubation and extubation [2,5,9,11,17,18]. Thus, we performed a structural review of the current knowledge about the SRG diagnosis and management, tried to answer relative inquiries and make some recommendations, and emphasized important issues of daily practice. Intentionally, a PubMed search of the MEDLINE database was conducted to retrieve the most recent English-language articles regarding various aspects of the SRGs, using the search terms "retrosternal", "substernal", "mediastinal", "intrathoracic", "goiter'' and "goitre''. Unpublished images from our own material, which latter has been presented in multiple occasions throughout years, are used.

Definition and Incidence

Retrosternal goiter (RG) was first described by Albrecht van Haller (1749) as the extension of the thyroid gland below the level of thoracic inlet [9]. Actually, this definition refers to the secondary RG (SRG), which has cervical origin of vessels and represents about 99 % of all RGs [1,19]. This thyroid enlargement is also called substernal, intrathoracic, mediastinal, cervicomediastinal, sub clavicular, plongeant (plunging) or diving goiter [1,7,9,18,20]. However, there is no consensus on a unique definition (notably, more than 10 definitions have been proposed), so the incidence of the disease varies across different case series and, above all, makes it difficult to consider indications for surgical removal and to compare results [2,4,6,8,9,11,13,19,21,22]. Identified widely used definitions of the SRG are: a thyroid gland enlargement (i) in which any part of the gland extends below the thoracic inlet with the patient in the supine position; (ii) reaching the level of aortic arch; (iii) reaching the level of T4 vertebra on chest x-ray, and (iv) in which > 50 % of the total bulk of thyroid tissue resides below the thoracic inlet [1,2,4,9,14,19-22]. More precise definitions have also been suggested, namely a goiter with an extension of at least 3 cm below the cervico-thoracic isthmus at computer tomography (CT) scan performed with hyperextended neck [23], or a goiter lying two (or more) finger births below the thoracic inlet with the patient in a supine position [3,5,6,9,11,17].

The prevalence of SRG is widely ranging between 2 % and 19 % of all thyroidectomies, mostly depending on the chosen definition [1,3,4,9,11,14,17-22,24-26]. The accumulative incidence of SRG was 1389 (6.28 %) out of a total of 22125 thyroid goiter patients in the systematic review of Huins et al [2], which comprised data from 17 articles. The disease is four times more common in females [1,9,13,18,27].

Pathophysiology and Classification

SRGs are the most frequent masses of the superior mediastinum, characterized by slow and steady progression [1,24,27]. Most commonly, SRGs are benign, composed of one or more adenomas [1,11,12,14]. Occasionally, Hashimoto's thyroiditis occurs, and haemorrhagic lesions and calcifications can be found [14]. In Torre's et al [15] analysis of 4688 thyroidectomies, the longer clinical history of goiter was related to higher risk of endothoracic development and neoplastic transformation. The rate of postoperatively discovered thyroid cancer in SRG patients is 3 -13.7 % [1,5,8,24,28-30], increased [1,20,30] or even being similar [5] when compared to that of patients with cervical goiters (CGs). Indeed, limited level III/IV evidence-based data suggest that the incidence of carcinoma in SRG is not higher than the incidence of carcinoma in CGs [28,29]. However, in the series of Testini et al [20] with 19662 patients who had undergone total thyroidectomy (TT), malignancy was significantly more frequent in the group of 1055 SRGs compared to the group of CGs.

SRGs originate from the thyroid gland located in its normal cervical site and develop as a continuing tissue extension in the anterior (or middle) mediastinum and rarely (10-15 % of cases) in the posterior mediastinum [1,6,9,11,13]. On the contrary, a primary intrathoracic goiter, representing 1 % of the RGs, arises from aberrant ectopic thyroid tissue in the mediastinum, has no or little connection with the cervical thyroid, and receives its blood supply from mediastinal vessels (aortic arch, innominate, subclavian, thoracic); in thyroidectomy, vascular control is possible only directly in the mediastinum [1,6,9,11,14,31]. In SRGs, the blood supply comes from the inferior thyroid artery and its branches (only rarely, CGs may receive some blood supply from thoracic vessels), while the venous drainage is similarly served from cervical veins [1,9,11,14].

No anatomic structure can prevent the downward migration of the thyroid gland into the mediastinum, when it happens [2,32]. It is even facilitated by (i) traction forces during swallowing (prethyroid muscles); (ii) respiratory movements and the negative intrathoracic pressure; (iii) weight of the gland, and (iv) presence of anatomical barriers in other directions (thyroid cartilage, vertebral bodies, strap muscles) [1,2,11,14,24,27,32]. The removed thyroid glands had a mean weight of 192 gr (range: 80-1600 gr/up to 350 gr in cervicotomies and up to 1600 gr in mediastinal approaches) in a recent large series [9].

The space-occupying growth of SRGs may lead to compression and dislocation of adjacent structures, namely the trachea, esophagus, major vessels, nerves, thoracic duct and lung(s) [1,6,17,18,32]. When SRGs enlarge inferiorly, extension to the right of trachea shows less resistance owing to the existent relatively loose areolar tissue. Importantly, this development alters the normal route of the laryngeal nerve (LN), with greater impact on the right side where lies the ipsilateral recurrent LN (RLN) [5]. The trachea may be deviated to one side, or affected by obstruction [2,11,12,26,33-35].

Airway distress associated to chronic tracheal compression can be exacerbated and even life-threatening, particularly if spontaneous or traumatic intraparenchymal bleeding happens or if tracheal infection occurs, and may require intubation or semi-emergent surgery [1,11,34].

The long-lasting tracheal compression in SRGs descending to the aortic arch or being mostly developed within the chest may cause the condition called "tracheomalacia", which is characterized by destruction of more than two tracheal cartilages; it is symptomatic in 10 % of SRG cases [1,2,11,17,24,26,34,35]. Tracheomalacia is clinically evident when the airway patency cannot be maintained in cases with more than 50 % reduction of the cross-sectional area of the trachea [17,26,34]. After the tumour resection, the trachea loses its structural support, and it may be indented to gentle pressure between thumb and fingers, or even totally collapsed with extubation, resulting in airway obstruction (suffocation) [1,17,26,33-35].

Superior vena cava (SVC) syndrome, as the result of the slow compressive obstruction of innominate veins, which impedes the blood flow through the SVC, may occur with a prevalence of 3.2 -9 % [1,2,32]. The incidence closely mirrors that of tracheomalacia with which may coexist, rising to more than 10 % in SRGs extending to the level of the aortic arch [2,32]. In most instances, this condition may be asymptomatic due to venous collateral development [32].

Several classification systems have been developed in order to better classify SRGs [36]. Huins et al [2] have proposed a classification system of SRGs based upon their mediastinal extension and the relationship with anatomical structures, namely, to the level of the aortic arch (grade 1 → cervical approach), to the level of pericardium (grade 2 → manubriotomy), or below the level of right atrium (grade 3 → full sternotomy). Similarly, Mercante et al [22] proposed a CT cross-sectional imaging classification system which defined SRGs in the cranio-caudal dimension as grade 1 (between thoracic outlet and aortic arch), grade 2 (level of aortic arch), and grade 3 (below aortic arch). The authors also examined the need for an extracervical approach to remove the mass in association to the grade.

Clinical Presentation

Among SRGs, 20-40 % can be diagnosed incidentally on a chest x-ray and 20-30 % are barely palpable [13,24]. White et al [29] found that 20-30 % of SRGs are not palpable, particularly if their extension is posterior. In Katlic et al [14] review, 15 % to 50 % of patients with SRG were asymptomatic and 10-20 % had no palpable mass or tracheal deviation.

SRGs can remain asymptomatic for many years because of their slow development [1,3,11-14,17]. In the series of 175 SRGs of Vadasz et al [24], 40 % of patients were symptom-free. Among 237 analyzed SRG patients of Torre et al [37], only 5.5 % were asymptomatic; instead, in Torre et al [15] series of 30 patients with thyroid carcinoma with cervico-mediastinal extension none of them was asymptomatic.

Presentation of symptoms usually follows the initiation of the mechanical compression to vital structures located in the thoracic inlet, and is more correlated to the amount of thyroid mass at this level, where the trachea is more easily compressed, than by the total mass of the mediastinal thyroid [3,6,27]. Respiratory symptoms due to airway compression predominate, mostly including dyspnea or anhelation on exertion, wheezing/stridor, dry cough, life-threatening orthopnea, and even sudden death [1,3,6,9-14,17,18,23].

The presence of SRG, especially when it exists for more than 5 years and exercises significant compression on the trachea, is a risk factor for tracheomalacia [2,12,26,33]. This condition may have a silent and insidious course, but later may be accompanied by dyspnea (30 % to 60 % of SRG cases with tracheal stenosis), barking cough and expiratory stridor or wheezing [33-35]. The airway obstruction can occur during induction of anaesthesia, change of posture, and most frequently, surgical mass removal and extubation (0.8 -5.8 %) [2,11,26,29,33,34].

SVC syndrome, gastrointestinal (GI) bleeding, transient ischaemic attacks and cerebral edema, all attributable to compression on various vascular structures, may also rarely occur in long-standing large SRGs [1,6,9,12,13,17,18,32].

The SVC syndrome is clinically manifested with dyspnea, associated with physical findings, such as venous distention at the neck, facial edema-flashing, plethora and cyanosis. The signs and symptoms may be aggravated by bending forward or in a supine position [1, 32].

Dysphagia due to compression of the esophagus, described as a "lump in the throat", may occur in up to one-third of patients [1,6,10,12-14,17,18]. Acid reflux may also be present sometimes [6,17]. In larger SRGs, the SVC obstruction may cause the so-called "downhill" esophageal varices, a condition prone to GI bleeding [1,12,14,32].

Compression of nerves is not common, mainly represented by voice changes, such as dysphonia and hoarseness (vocal cords paresis) [10,13,14,18,32,35]. Extremely rare are the Horner's syndrome, caused by sympathetic chain/peripheral adrenergic nerve compression [9,11,13,32,35], and the phrenic nerve palsy with raised hemidiaphragm caused by compression at the thoracic inlet adjacent to the 5th rib [5,13,27]. The former has also been reported as rare complication after TT for large SRG [27].

The extremely rare compression of the carotid artery may cause central nervous system symptoms, such as transient ischaemic attacks and cerebral edema [1,14].
Chest pain and otalgia are rare manifestations [6,14,17]. A large SRG can also very rarely cause chylothorax by damaging the thoracic duct [38].

Diagnostic Evaluation

The diagnosis of SRGs is based on patient's history, clinical examination, laboratory results and imaging findings [1,9,12,13,24].

SRGs are often detected incidentally on neck-chest x-ray in 5th or 6th decade of life (20-40 % of cases) [1,9,14,24,27]. This simple examination provides an initial radiologic evidence of the goiter, since it may reveal widening and oval shadow in the superior mediastinum, or tracheal deviation contralateral to the prominent side of the pathology [1,5,12,13,17,18,35].

Inspection and neck palpation may aid to detect whether the caudal extension of the mass is below the clavicles or the sternal notch (Fig. 1 a).

Fig. 1a   Fig. 1b

Figure 1: On the surgical table: a) Large SRG in a 66-year-old female; b) difficult intubation in a 62-year-old female (white arrow for vocal cords on the monitor).

The Pemperton's manoeuvre may contribute to identify some latent cases and masses compressing the great vessels, as well as to palpate a deep goiter component. In this case, by raising both arms or hyperextending the neck for some minutes while swallowing, some patients may develop facial plethora-flashing, cyanosis with dilatation of external jugular veins and respiratory distress or stridor; their deeper intrathoracic goiter component may be elevated and rendered palpable (positive Pemberton's sign); symptoms and signs are resolved when the arms are lowered [1,12,14,32].

Thyroid ultrasound / Doppler is simple and useful. In large SRGs, however, this modality is combined with fine needle aspiration (FNA) only with great caution and particularly for the cervical component, since the lower part of the goiter lies deeply within the mediastinum and the surrounding structures can limit the sonographic window [1,12,18,27,35]. In these cases, injury to the great vessels may lead to life-threatening arterial bleeding, and puncture of the pleura may result in pneumothorax [1,14].

CT scan of neck and upper chest (Fig. 2) is the examination of choice for goiter masses, as it allows evaluation of the nature, size, endothoracic depth, and pressure effects (displacement, luminal stenosis/obstruction etc) on the surrounding structures [1,5,7,9,12,13,17,18,24,39].

Fig. 2a **Fig. 2b**

Figure 2: Neck-upper mediastinal CT scan: a) axial images indicating SRGs descending into the mediastinum in a 56-year-old male (left) and a 64-year-old female (right), compressing and dislocating the trachea (white arrows); b) coronal image indicating SRG entering the thoracic inlet in a 63-year-old female (white arrow).

It is also very useful for the preoperative establishment of the need for sternotomy [1,5,9,11,24,32,40]. Before performing this modality, the practitioner should have evaluated the patient's thyroid status, because of the potential effects of the injection of iodinated contrast media in some cases [3,7]. Magnetic resonance imaging is not routinely used, as it adds little information to what can be obtained by CT scan [3,9,13,39]. Similarly, the thyroid radioisotope scan can determine whether an intrathoracic mass consists thyroid tissue, but it is rarely used in clinical practice [1,24,35].

Thyroid function tests help to detect possible functional abnormalities of the thyroid gland, including levels of thyroid-stimulating hormone (TSH), free thyroxine and triiodothyronine, antibodies for autoimmune diseases, calcitonin/ thyroglobulin (when malignancy is suspected), and parathyroid hormone and plasma calcium [6,11,12,35]. The majority of Vadasz et al [24] patients were euthyroid, while 11 % were hyperthyroid. In many patients, arterial blood analysis may show increased $PaCO_2$ and decreased PaO_2 and SpO_2 [34]. Pulmonary function evaluation, such as spirometry or flow-volume loop testing, are usually indicative of upper airway obstruction (i.e., low vital capacity), even in asymptomatic SRG patients [1,14].

Before surgery, laryngological / bronchological and even barium /Gastrographin® swallow (occasionally) investigations can be performed [1,18,24,26,35]. The vocal cords and their movements can be easily visualized on fiberoptic laryngoscopy (Fig. 1b) [35]. Current gold-standard for the diagnosis of tracheomalacia is bronchoscopy, which allows direct visualization of the severity and extent of the airway collapse [26].

Differential diagnosis of masses in the anterosuperior compartment includes aneurysms, lymphomas, fibromas, dermoid cysts, teratomas, tuberculomas, pleural cysts and secondary carcinomas; in the posterior mediastinum, it includes neurogenic tumours [1].

Treatment

I. Medical Treatment

The ‘‘wait and watch’’ approach can be an option in selected asymptomatic SRG patients who (i) have normal flow-volume loops with goiters above the level of the brachiocephalic vein and (ii) are very old and frail [13]. The American Thyroid Association Statement (ATAS) on optimal surgical management of goiter in 2014 [12] supported that, poor candidates for surgery whose goiters range in size from modest to large, manifesting with compressive symptoms, may be appropriate candidates for ^{131}I. Levothyroxine (or propylthiouracile) therapy has also been proposed [1,12-14]. However, neither of these treatments is effective in the case of large SRGs: on the one hand, ^{131}I does not achieve definite control of the disease and may cause acute inflammatory reactions, resulting in exacerbating tracheal compression and airway compromise; on the other hand, levothyroxine does not work in the patient with low serum TSH levels and may achieve very slow size reduction [1,13,14,17,21,29]. Notably, the tracheobronchial stenting has recently been employed as a procedure to prevent tracheal obstruction and delay definite surgery [17,34].

II. Surgical Treatment

Arguments and indications for surgery

It is widely accepted that "the presence of SRG is itself an indication for operation", and surgical resection is considered as the gold- standard management in all symptomatic and most of the asymptomatic cases [1,6,10,13,18,21,23,28]. This is supported by the following: (i) long history of continuously enlarging multinodular goiter precludes neither complications, such as tracheal and esophageal compression, nor malignancy or hyperfunction; (ii) ^{131}I ablation is very rarely effective and can be associated with acute reactions resulting in respiratory distress; (iii) sudden enlargement of the mass (from haemorrhage or malignant changes) can cause acute airway obstruction; (iv) approximately 40 % of the clinically asymptomatic patients show evidence of upper airway obstruction on flow volume loops examination, and the hidden malignancy is reported more frequently (3-21 %) than in CGs; (v) nearly all SRGs can be removed through a simple cervicotomy, achieving both therapeutic and preventive results [1,11-15,18-21,24,29,41].

A multidisciplinary approach by a skilled team that decides the type of anaesthesia and surgery, issues of controversy, as well as the postoperative care, is crucial to achieve optimal results [9,11,12,18,42].

Preoperative assessment and perioperative anaesthesia

The CT-imaging is the gold-standard modality for diagnosis [9,11,32,40]. Values of thyroid hormones and calcaemia markers are used to treat hyperfunctional patients with methimazole/propylthiuracil and/or beta-blockers [5-7,11,12,35]. Cardiac arrhythmias and high blood pressure should also be appropriately controlled [12]. Laryngoscopy is important to assess the vocal cords, the grade of tracheal compression and the tracheal invasion by a suspicious neoplasm [1,11,33]. Postoperatively, laryngoscopy aims to detect RLN palsy or laryngeal edema, and evaluate and manage exacerbated tracheomalacia [11,12,17,26,33].

The anaesthesiologic activity is of triple importance: (i) to overcome a difficult intubation; (ii) to maintain patent airways intraoperatively; and (iii) to manage airway problems at extubation [1,11,12,34]. The majority of SRG patients can easily be intubated and extubated without problems [12]. However, equipment should always include a rigid bronchoscope, a flexible bronchoscope for fiberoptic-guided intubation, and a laryngeal mask [11,12,34]. The fiberoptic intubation for induction of general anaesthesia is recommended in all cases with significant stenosis and compression, and is also used in the awake difficult patient [1,12,13,34,35]. Furthermore, it helps to assess the tracheomalacia component as post-procedure condition [13,26,35]. Intraoperative cardiac output decrease caused by changes in patient's position also requires intervention by the experts [12]. Temporary tracheobronchial stent (i.e., self-expandable metallic stent/ SEMS) can be placed in difficult cases with significant tracheal narrowing and displacement [12,17,34].

Severe tracheomalacia is largely addressed with conservative management, such as prolonged endotracheal intubation with continuous or bilevel positive airway pressure ventilation (CPAP, BiPAP), and the tracheal stenting (SEMS) [1,2,11,12,17,26,34]. Accordingly, invasive methods include intraoperative tracheopexy (suturing), external tracheal stabilization with Marlex mesh, tracheal resection with anastomosis, and tracheostomy [1,2,11,12,26,33-35].

Indications for tracheostomy are: (i) long-term compression by a huge goiter and destruction of more than two rings (CT scan); (ii) significant compression which causes tracheal deviation and narrowing, resulting in difficulty in intubation and induction of anaesthesia; and (iii) tracheal collapse after the tumour removal and inability to pull out the endotracheal tube [26,33,35].

Surgical technique and approaches

TT is performed in patients with bilateral disease; a "relieve" lobectomy can rarely be performed if the SRG is unilateral and the contralateral lobe is essentially normal [1,6,12]. With cervicotomy, the mediastinal goiter component can be delivered out of the chest after breaking the mediastinal negative pressure (with index finger, spoon or retractor) to reach its most caudal portion, using blind/sharp dissection, and exercising simultaneous gentle traction [1,5,9,12,18,21,35]. Esophageal injuring can be prevented during dissection by placing a large esophagogastric tube [7]. Prerequisite for safe and effective surgery is the dissection in the avascular plane between the true and surgical thyroid capsules [11,32,35]. Direct control of the pedicles of the cervical vessels is required [1,32]. Furthermore, each vital structure must be identified and protected [1]. The RLNs should not routinely be exposed but only dislocated with the outer surface of the posterior capsule; a normal thyroid lobe may be preserved if there is concern about the RLN on the ipsilateral site or for parathyroid preservation [1,12,35,43] (Fig.3).

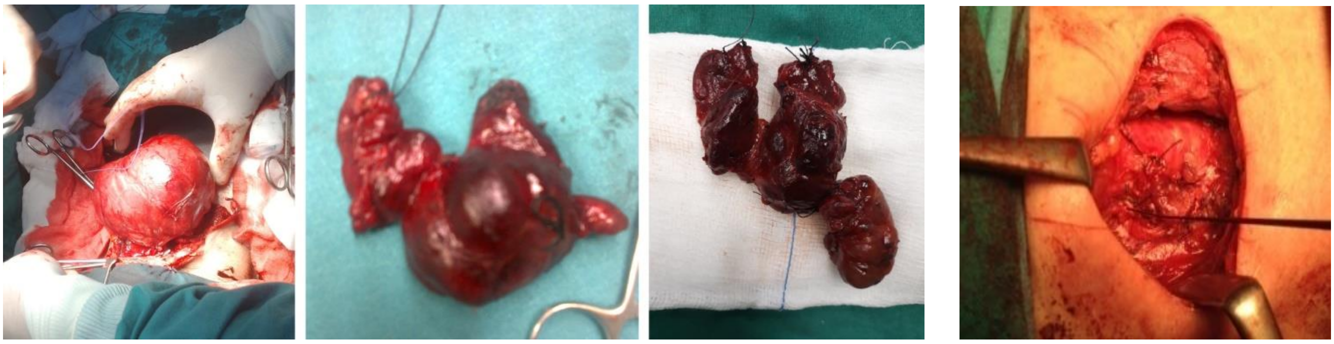

Fig. 3a **Fig. 3b**

Figure 3: Intraoperative views: a) extracted mediastinal component of SRG and surgical specimens of SRG; b) right RLN in the tracheoesophageal groove (not dislocated / exposed) after SRG removal (indicator).

In the case of relapse goiter, adhesions and neo-blood supply are often present and may interfere with the correct surgical dissection plane [6,18]. In case of accidentally resected parathyroid gland, auto transplantation into a neck muscle is a valuable method [12].

The use of electrophysiologic nerve monitoring during the resection of bulky goiters has been suggested in order to prevent RLN injuries [5,11]. The careful use of ultrasonic knife (Harmonic scalpel) provides safe sealing and cutting of vessels, particularly deeply in the mediastinum [9,35]. At the end of the operation, a negative pressure drainage (Jackson-Pratt) is placed to manage the residual dead space after resection, and is removed based on the clinical course [1,11,12,35].

The surgical approach is determined by the cervical origination of the disease, the patient's perioperative risk, whether the SRG is mono- or bi-lateral, and by the (known) cytomorphology of the mass.

Open surgery is started with a low cervical Kocher collar incision, which, for the head/neck and endocrine surgeons, is sufficient for the goiter removal in up to 98 % of the cases [1-5,9,10,17,18,23,25,29,36]. Efforts to excise the lesion through a cervicotomy should always be made, considering the less risk of surgical damage and complications associated with this approach [9,25]. Video-mediastinoscopy (0º 5 mm endoscope) has been used as an adjunct to cervicotomy in some large SRG cases, aiming at identifying a bleeding intrathoracic tributary and putting a metallic clip [11,25].

Open extracervical / intrathoracic approach, such as the partial sternotomy (manubriotomy), full sternotomy and the partial thoracotomy, is occasionally required, exclusively combined with a cervicotomy and never being performed alone (inaccessible upper pole blood supply, possible RLN injury) [1-6,17,18,20,24,25]. The likelihood of using a complementary approach depends on CT scan and intraoperative findings: (i) SRG mass with size greater than that of the thoracic inlet, extending beyond the tracheal bifurcation; (ii) suspected invasive malignancy with associated lymphadenopathy-loss of clear tissue planes around mediastinal nodules (risk of haemorrhage or tumour spillage) or adhesions in recurrent cases; and (iii) posterior mediastinal location or anomalous blood supply [1,2,5,9,11,13,23,29,31]. The final decision for this approach should be made on the surgical table [9,13]. Accordingly, a complementary approach is associated with higher risk of tissue damage, greater postoperative morbidity, and slower rehabilitation than a simple cervicotomy [4,35].

Recently, newer minimally invasive techniques, such as endoscopic and robotic methods, have been developed to facilitate a safer dissection of the mediastinal structures with limited morbidity in large SRG cases where a cervicotomy is not sufficient [11,13,16,17,44-46]. The video-assisted thoracoscopic surgery (VATS) techniques are limited by difficult access and poor 2D visualization [13]. Robotic techniques offer 3D visualization, depth perception and superior manoeuvrability of the instruments [13,16,17].

Immediate postoperative care and treatment

The patient is placed in a semi-recumbent position aiming at coughing and deep breathing exercises, in order to improve pulmonary gas exchange and drainage of the residual post-thyroidectomy cavity, and is examined for voice changes and possible pneumothorax [12,35]. In case of tracheostenosis, the intubated patient should stay in the Intensive Care Unit for 1-2 days; if required, a tracheostomy is carried out, with the tracheal tube removed after 5-7 days [35]. Wound negative pressure drainage should be performed consistently for ~ 48-72 hours in order to prevent effusion and protect the surgical space [1,35]. Should bleeding occur (0.5 -0.7 %), a second surgery is required for haemostasis [5,7,11,21]. Acute postoperative hypocalcaemia, usually attributable to temporary parathyroid ischaemia, can be managed by supplement of calcium glyconate [8,11,12,35]. Steroids (i.e., hydrocortisone) can be used for 1 to 2 days to prevent or lessen laryngeal edema and to reduce transient hoarseness [33,35].

Operative results and complications

After surgery, obstructive airway signs, dysphagia and neurologic symptoms generally disappear completely [1]. Several studies have demonstrated improved breathing and dysphagia outcomes after thyroidectomy [1,12]. Both maximum breathing capacity and vital capacity may be markedly ameliorated [1,14]. In most cases, compressive symptoms disappear either immediately or progressively within 12 months, with the exception of dysphagia associated with swallowing motor disorders (~4 % in large SRGs) which may persist more [1,6].

In general, both intraoperative and postoperative complications of the SRG removal can be serious. However, most authors suggest that complications to surgery for large SRGs are rather similar to those of standard thyroid surgery for CGs provided that the operating surgeon is accordingly skilled [12,18]. Many others have reported that, the peri- and post-operative complications and morbidity after TT are higher in SRG compared to CG [6,17,20,21,29,33]. In SRGs, the incidence of complications may be higher if extensive resection is required (i.e., malignant cases), where the location /status of the parathyroid glands and the RLN is difficult to be evaluated, and "hidden" tracheomalacia may exist [1,6,9,15,20,43].

Postoperatively, immediate airway complications due to airway edema, vocal cord paralysis, obstructive tracheomalacia, and bleeding/haematoma are extremely serious but occur rarely [9,12-14,18]. "Hidden" tracheomalacia may be acutely manifested with respiratory distress immediately after extubation (see, prevention and treatment, above) [1,2,26,29,33].

Damage of bilateral RLNs may lead to vocal cord paresis on both sides, resulting in acute severe airway problems (stridor, suffocation), and requiring immediate re-intubation and evaluation of the vocal cords with fiberoptic endoscopy; tracheostomy can usually be avoided until re-evaluation of the patient 24-48 hours later [2,11,12,26,33]. Permanent RLN palsy (paralysis for > 1 year) is seen in 1.4 -2.1 % of cases [6,8,35]; higher frequencies (up to 14.3 %) have been reported in some series [5,29]. Transient RLN palsy has been reported in 1.8 -5.6 % of cases [6-9,35]. Non-serious injuries of the laryngeal nerves may be manifested as hoarseness (dysphagia) or inability to raise the voice [18,35]. All patients should be examined both pre- and post-operatively with the laryngoscope [6].

Severe postoperative haemorrhage requires immediate re-operation to suture the bleeding vessel [1,12]; a recent series reported an incidence as high as 5.6 % [9]. Detection of any haematoma is achieved by physical examination of the neck at regular intervals [18,40]; a large series [6] reported an incidence of 2.1 % for postoperative seroma and/or haematoma.

Permanent or transient hypoparathyroidism have been reported in 2.8-5 % [5,6,9,13] and 13 -33 % [6-9,35] respectively. The use of early markers, such as parathyroid hormone levels (at 1 hour) and daily controls of calcium level, allows an earlier detection and treatment [6]. In patients with acute symptomatic hypocalcaemia, intravenous administration of calcium glyconate is the preferred therapy, whereas chronic disease is managed with oral calcium and vitamin D supplements. For all patients, hormone replacement therapy is routinely achieved by the prescription of thyroid tablets [7,35].

Surgical site infections (SSIs) have been reported in a rate between 0.36 % and 3 % [20,47]. Obesity, diabetes mellitus, central lymph node dissection, and other variables are associated with increased risk of SSIs [47]. Although thyroid surgery is considered a clean one, SSIs have consequences that can be costly and morbid for the patients: (i) a neck wound infection is proximal to critical structures and often cannot be treated with simple incision and drainage with open packing, neither be hidden under usual clothing; (ii) some of the complications of sternotomy or thoracotomy (wound infection, suture dehiscence, mediastinitis, pneumothorax, post-operative pain) are related to the surgical access itself, and are much less tolerated by the patients than those of a simple cervicotomy [7,11,12,18,47].

Conclusion

Controversy and confusion regarding issues in diagnosis and management of SRG still exists, and clear evidence for some aspects of the disease is missing. Specifying the degree of gland extension into the mediastinum aims at resolving uncertainty about the incidence of the disease and the comparison of results. SRG can be seriously symptomatic and even life-threatening due to mediastinal extension that results in compression of the aerodigestive tract or the vascular and nervous adjacent structures. The CT scan should always be included in the diagnostic work-up. There is general agreement that medical treatments are not effective. For the surgical treatment, appropriate preparation of the patient and evaluation of risks at tracheal intubation are required. Removal of the SRG, mostly via a cervicotomy, represents a challenge for the skilled surgeon, and it is considered as the gold standard management in all symptomatic and most of the asymptomatic cases, even if it involves a higher risk of complications. There are specific indications for combined extracervical approach or tracheostomy. Proposed minimally invasive methods (VATS, robotic) are technically demanding, but have provided encouraging early results. Several studies have reported improved breathing and swallowing outcomes after thyroidectomy.

Abbreviations

$PaCO_2$: Partial pressure of carbon dioxide, PaO_2: Partial pressure of oxygen, SpO_2: Oxygen saturation

Conflict of interest

The authors have no conflicts of interest to declare.

Ethical Approval/ Informed Consent

Written informed consents were obtained from the patients whose images are used.

Authors' contributions

CA- chief operator, manuscript conception / writing; DJ- assistant operator, manuscript design; EA- review of literature, manuscript correction / submission.

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