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ORIGINAL ARTICLE – ENDOCRINE TUMORS

Does Mediastinal Extension of the Goiter Increase Morbidity of Total Thyroidectomy? A Multicenter Study of 19,662 Patients

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ABSTRACT

Purpose. To compare the outcome in patients with cervical goiters and cervicomediastinal goiters (CMGs) undergoing total thyroidectomy using the cervical or extracervical approach.

Methods. This was a retrospective study conducted at six academic departments of general surgery and one endocrine-surgical unit in Italy. The study population consisted of 19,662 patients undergoing total thyroidectomy between 1999 and 2008, of whom 18,607 had cervical goiter (group A) and 1055 had CMG treated using a cervical approach (group B, $n = 986$) or manubriotomy (group C, $n = 69$). The main parameters of interest were symptoms, gender, age, operative time, duration of drain, length of hospital stay, malignancy and outcome.

Results. A split-sternal approach was required in 6.5% of cases of CMG. Malignancy was significantly more frequent in group B (22.4%) and group C (36.2%) versus group A (10.4%; both $P < .001$), and in group C versus group B ($P = .009$). Overall morbidity was significantly higher in groups B + C (35%), B (34.4%) and C (53.5%) versus group A (23.7%; $P < .001$). Statistically significant increases for group B + C versus group A were observed for transient hypocalcemia, permanent hypocalcemia, transient recurrent laryngeal nerve (RLN) palsies, permanent RLN palsies, phrenic nerve palsy, seroma/hematoma, and complications classified as other. With the exception of transient bilateral RLN palsy, all of these significant differences between group B + C versus group A were also observed for group B versus group A.

Conclusions. Symptoms, malignancy, overall morbidity, hypoparathyroidism, RLN palsy and hematoma are increased in cases of substernal goiter.

The cervicomediastinal goiter (CMG) was first described by Haller.[1] The clinical significance of this condition

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progressively increases due to clinical features that include impingement on surrounding structures and onset of compressive symptoms.

There is no standard definition for CMG.[2–6] Some authors have considered a substernal goiter as one that extends to the fourth thoracic vertebra on a chest x-ray, or reaches the aortic arch.[4,5,7,8] Others have defined a mediastinal thyroid as one in which most of the gland extends below the thoracic inlet with the patient in the surgical position.[3]

Terms such as retrosternal, substernal, and intrathoracic have been used to define an extension of >50% of the thyroid gland beyond the thoracic inlet.[6,9] The reported incidence of CMG is highly variable, ranging from 1–30% of thyroidectomies.[2,10–20] in studies with different defining criteria.

The classification of CMGs as primary or secondary has surgical relevance because of differences in blood supply. Primary substernal goiter is rare (1%), arising from ectopic thyroid tissue in the mediastinum, with blood supplied by nonanatomic mediastinal vessels.[17,18,21] Most CMGs are secondary, originating from extension of the cervical gland into the chest, with a blood supply drawn from the cervical vessels.[9,11,21]

Total thyroidectomy (TT) is a standardized procedure characterized by low morbidity and virtually no mortality, especially when performed in high-volume centers.[22–25] TT represents the treatment of choice for all substernal goiters, and is achieved through a cervical or extracervical approach. In the majority of cases, thyroidectomy can be performed using cervical access, but a sternotomy or thoracotomy is always necessary for primary CMG and when the gland is predominantly intrathoracic, or when preoperative assessment suggests infiltration into surrounding structures.[4,13–20,26–37]

Although standardization of the capsular dissection technique has significantly decreased the overall morbidity of thyroid surgery, hypoparathyroidism and recurrent laryngeal nerve (RLN) palsy remain the most frequent postoperative complications.[23,38]

When TT is performed for CMG, a higher risk of postoperative hypoparathyroidism and unintentional RLN injury is reported.[12,13,20,37,39–42] However, the small sizes of the series and their lack of control groups prevent a comparison of the complication rates of thyroidectomy performed through the cervical and extracervical approaches.

The aim of this study was to compare overall outcome in patients with cervical goiters and CMGs undergoing TT using the cervical or extracervical approach. We also investigated the impact of surgical access on postoperative morbidity, and evaluated whether a substernal goiter is associated with increased malignancy.

METHODS

Six academic departments of general surgery and one endocrine-surgical unit in Italy (Piedmont, Lombardia, Lazio, Umbria, Apulia, and Sicily) participated in the study. All units provided relevant information regarding thyroid surgery performed between January 1, 1999, and December 31, 2008.

Exclusion criteria included TT for recurrent disease, lymph node dissection or laryngectomy plus thyroidectomy, subtotal thyroidectomy, loboisthmectomy, minimally invasive video-assisted thyroidectomy, concurrent primary hyperparathyroidism, and anaplastic carcinomas.

Medical records of all eligible patients who underwent TT were evaluated. Demographic data, preoperative diagnosis of thyroid disease and preoperative clinical manifestations, thyroid histology, type of surgical access, operative time, postoperative complications, duration of drain, and length of hospitalization were recorded. CMG was defined as a goiter with >50% of the gland below the clavicle.

Patients were divided into three groups: A, affected by cervical goiters (control group); B, affected by CMG with TT performed through a cervical approach; and C, affected by CMG with TT performed using manubriotomy.

Preoperative workup included measurement of thyroid function and autoantibodies, serum calcium, inorganic phosphorus, and magnesium. Ultrasound-color Doppler imaging of the neck with thyroid volume determination, plain chest and neck radiography, and evaluation of preoperative vocal cord function were always performed.

Thyroid scintigraphy (17.3%), and fine-needle aspiration biopsy (12.9%) were limited to patients with hyperthyroidism and suspected nodules, respectively.

When the lower limit of the gland could not be clearly defined using ultrasound–color Doppler imaging, a multidetector computed tomographic scan with multiplanar reformatting and volume-rendering reconstructions of the neck and chest was performed in 2969 (15.1%) patients: in 1055 of these (35.5%), >50% of the gland was below the clavicle. The remaining patients were included in the cervical group.

Written informed consent was obtained and all thyroidectomies were performed by highly experienced surgeons. TT was conducted using a standardized capsular dissection technique through a collar incision (group A).[38] Thyroid vessels were controlled individually and divided either with the harmonic scalpel (Harmonic Wave and Harmonic Focus, Ethicon EndoSurgery, Cincinnati, OH) or with conventional knot-tying. The thoracic component of the CMG was manually retracted to the cervical region (group B) but when digital blunt dissection was considered dangerous, a manubriotomy was performed (group C).

Hemostasis was achieved by bipolar scissors, pliers and biosurgical agents.[43] Electrocautery was avoided close to the nerves or parathyroid glands. Parathyroids and RLNs were meticulously dissected using loupe magnification.[44] In 1,060 cases of group A (5.7%), 96 of B (9.7%) and 11 of C (15.9%), a single parathyroid autotransplantation was performed.[23] Drainage was used.

Postoperative clinical evaluation tested for vocal changes, dyspnea, dysphagia, numbness, paresthesia, facial muscle spasm, irritability, carpopedal spasm, weakness, and cardiac arrhythmias. Laryngoscopy was performed in patients with hypofunctioning vocal cords at extubation or with an immediate postoperative change in voice. Serum calcium levels were routinely evaluated 2–3 times/day for 2 days after the operation, daily for 1 week and 2 times per week thereafter up to 4 weeks. If levels of serum calcium were <10% of preoperative levels in asymptomatic patients, or when symptomatic hypocalcemia was evident, oral calcium carbonate (1–6 g/day) was administered. Hypoparathyroidism was considered permanent if the patient could not achieve eucalcemia by 6 months after surgery, despite calcium and vitamin D supplementation.

Between-group comparisons were made using Student's *t* test for independent samples. Frequencies were compared by χ^2 test. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the association of symptoms, malignancy and postoperative complications in CMGs. Age-adjusted ORs for malignancy were estimated by multivariate logistic-regression analysis. $P < .05$ was considered statistically significant.[45,46] Statistical analyses were performed using Statistica 6.1 software (StatSoft Inc., Tulsa, OK).

RESULTS

The study population consisted of 19,662 patients (mean age of 57.1 years, range: 17–88), of which 12,948 (65.9%) were women (Table 1). Group A comprised 18,607 patients (94.6% of the total). 5.4% of the study population (group B + C) had CMG. Group A was significantly younger than groups B and C ($P < .001$ for both comparisons). 19,268 (98%) patients had a preoperative diagnosis of benign disease, and in 394 (2%) malignancy was detected by fine-needle aspiration biopsy. At preoperative evaluation, benign disease was significantly more frequent in group B than A ($P = .001$) and, in comparison with group A, B and C showed significantly more hyperthyroid disease ($P < .001$ for both).

Table 2 summarizes clinical manifestations at admission. A total of 6,172 (31.4%) patients were symptomatic at presentation with 3,404 (17.3%) cases of preoperative hyperthyroidism. In group A, 55.4% of patients ($n = 2989$) showed only one symptom; 31.7% ($n = 1711$) and 12.9% ($n = 699$) presented 2 or >2 symptoms, respectively. In group B, 47.9% of patients ($n = 359$) had only one symptom; 27.8% ($n = 209$) and 24.3% ($n = 182$) showed 2 or >2 symptoms, respectively. In group C, 47.8% of patients ($n = 11$) showed only one symptom; 26.1% ($n = 6$) and 26.1% ($n = 6$) presented 2 and >2 symptoms, respectively. The prevalence of symptomatic patients was significantly greater in group B + C (73.3%) than in A (29%; $P < .001$). The proportion of symptomatic patients was also significantly higher in group B (76.1%) versus A ($P < .001$).

In particular, patients in group B + C, as well as those in group B, had significantly more neck mass, thyrotoxicosis and dysphagia, versus control subjects. No cases of vena cava syndrome were observed in group A, whereas five were observed in group B + C ($P < .001$). Group C showed a similar prevalence of symptomatology (33.3%; $P = .43$), neck mass and dysphagia relative to A. The main symptom in group C was thyroid hyperfunction, which was significantly more frequent than in A. The appearance of neck mass was significantly less frequent in group C versus B, while vena cava syndrome was more frequent ($P = .002$); between-group differences for other symptoms

TABLE 1 Demographic variables and preoperative diagnosis at admission

	Group A ($n = 18,607$)	Group B ($n = 986$)	Group C ($n = 69$)	*P* value		
Female, *n* (%)	12,231 (66)	674 (68)	43 (62)	$P = .09$	$P = .55$	$P = .30$
Age, y	55 ± 22	65 ± 15	68 ± 15	$P < .001$*	$P < .001$*	$P = .14$
Disease, *n* (%)				$P = .001$*	$P = .71$	$P = .41$
Malignant	387 (2.1)	6 (0.6)	1 (1.4)			
Benign	18,220 (97.9)	980 (99.4)	68 (98.6)			
Benign disease, *n* (%)				$P < .001$*	$P < .001$*	$P = .37$
Euthyroid	15,120 (83.0)	699 (71.3)	45 (66.2)			
Hyperthyroid	3,100 (17.0)	281 (28.7)	23 (33.8)			

Age data are mean ± standard deviation

* *P* value is statistically significant

TABLE 2 Clinical manifestations at admission

Symptoms, n (%)	Group A (n = 18,607)	Group B + C (n = 1,055)	Group B (n = 986)	Group C (n = 69)	OR (95% CI) B + C vs. A	OR (95% CI) B vs. A	OR (95% CI) C vs. A	OR (95% CI) C vs. B
Neck mass	6,194 (33.3)	401 (38.0)	383 (38.8)	18 (26.1)	1.23 (1.08–1.40) P = .002*	1.27 (1.12–1.45) P < .001*	0.71 (0.41–1.21) P = .21	0.56 (0.32–0.97) P = .035*
Respiratory symptoms	3,029 (16.3)	163 (15.5)	154 (15.6)	9 (13.0)	0.94 (0.79–1.12) P = .48	0.95 (0.80–1.14) P = .58	0.77 (0.38–1.56) P = .47	0.81 (0.39–1.67) P = .57
Thyrotoxicosis	3,100 (16.7)	304 (28.8)	281 (28.5)	23 (33.3)	2.02 (1.76–2.33) P < .001*	1.99 (1.73–2.30) P < .001*	2.50 (1.51–4.13) P < .001*	1.25 (0.75–2.11) P = .39
Dysphagia	439 (2.4)	56 (5.3)	53 (5.4)	3 (4.3)	2.32 (1.74–3.09) P < .001*	2.35 (1.75–3.15) P < .001*	1.88 (0.59–6.01) P = .28	0.80 (0.24–2.63) P = .71
Superior vena cava syndrome	0 (0)	5 (0.47)	3 (0.3)	2 (2.9)	NA P < .001*	NA P < .001*	NA P < .001*	9.78 (1.61–59.54) P = .002*
Symptom-free	13,208 (71.0)	282 (26.7)	236 (23.9)	46 (66.7)	0.15 (0.13–0.17) P < .001*	0.13 (0.11–0.15) P < .001*	0.82 (0.50–1.35) P = .43	6.36 (3.77–10.71) P < .001*

OR odds ratio, *CI* confidence interval, *NA* not applicable

* P value is statistically significant

were not significant. Respiratory symptoms caused by laryngotracheal compression were observed in 16.3, 15.6, and 13% in groups A, B and C (P = NS for intergroup comparisons).

Operative time was significantly greater (all P < .001) in group B + C (115 ± 37 min) compared with group A (88 ± 19 min) and in C (195 ± 38 min) compared with A and B (109 ± 30). Duration of drain was significantly higher (all P < .001) in group B + C (72 ± 20 h) versus A (39 ± 10 h) and group C (119 ± 13 h) versus A and B (69 ± 16). Length of hospitalization was significantly longer (all P < .001) in group B + C (89 ± 21 h) in comparison with A (69 ± 11 h) and group C (139 ± 46 h) in comparison with A and B (86 ± 12). All these variables were significantly lower in group A than in B (all P < .001).

Malignancy (Table 3 and Fig. 1) was present in 2,181 patients (11%) overall and was significantly more frequent in group B + C than in group A (OR 2.62; 95% CI 2.25–3.04; P < .001). The frequency of malignancy in group B + C was also significantly higher compared with group B alone (OR 2.49; 95% CI 2.13–2.91; P < .001) and versus group C alone (OR 4.90; 95% CI 2.99–8.02; P < .001). Compared with group B, group C also had a significantly higher

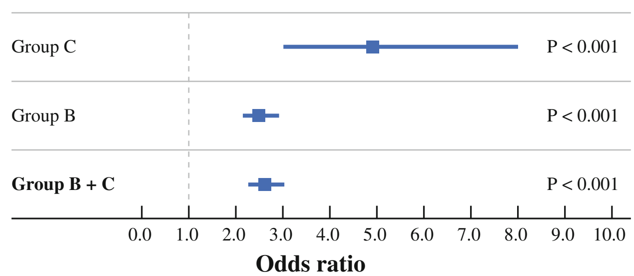

FIG. 1 Odds ratios and 95% confidence intervals for the association between malignancy and CMGs. Group A was considered as the reference

TABLE 3 Analysis of histological findings

Histology	Group A (n = 18,607)	Group B + C (n = 1055)	Group B (n = 986)	Group C (n = 69)
Benign, n (%)	16672 (89.6)	809 (76.7)*	765 (77.6)*	44 (63.8)*†
Euthyroid	13626 (81.7)	709 (87.6)*	672 (87.8)*	37 (84.1)
Hyperthyroid	3046 (18.3)	100 (12.4)*	93 (12.2)*	7 (15.9)
Malignant	1935 (10.4)	246 (23.3)*	221 (22.4)*	25 (36.2)*†
Papillary carcinoma	1544 (79.8)	178 (72.4)* P = 0.007	165 (74.7)	13 (52.0)* P < .001 †P = .016
Follicular carcinoma	368 (19.0)	66 (26.8)* P = 0.004	54 (24.4)	12 (48.0)* P < .001 †P = .012
Medullary carcinoma	23 (1.2)	2 (0.8)	2 (0.9)	0 (0)

* P < .05 vs. group A; † P < .05 vs. group B

rate of malignancy (OR: 1.97; 95% CI 1.18–3.29; $P = .009$).

Age-corrected multivariate analysis showed that malignancy remained statistically greater in group B + C in comparison with group A (OR 3.03; 95% CI 2.49–3.69; $P < .001$), and in group B (OR 2.92; 95% CI 2.39–3.56; $P < .001$) and C (OR 6.12; 95% CI 3.64–10.30; $P < .001$), separately. The age-corrected rate of malignancy also remained significantly higher in group C than B (OR 1.84; 95% CI 1.08–3.15; $P = .026$).

Among the 2,181 malignancies, 1,722 (79.0%) were papillary carcinoma, 434 (19.9%) were follicular carcinoma, and 25 (1.1%) were medullary carcinoma (Table 3). Group B + C had significantly less papillary carcinoma and significantly more follicular carcinoma than group A. These differences versus A remained statistically significant for group C but not for B. Of the papillary carcinomas, 482 (28.0%) were microcarcinomas; no differences were observed between groups A (429; 27.8%), B (50; 30.3%), and C (3; 23.1%).

One patient died, for an overall mortality rate of 0.005%. Overall postoperative morbidity was 24.3%. Table 4 shows overall morbidity according to histological findings. Malignancy (Fig. 2) was significantly associated with an increased risk of morbidity in all patients (OR 1.46; 95% CI 1.33–1.61; $P < .001$), and separately, in group A (OR 1.39; 95% CI 1.26–1.55; $P < .001$) and B (OR 1.61; 95% CI 1.18–2.19; $P = .002$), but not in C (OR 1.03; 95% CI 0.38–2.78; $P = .95$).

Overall morbidity was significantly higher in group B + C versus A (35% vs. 23.7%; $P < .001$) and significant increases for B + C versus A were observed for transient and permanent hypocalcemia, transient monolateral and bilateral RLN palsy, permanent monolateral and permanent bilateral RLN palsy, phrenic nerve palsy, seroma/hematoma, and complications classified as other (Table 5). All significant differences between group B + C versus A were also observed for B versus A, with the exception of transient bilateral RLN palsy. Tracheotomy was performed temporarily in 3 transient bilateral nerve palsy, and permanently in two of permanent bilateral RLN palsy. The incidence of seroma/hematoma was significantly more frequent in groups B + C and B versus A.

TABLE 4 Overall morbidity and histological findings

Overall morbidity	Benign	Malignant	*P* Value
All patients			
No	13383 (76.6%)	1506 (69.1%)	
Yes	4098 (23.4%)	675 (30.9%)	$P < .001$*
Group A			
No	12837 (77.0%)	1366 (70.6%)	
Yes	3835 (23.0%)	569 (29.4%)	$P < .001$*
Group B			
No	521 (68.1%)	126 (57.0%)	
Yes	244 (31.9%)	95 (43.0%)	$P = .002$*
Group C			
No	25 (56.8%)	14 (56.0%)	
Yes	19 (43.2%)	11 (44.0%)	$P = .95$

OR odds ratio, *CI* confidence interval

* *P* value is statistically significant

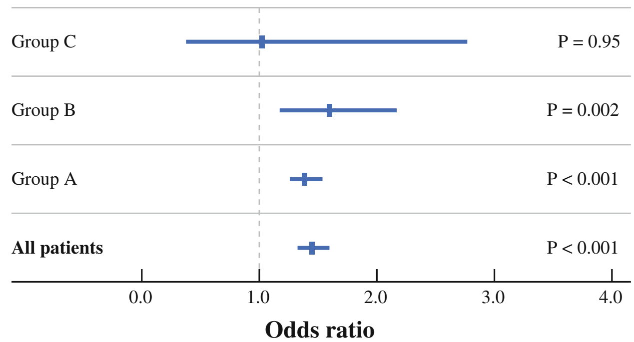

FIG. 2 Odds ratios and 95% confidence intervals for the association between malignancy and overall morbidity in each group. Benign histology was considered as the reference group

DISCUSSION

The retrosternal extent of the goiter has an impact on clinical significance, especially regarding the severity of compressive symptoms, risk of malignancy and postoperative complications.[10,12,20]

In this large series, CMGs showed a prevalence of 5.4%, similar to previous reports.[2,9,10,20] However, no significant difference in gender distribution between cervical goiters and CMGs was detected, contrasting with previous data.[2,9,10,20] Moreover, compared with group A, B and C were significantly older, probably due to the slow enlargement of the mass, and more symptomatic, despite the late appearance of clinical manifestations. Thyrotoxicosis was more common in CMGs than in cervical goiters, most likely because Graves' disease tends to cause larger glands because of constant stimulation, leading to hypertrophy.

A thyroid that extends beyond the thoracic inlet is responsible for the significantly increased frequency of neck mass, dysphagia and superior vena cava syndrome in the CMGs; however, neck mass and dysphagia seem to be clinically relevant when the cervical component predominates over the extracervical one, as in group B. Superior vena cava syndrome is clinically relevant when the veins that drain through the neck become blocked, as in group C. Comparable frequencies of laryngotracheal compression in each group account for the similar frequencies of respiratory symptoms.

TABLE 5 Postoperative morbidity

Complications, *n* (%)	Group A ($n = 18{,}607$)	Group B + C ($n = 1{,}055$)	Group B ($n = 986$)	Group C ($n = 69$)	B + C vs. A OR (95% CI)	B vs. A OR (95% CI)	C vs. A OR (95% CI)	C vs. B OR (95% CI)
Transient hypocalcemia	4,011 (21.6)	357 (33.8)	334 (33.9)	23 (33.3)	1.86 (1.63–2.12) $P < .001$*	1.86 (1.63–2.14) $P < .001$*	1.82 (1.10–3.01) $P = .018$*	0.98 (0.58–1.64) $P = .93$
Permanent hypocalcemia	177 (1.0)	23 (2.2)	21 (2.1)	2 (2.9)	2.32 (1.50–3.60) $P < .001$*	2.27 (1.43–3.58) $P < .001$*	3.11 (0.76–12.78) $P = .098$	1.37 (0.31–5.97) $P = .67$
Transient monolateral RLN palsy	594 (3.2)	58 (5.5)	53 (5.4)	5 (7.2)	1.76 (1.34–2.33) $P < .001$*	1.72 (1.29–2.30) $P < .001$*	2.37 (0.95–5.91) $P = .056$	1.38 (0.53–3.56) $P = .51$
Permanent monolateral RLN palsy	195 (1)	34 (3.2)	32 (3.2)	2 (2.9)	3.14 (2.17–4.55) $P < .001$*	3.17 (2.17–4.63) $P < .001$*	2.82 (0.69–11.59) $P = .13$	0.89 (0.21–3.79) $P = .87$
Transient bilateral RLN palsy	33 (0.2)	5 (0.5)	4 (0.4)	1 (1.4)	2.68 (1.04–6.88) $P = .033$	2.29 (0.81–6.48) $P = .11$	8.28 (1.12–61.39) $P = .013$	3.61 (0.40–32.75) $P = .22$
Permanent bilateral RLN palsy	1 (0.05)	1 (0.1)	1 (0.1)	0 (0)	17.65 (1.10–282.43) $P = .005$*	18.89 (1.18–302.23) $P = .004$*	NA $P = .95$	NA $P = .79$
Phrenic nerve palsy	0 (0)	1 (0.1)	0 (0)	1 (1.4)	NA $P < .001$*	NA	NA $P < .001$*	NA $P < .001$*
Seroma/hematoma	179 (1)	20 (1.9)	19 (1.9)	1 (1.4)	1.99 (1.25–3.17) $P = .003$*	2.02 (1.26–3.26) $P = .003$*	1.51 (0.21–10.96) $P = .68$	0.75 (0.10–5.68) $P = .78$
Wound infection	93 (0.5)	4 (0.4)	4 (0.4)	0 (0)	0.76 (0.28–2.07) $P = .59$	0.81 (0.30–2.21) $P = .68$	NA $P = .56$	NA $P = .60$
Other	2 (0.01)	3 (0.3)	2 (0.2)	1 (1.4)	26.53 (4.43–158.94) $P < .001$*	18.91 (2.66–134.37) $P < .001$*	136.8 (12.26–1526.62) $P < .001$*	7.24 (0.65–80.80) $P = .06$
Nil	14,203 (76.3)	686 (65.0)	647 (65.6)	39 (56.5)	0.58 (0.51–0.66) $P < .001$*	0.59 (0.52–0.68) $P < .001$*	0.40 (0.25–0.65) $P < .001$*	0.68 (0.42–1.12) $P = .13$

OR odds ratio, *CI* confidence interval, *NA* not applicable, *RLN* recurrent laryngeal nerve

* *P* value is statistically significant

In our series, 6.5% of CMG patients required a split-sternal approach. This incidence is slightly different from previous literature data (<5%), but confirms that the cervical approach is feasible in most cases.[4,14,20,29,30,47,48] Furthermore, in the small reported series, externalization of the mass was performed using Fogarty or Foley catheters too.[49,50] However, operation time, duration of drainage and length of hospitalization significantly increased in CMGs compared with the control group, and especially in group C, probably due to difficulties associated with the surgical technique in these patients.

Literature data are discordant regarding the increased incidence of malignancy in cases of substernal goiter relative to cervical goiters. Some authors have reported a range from 18–22%.[8,10,19,30,33,51,52] Others have reported that malignancy is less common in CMGs than in cervical goiters.[14,18,20,29,53] In our series, the association of malignancy with thyroid disease was significantly higher in the CMGs (group B + C; 23.3%) versus the control group (10.4%) and in the sternal-split group (36.2%) compared with group B (22.4%), also when an age-corrected multivariate analysis was performed. Although a multivariate analysis adjusting for thyroid size was not feasible, we speculate that these data may be explained by the increased likelihood of time-related neoplastic transformation in tandem with slow enlargement of the mass. In addition, the inability to perform a fine-needle aspiration biopsy in the presence of mediastinal disease, because of the risks of bleeding or thoracic-organ damage, limits the preoperative diagnosis of malignancy. Therefore, in accordance with other groups, when a CMG was diagnosed, we consider the indication to TT mandatory.[8,19,27,51]

Hypoparathyroidism and RLN palsy remain the most common postoperative complications after TT. The reported incidence of transient hypocalcemia ranges 0.6–83%.[23–25,54] Permanent hypoparathyroidism shows an incidence of 0–32%, but it is debilitating, severe, and potentially lethal.[23,55–60] Regarding transient RLN palsy, an incidence of 0.5–18% has been reported after extracapsular thyroidectomy.[22,55,61–63] Permanent RLN palsy occurs less frequently (0–4%).[22,55,61–63] Similar to previous series, the present study observed an overall morbidity of 24%.[9,18,19,42,64] Moreover, comparison with the control group demonstrated a higher overall morbidity in the CMGs, whereas the difference in global outcome between the split-sternal group and group B was not statistically significant. This study also shows a significantly higher risk of morbidity for malignancy compared with benign status.

The literature shows an increased incidence of permanent hypoparathyroidism and definitive RLN palsy after TT for CMG, rather than for cervical goiter.[5,13,14,17–19,32,33,39,42,64–67] Our results specifically demonstrate that CMGs were significantly associated with transient and permanent hypocalcemia, transient and permanent monolateral RLN palsy, and transient and permanent bilateral recurrent palsy.

Compared with control subjects, a relevant statistical association with postoperative transient and permanent hypoparathyroidism, transient and permanent monolateral, and permanent bilateral RLN palsies were detected in CMGs treated using the cervical approach. In the sternal-split group, however, a similar association was only found regarding transient hypoparathyroidism and transient bilateral RLN palsy.

Some authors suggest the use of the recurrent nerve monitor, especially in the presence of a large goiter.[68,69] In our experience, the use of loupe magnification and parathyroid autotransplantation during thyroid surgery showed a significant improvement of results, with faster and safer identification of the nerve, and decreasing permanent and transient hypoparathyroidism.[23,44]

Postoperative hemorrhage is rare but potentially fatal, occurring in 0.3–2% of literature cases.[24,39,43,70,71] Confirming the reported literature range, our series showed a significant association of hematoma with CMG surgery, particularly in group B. Intraoperative bleeding complicates the surgical dissection, staining and obscuring important structures, and causing indirect morbidity related to RLNs and parathyroids due to blind surgical maneuvers.[43] Therefore, innovative devices, such as the harmonic scalpel and topical hemostatic, are popular.[43,72–79] Specifically, the use of ultrasonic dissectors in thyroid surgery has proved valuable for preventing bleeding, reducing internal electrical burns, and reducing operative time, blood loss, and organ injury.[72–77]

Confirming an increased frequency of complications in CMG cases, this study demonstrates improved outcome in CMGs treated with sternal split rather than cervical externalization. The explanation could be that the sternal split provides the control of all the structures of the neck and upper mediastinum to the surgeon. Conversely, during digital dissection of the mediastinal component, removal of the intrathoracic part of the goiter through the cervical access forces the surgeon to perform blind maneuvers, placing the inferior parathyroids and the RLNs at risk of injury. Consequently, stringent preoperative diagnosis through correct imaging is important, to avoid hazardous digital dissection, and simultaneously, improper sternal split. Magnetic resonance imaging and more recently multidetector computed tomographic scanning may provide better anatomical assessment.[20,33,80–85]

When the upper mediastinum is occupied by a goiter, it could be considered a no-man's land. Indeed, the endocrine surgeon is not usually familiar with the course of the RLNs and their anatomical variability in this district, and the cardiothoracic surgeon is not familiar with the endocrinosurgical challenges. Therefore, the extracervical approach requires multidisciplinary collaboration.

In conclusion, when a mediastinal extension of the thyroid goiter appears, overall morbidity increases, as do clinical manifestations, malignancy, postoperative hypoparathyroidism, RLN palsy, and hemorrhage. In the presence of a large cervicomediastinal mass, extracervical access by sternal split with a multidisciplinary approach should be considered. Finally, assessment and surgical treatment of CMGs should be performed in specialized high-volume centers.

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REFERENCES

1. Haller A. Disputationes anatomicae selectae. Gottingen, Holland: Vandenhoeck, 1749:96.
2. Huins CT, Georgalas C, Mehrzad H, Tolley NS. A new classification system for retrosternal goitre based on a systematic review of its complications and management. *Int J Surg.* 2008;6:71–6.
3. Cougard P, Matet P, Goudet P, et al. Les goitre plongeants: 218 cas operas. *Ann Endocrinol (Paris).* 1992;53:230–5.
4. Vadasz P, Kotsis L. Surgical aspects of 175 mediastinal goiters. *Eur J Cardiothorac Surg.* 1998; 14:393–7.
5. Chow TL, Chan TT, Suen DT, Chu DW, Lam SH. Surgical management of substernal goitre: local experience. *Hong Kong Med J.* 2005;11:360–5.
6. deSouza FM, Smith PE. Retrosternal goiter. J Otolaryngol. 1983;12:393–6.
7. Goldenberg IS, Lindskog GE. Differential diagnosis, pathology, and treatment of substernal goiter. *JAMA.* 1957;163:527–9.
8. Sanders LE, Rossi RL, Shahian DM, Williamson WA. Mediastinal goiters: the need for an aggressive approach. *Arch Surg.* 1992;127:609–13.
9. Katlic MR, Wang C, Grillo HC. Substernal goiter. J Otolaryngol. 1992;21:165–70.
10. Pieracci FM, Fahey TJ 3rd. Substernal thyroidectomy is associated with increased morbidity and mortality as compared with conventional cervical thyroidectomy. *J Am Coll Surg.* 2007;205:1–7.
11. Singh B, Lucente FE, Shaha AR. Substernal goiter: a clinical review. *Am J Otolaryngol.* 1994;15:409–16.
12. Shen WT, Kebebew E, Duh QY, Clark OH. Predictors of airway complications after thyroidectomy for substernal goiters. *Arch Surg.* 2004;138:656–60.
13. Ozdemir A, Hasbahceci M, Hamaloglu E, Oznec A. Surgical treatment of substernal goiter. *Int Surg.* 2000;85:194–7.
14. Hedayati N, McHenry C. The clinical presentation and operative management of nodular and diffuse substernal thyroid disease. *Am Surg.* 2002;68:245–51.
15. Rodriguez JM, Hernandez Q, Pinero A, et al. Substernal goiter: clinical experience of 72 cases. *Ann Otol Rhinol Laryngol.* 1999;108:501–4.
16. Moran JC, Singer JA, Sardi A. Retrosternal goiter: a six-year institutional review. *Am Surg.* 1998;64:889–93.
17. Erbil Y, Bozbora A, Barbaros U, Ozarmagan S, Azezli A, Molvalilar S. Surgical management of substernal goiters: clinical experience of 170 cases. *Surg Today.* 2004;34:732–6.
18. Chauhan A, Serpell JW. Thyroidectomy is safe and effective for retrosternal goitre. *ANZ J Surg.* 2006;76:238–42.
19. Netterville JL, Coleman SC, Smith JC, Smith MM, Day TA, Burkey BB. Management of substernal goiter. *Laryngoscope.* 1998;108:1611–7.
20. White ML, Doherty GM, Gauger PG. Evidence-based surgical management of substernal goiter. *World J Surg.* 2008;32:1285–300.
21. Hall TS, Caslowitz P, Propoper C, Smith GW. Substernal goiter versus intrathoracic aberrant thyroid: a critical difference. *Ann Thorac Surg.* 1988;46:684–6.
22. Sancho JJ, Pascual-Damieta M, Pereira JA, Carrera MJ, Fontané J, Sitges-Serra A. Risk factors for transient vocal cord palsy after thyroidectomy. *Br J Surg.* 2008;95:961–7.
23. Testini M, Rosato L, Avenia N, et al. The impact of single parathyroid gland autotransplantation during thyroid surgery on postoperative hypoparathyroidism: a multicenter study. *Transplant Proc.* 2007;39:225–30.
24. Thompson NW, Reeve T. Complications of thyroid surgery: how to avoid them, how to manage them, and observation on their possible effect on the whole patient. *World J Surg.* 2000;24:971–5.
25. Al-Suliman NN, Ryttov NF, Qvist N, Blichert-Toft M, Graversen HP. Experience in a specialist thyroid surgery unit: a demographic study, surgical complications and outcome. *Eur J Surg.* 1997;163:13–20.
26. Maruotti RA, Zannini P, Viani MP, Voci C, Pezzuoli G. Surgical treatment of substernal goiters. *Int Surg.* 1991;76:12–7.
27. Madjar S, Weissberg D. Retrosternal goiter. *Chest.* 1995;108:78–82.
28. Monchik JM, Materazzi G. The necessity for a thoracic approach in thyroid surgery. *Arch Surg.* 2000;135:467–71.
29. Hsu B, Reeve TS, Guinea AI, Robinson B, Delbridge L. Recurrent substernal nodular goiter: incidence and management. *Surgery.* 1996;120:1072–5.
30. Hashmi SM, Premachandra DJ, Bennet AM, Parry W. Management of retrosternal goitres: results of early surgical intervention to prevent airway morbidity, and a review of the English literature. *J Laryngol Otol.* 2006;120:644–9.
31. de Perrot M, Fadel E, Mercier O, et al. Surgical management of mediastinal goiters: when is a sternotomy required? *Thorac Cardiovasc Surg.* 2007;55:39–43.
32. Grainger J, Saravanappa N, D'Souza A, Wilcock D, Wilson PS. The surgical approach to retrosternal goiters: the role of computerized tomography. *Otolaryngol Head Neck Surg.* 2005;132:849–51.
33. Testini M, Nacchiero M, Miniello S, et al. Management of retrosternal goiters: experience of a surgical unit. *Int Surg.* 2005;90:61–5.
34. Burns P, Doody J, Timon C. Sternotomy for substernal goitre: an otolaryngologist's perspective. *J Laryngol Otol.* 2007;11:1–5.
35. Page C, Strunski V. Cervicothoracic goiter: an anatomical or radiological definition? Report of 223 surgical cases. *J Laryngol Otol.* 2007;121:1083–7.
36. Ahmed ME, Ahmed EO, Mahadi SI. Retrosternal goiter: the need for median sternotomy. *World J Surg.* 2006;30:1945–8.
37. Sancho JJ, Kraimps JL, Sanchez-Blanco JM, et al. Increased mortality and morbidity associated with thyroidectomy for intrathoracic goiters reaching the carina tracheae. *Arch Surg.* 2006:141:82–5.
38. Thompson NW, Olsen WR, Hoffman GL. The continuing development of the technique of thyroidectomy. *Surgery.* 1973;73:913.
39. Zambudio AR, Rodriguez J, Riquelme J, Soria T, Canteras M, Parrilla P. Prospective study of postoperative complications after total thyroidectomy for multinodular goiters by surgeons with experience in endocrine surgery. *Ann Surg.* 2004; 240:18–25.

40. Bhattacharyya N, Fried MP. Assessment of the morbidity and complications of total thyroidectomy. *Arch Otolaryngol Head Neck Surg.* 2002;128:389–92.
41. McHenry CR, Piotrowski JJ. Thyroidectomy in patients with marked thyroid enlargement: airway management, morbidity, and outcome. *Am Surg.* 1994;60:586–91.
42. Arici C, Dertsiz L, Altunbaş H, Demircan A, Emek K. Operative management of substernal goiter: analysis of 52 patients. *Int Surg.* 2001;86:220–4.
43. Testini M, Marzaioli R, Lissidini G, et al. The effectiveness of FloSeal® matrix hemostatic agent in thyroid surgery: a prospective, randomized, control study. *Langenbecks Arch Surg.* 2009;394:837–42.
44. Testini M, Nacchiero M, Piccinni G, et al. Total thyroidectomy is improved by loupe magnification. *Microsurgery.* 2004;24:39–42.
45. Armitage P, Berry G. Statistical methods in medical research. 3rd ed. Oxford: Blackwell Science; 1994.
46. Dawson B, Trapp RG. Basic and clinical biostatistics. 3rd ed. New York: McGraw-Hill; 2001.
47. Armour RH. Retrosternal goitre. *Br J Surg.* 2000;87:519.
48. Young AE. Retrosternal goitre: a wider view. *Br J Surg.* 1997;84:1170.
49. Testini M, Piccinni G, Lissidini G, Nacchiero M. The lifting of substernal goitres using a Fogarty catheter. *Ann R Coll Surg Engl.* 2005;87:63–4.
50. Pandya S, Sanders LE. Use of a Foley catheter in the removal of a substernal goiter. *Am J Surg.* 1998;175:155–7.
51. Allo MD, Thompson NW. Rationale for the operative management of substernal goiters. *Surgery.* 1983;94:969–77.
52. Saha SP, Rogers AG, Early GF, Nachbauer C, Baker M. Surgical management of intrathoracic goiter. *J Ky Med Assoc.* 1997;95:421–3.
53. Rios A, Rodriguez JM, Balsalobre MD, Torregrosa NM, Tebar FJ, Parrilla P. Results of surgery for toxic multinodular goiter. *Surg Today.* 2005;35:901–6.
54. Thomusch O, Machens A, Sekulla C, et al. Multivariate analysis of risk factors for postoperative complications in benign goiter surgery: prospective multicenter study in Germany. *World J Surg.* 2000;24:1335–41.
55. Liu Q, Djuricin G, Prinz RA. Total thyroidectomy for benign thyroid disease. *Surgery.* 1998;123:2–7.
56. Zedenius J, Wadstrom C, Delbridge LW. Routine autotransplantation of at least one parathyroid gland during total thyroidectomy may reduce permanent hypoparathyroidism to zero. *Aust N Z J Surg.* 1999;69:794–9.
57. Gauger PG, Reeve TS, Wilkinson M, Delbridge LW. Routine parathyroid autotransplantation during total thyroidectomy: the influence of technique. *Eur J Surg.* 2000;166:605–9.
58. Harness JK, Fung L, Thompson NW, Burney RE, McLeod MK. Total thyroidectomy: complications and technique. *World J Surg.* 1986;10:781–6.
59. de Roy van Zuidewijin DB, Songun I, Kievit J, van de Velde CJ. Complications of thyroid surgery. *Ann Surg Oncol.* 1995;2:56–60.
60. Wingert DJ, Frisen SR, Lliopoulos JI, Pierce GE, Thomas JH, Hermreck AS. Post-thyroidectomy hypocalcemia. Incidence and risk factors. *Am J Surg.* 1986;152:606–10.
61. Moalem J, Suh I, Duh QY. Treatment and prevention of recurrence of multinodular goiter: An evidence-based review of the literature. *World J Surg.* 2008;32:1301–12.
62. Muller PE, Jakoby R, Heinert G, Spelsberg F. Surgery for recurrent goitre: its complications and their risk factors. *Eur J Surg.* 2001;167:816–21.
63. Erbil Y, Bozbora A, Yanik BT, Ozbey N, Salmaslioglu A, Ozarmagan S. Predictive factors for recurrent non-toxic goitre in an endemic region. *J Laryngol Otol.* 2007;121:231–6.
64. Deviditis RA, Guimãraes AV, Machado PC, Suehara AN, Noda E. Surgical treatment of the substernal goitre. *Int Surg.* 1999;84:190–2.
65. Wilson RB, Erskine C, Crowe PJ. Hypomagnesemia after thyroidectomy: prospective study. *World J Surg.* 2000;24:722–6.
66. Shemen L, Ko W. Current technique for resection of mediastinal goiter. *Ear Nose Throat J.* 2006;85:609–11.
67. Ben Nun A, Soudack M, Best L-A. Retrosternal thyroid goiter: 15 years experience. *Isr Med Assoc J.* 2006;8:106–9.
68. Donnellan KA, Pitman KT, Cannon CR, Replogle WH, Simmons JD. Intraoperative laryngeal nerve monitoring during thyroidectomy. *Arch Otolaryngol Head Neck Surg.* 2009;135:1196–8.
69. Terris DJ, Anderson SK, Watts TL, Chin E. Laryngeal nerve monitoring and minimally invasive thyroid surgery: complementary technologies. *Arch Otolaryngol Head Neck Surg.* 2007;133:1254–7.
70. Rosato L, Avenia N, Bernante P, et al. Complications of thyroid surgery: analysis of a multicentric study on 14,934 patients operated on in Italy over 5 years. *World J Surg.* 2004;28:271–6.
71. Burkey SH, van Heerden JA, Thompson GB, Grant CS, Scleck CD, Farley DR. Reexploration for symptomatic hematomas after cervical exploration. *Surgery.* 2001;130:914–20.
72. Defechereux T, Rinken F, Maweja S, Hamoir E, Meurisse M. Evaluation of the ultrasonic dissector in thyroid surgery. A prospective randomised study. *Acta Chir Belg.* 2003;103:274–7.
73. Meurisse M, Defechereux T, Maweja S, Degaugue C, Vandelaer M, Hamoir E. Evaluation of Ultracision ultrasonic dissector in thyroid surgery. Prospective randomized study. *Ann Chir.* 2000;125:468–72.
74. Ortega J, Sala C, Flor B, Lledo S. Efficacy and cost-effectiveness of the UltraCision harmonic scalpel in thyroid surgery: an analysis of 200 cases in a randomized trial. *J Laparoendosc Adv Surg Tech A.* 2004;14:9–12.
75. Siperstein AE, Berber E, Morkoyun E. The use of the harmonic scalpel vs. conventional knot tying for vessel ligation in thyroid surgery. *Arch Surg.* 2002;137:137–42.
76. Kilic M, Keskek M, Ertan T, Yoldas O, Bilgin A, Koc M. A prospective randomized trial comparing the harmonic scalpel with conventional knot tying in thyroidectomy. *Adv Ther.* 2007;24:632–8.
77. Shemen L. Thyroidectomy using the harmonic scalpel. Analysis of 105 consecutive cases. *Otolaryngol Head Neck Surg.* 2002;127:284–8.
78. Oz MC, Cosgrove DM 3rd, Badduke BR, et al. Controlled clinical trial of a novel hemostatic agent in cardiac surgery. *Ann Thorac Surg.* 2000;69:1376–82.
79. Weaver FA, Hood DB, Zatina M, Messina L, Badduke B. Gelatin-thrombin-based hemostatic sealant for intraoperative bleeding in vascular surgery. *Ann Vasc Surg.* 2002;16:286–93.
80. Shah PJ, Bright T, Singh SS, et al. Large retrosternal goitre: a diagnostic and management dilemma. *Heart Lung Circ.* 2006;15:151–2.
81. Buckley JA, Stark P. Intrathoracic mediastinal thyroid goiter: imaging manifestation. *Am J Roentgenol.* 1999;173:471–5.
82. Nakahara H, Noguchi S, Muratami N, et al. Gadolinium-enhanced MR imaging of thyroid and parathyroid masses. *Radiology.* 1997;202:765–72.
83. Tezuka M, Murata Y, Ishida R, Ohashi I, Hirata Y, Shibuya H. MR imaging of the thyroid: correlation between apparent diffusion coefficient and thyroid gland scintigraphy. *J Magn Reson Imaging.* 2003;17:163–9.
84. Cooper JC, Nakielny R, Talbot CH. The use of computed tomography in the evaluation of large multinodular goitres. *Ann R Coll Surg Engl.* 1991;73:32–5.
85. Brown LR, Aughenbaugh GL. Masses of the anterior mediastinum: CT and MR imaging. *Am J Roentgenol.* 1991;157:1171–80.