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The value of total thyroidectomy as the definitive treatment for Graves' disease: A single centre experience of 594 cases

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ABSTRACT

Purpose: Thyroidectomy is the preferred approach as the definitive treatment for Graves' disease. The outcomes for total thyroidectomy in a large series of 594 patients, who were observed in the last decade, will be presented in this study.

Methods: The study concerned a retrospective review of 594 patients, undergoing a total thyroidectomy for Graves' disease. The incidence of complications and outcomes on hyperthyroidism and correlated symptoms resolution were also evaluated.

Results: The mean age of the patients was of 44.7 ± 12.7 years and 456 patients (76.7%) were females. The mean gland weight was 67.3 ± 10.8 g (range: 20–350 g) and, in 397 patients (66.8%), the gland weighed > 40 g. The mean operative time was 125 ± 23.1 min (range: 65–212 min). Temporary and permanent hypocalcaemia developed in 241 (40.6%) and 3 patients (0.5%), respectively. Temporary and permanent recurrent laryngeal nerve palsy were recorded in 31 (5.2%) and 1 patients (0.16%) respectively. No patient developed a thyroid storm. On multivariate analysis, patient age ≤50 years (Odds ratio: 1; 95% Confidence Interval: 0.843–0.901) and thyroid weight > 40 g (Odds ratio: 1; 95%, Confidence Interval: 0.852–0.974), were mainly associated with the occurrence of complications.

Conclusion: This high-volume surgeon experience demonstrates that total thyroidectomy is a safe and effective treatment for Graves' disease. It is associated with a very low incidence rate of post-operative complications, most of which are transitory; therefore, it offers a rapid and definitive control of hyperthyroidism and its related symptoms.

Introduction

Graves' disease (GD) is an autoimmune disorder of the thyroid gland in which thyrotropin receptor antibodies (TRAb) stimulate thyroid stimulating hormone receptors (TSH-R), thereby increasing thyroid hormone production and release.

GD is the most common cause of hyperthyroidism, representing the underlying aetiology of 50–80% of hyperthyroidism cases. Options for the treatment of GD include: anti-thyroid drugs (ATDs), used to normalize thyroid hormone production, the destruction of the thyroid using radioactive iodine (RAI), and the surgical removal of the thyroid through total or near total thyroidectomy. ATDs generally represent the first-line treatment for normalizing serum hormone levels. Remission rates in patients treated with ATDs range from 14% to 80% [1]. The duration of the treatment varies from 12 to 18 months, although the remission rate does not improve after > 8 months of therapy. Furthermore, a relapse in hyperthyroidism can occur within 3–6 months after therapy has been suspended [2,3].

The use of RAI, in obtaining definitive hypothyroidism after the failure of anti-thyroid drugs, is currently the treatment of choice in some countries, particularly in the United States. The incidence of persistent hyperthyroidism after RAI ranges from 5% to 25% of cases, whereas definitive hypothyroidism may occur in approximately 40% of patients by 8 weeks and in ca. 80% of patients by 16 weeks [4–6]. Moreover, a relevant complication of RAI is the potential risk of an exacerbating Graves' ophtalmopathy (GO) in 15% to 20% of patients [2,7].

Thyroidectomy was for a long time the main definitive treatment for GD, at least until ATDs and RAI were developed in the 1940s–1950 s. Since then, particularly in the United States, RAI and ATDs were indeed preferred to surgery for the treatment of GD. However, recent data have indicated a return of thyroidectomy as the main, definitive treatment

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for GD and even in some US centres with low income patients [8,9], total thyroidectomy (TT) seems to be the most cost-effective therapy to definitively treat GD [10]. It also insures a risk of recurrent hyperthyroidism in nearly 0% in patients, who have been treated with near-total or total thyroidectomy with minimal, concomitant complications.

This study will present the experience of total thyroidectomy as a definitive treatment of GD, also evaluating the incidence of complications, the outcomes on hyperthyroidism and correlated symptom resolution.

Materials and methods

After approval by the institutional review board at the Department of Surgical Oncological and Oral Sciences (University of Palermo), a retrospective analysis of the medical records of a large series of 594 patients was conducted. All adult patients undergoing TT with a preoperative diagnosis of GD from 2008 to 2018, were eligible for inclusion in the study. The primary outcome of interest was evaluating the incidence of any complications occurring during TT and within the first six months after TT, whereas the second outcome was the evaluation of the incidence rate of hyperthyroidism after TT.

The mean age of the patients was 44.7 ± 12.7 years: 138 (23.2%) patients were males and 456 (76.7%) were females. The majority of patients were euthyroid or mildly hyperthyroid at the time of thyroidectomy. A history of GO was present in 196 patients (32,9%) and, in most cases, in progression. The patients' characteristics are reported in Table 1.

The preoperative diagnosis of GD was based on presentation of clinical signs and symptoms of hyperthyroidism, thyroid hormones (free-T3, free-T4, TSH), and value of TRAb (increase above 1.0 IU/L). A fiberoptic videolaryngoscopy was always performed in order to observe preoperatively vocal cord motility.

All patients received a preoperative, pharmacologic treatment with ATDs to achieve euthyroidism. Specifically, 446 patients (75.1%) received methimazole and 148 patients (24.9%) received propylthiouracil, 24 of these as they had developed an intolerance to methimazole. A beta-adrenergic antagonist were used in 432 patients (72.7%). Moreover, allergies and intolerances to the ATDs appeared in 71 patients (11.9%). Lugol's iodine solution, used to reduce the risk of intraoperative blood loss, was not routinely used, being administered only to 152 patients (25.6%) with a dose of 10 drops, 3 times daily for 10–12 days prior to thyroidectomy. No patient had previously undergone thyroid RAI ablation.

Table 1
Characteristics of 594 patients.

Characteristic	n (%)
Age, yrs, mean	44.7 ± 12.7
Sex	
Male	138 (23.2)
Female	456 (76.7)
BMI status	
Underweight	31 (5.2)
Normal weight	292 (40.7)
Overweight	86 (14.5)
Obese*	185 (31.1)
Smokers	251 (42.2)
Graves' Ophtalmopathy	196 (32.9)
Preoperative medications	
Methimazole	446 (75)
Propylthiouracil	148 (24.9)
Beta-adrenergic antagonist	432 (72.2)
Lugol iodine	152 (25.6)
Thyroid hormone status	
Euthyroid	409 (69.8)
Hypothyroid	35 (5.9)
Mildly hyperthyroid	119 (20.1)
Moderately hyperthyroid	31 (5.2)
Follow-up, months, median, rage	16.7 (0–118)

* Obesity defined as BMI > 30Kg/m^2.

The indications for surgery were discussed and established with the referring endocrinologist for every patient. The main indications for TT were: the persistence or recurrence of hyperthyroidism after the withdrawal of ATDs, the onset and/or the worsening of local compressive symptoms, the patient's preference in generally acquiring rapid control of the symptoms, the progression of GO, and the development of allergy or intolerance to ATDs. In no case did the indication for thyroidectomy depended on the presence of thyroid nodules which were suspicious of malignancy at cytology and on the failure of a precedent RAI ablation.

TT was the surgical procedure of choice for all patients under consideration in this study, and it was always performed by the same surgical team. The most important principles used in performing thyroidectomy were: 1) the visualization of the recurrent laryngeal nerves and the parathyroid glands bilaterally; 2) an attempt to identify the external branch of the superior laryngeal nerve before ligation of the superior thyroid vessels; 3) the selective and individual ligation of the superior thyroid vessel; and 4) the ligation of the branches of the inferior thyroid artery on the thyroid gland capsule to preserve the bloody supply to the parathyroid glands.

Total thyroidectomies were always performed by the same surgeons' team. Each surgeon had an over 10-years of experience in thyroid surgery and used to perform, on average, > 50 interventions per year. In all patients considered in this study, TT was performed using traditional haemostatic methods of knot-tying and bipolar electrocoagulation. Almost the operations were performed without the aid of neural monitoring, which was used only in a very few cases operated during the last two-years period.

Operative site drainage was placed in all patients and removed the day after the operation. The patients were observed for a further 24 h after drainage removal and discharged in the second postoperative day unless a complication developed, resulting in a prolonged hospitalization.

Calcium serum levels were routinely checked on the second postoperative day, and hypocalcaemia was defined as a serum calcium level of < 8.4 mg/dL. A calcium supplementation of elemental calcium was administered *per os* from 1 g to 4 g daily, depending of the calcium shortage; calcitriol was added when calcium levels were < 7.5 mg/dL. Calcium serum levels were rechecked two weeks after the thyroidectomy and then every two weeks in those patients who developed postoperative hypocalcaemia. These patients were treated with calcium supplementation until normalization of the calcium serum levels [11].

After thyroidectomy, all patients commenced hormonal replacement therapy with L-Thyroxin; free-T4, and TSH levels were initially checked thirty days after the thyroidectomy. In defining euthyroidism in the early period of treatment, only the normalization of the free-T4 serum level was considered; subsequently, euthyroidism was defined as a normal TSH and free-T4 levels.

The main purpose of this study is to evaluate the incidence of postoperative complications occurring during and after TT; the results on relapses of hyperthyroidism and GO were also evaluated. Postoperative complications included: transient hypocalcaemia and permanent hypoparathyroidism, a transient and permanent recurrent laryngeal nerve (RLN) injury, and a neck hematoma requiring an emergency surgical re-exploration. Transient hypocalcaemia was defined as having a serum calcium level less than the reference range (associated or not with hypocalcaemic symptoms), requiring a replacement therapy and resolved within 12 months after thyroidectomy; permanent hypoparathyroidism was defined as a hypocalcaemia with low PTH serum levels (< 15 pg/mL), persistent beyond 12 months after thyroidectomy. RLN injuries were evaluated by means of fiberoptic videolaryngoscopy in those patients who complained of voice disorders within 48 h after thyroidectomy. A definitive injury of RLN was defined

Table 2
Indications for total thyroidectomy.

Characteristic	n (%)
Recurrent or persistent hyperthyroidism (Failure of ATDs)	269 (45.3%)
Patient preference	215 (36.2%)
Local compressive symptoms	183 (30.8%)
Progression of GO	87 (14.6%)
Allergy to ATDs	71 (11.9%)
Desire for a pregnancy	14 (2.3%)
Failure of RAI	0

Total indications = 83. There was more than one cause for indications for thyroidectomy in many patients.

as the paralysis of one or both of the vocal cords at fiberoptic videolaryngoscopy, persisting beyond six months after thyroidectomy.

Risk factors for complications were compared with bivariate and multivariate analyses. The statistical significance was determined by using the X^2 test. According to the authors' opinion on covariate of clinical relevance, a multivariate analysis using logistic regression model was performed. Values were considered statistically significant when $p < 0.05$.

Results

A total of 594 patients underwent TT for GD at the Department of Surgical, Oncological and Oral Sciences (University of Palermo) from 2008 to 2018. The most frequent indications for TT are summarized in Table 2. In many cases more than one reason determined indications for thyroidectomy.

Mean gland weight, evaluated at histopathological examination on a formalin-fixed surgical specimen, was 67.3 ± 10.8 g (range 20–350 g); in 397 patients (66.8%) the gland weighed > 40 g. A papillary thyroid carcinoma was identified in 42 (7.1%) patients at histopathological examination. In 28 cases the carcinoma was a microcarcinoma, measuring ≤5 mm maximum diameter, in 9 cases the diameter of the carcinoma was < 1 cm, and in only in 5 cases the nodules exceeded 1 cm maximum diameter.

The mean operative time was 125 ± 23.1 min (range 65–212 min), and in 131 cases (22.1%) it was longer than 180 min. RLNs and parathyroid glands were routinely searched. In 46 patients (7.7%) accidentally excised parathyroid tissue was found at histopathological examination while in 72 cases (12.1%) a parathyroid auto-transplantation was performed.

The surgical drainage was always removed within 24 h after surgery. The majority of patients (428 patients, 72.1%) were discharged within 48 h after thyroidectomy; the duration of hospitalisation for the remaining cases was between 4 and 9 days. In only 3 cases (0.5%) an emergency reoperation was required due to a postoperative hematoma.

A total of 290 distinct complications occurred in 261 patients (43.8%). Vocal disorders were recorded in 32 (5.4%) patients for whom a unilateral RLN paralysis was documented at post-operative fiberoptic videolaryngoscopy. In 31 cases (5.2%) this paralysis was a transient palsy, which was resolved between 4 and 12 weeks after thyroidectomy. Only in one patient (0.16%) the paralysis was definitive, persisting as dysphonia over six months after operating. No cases of bilateral nerve injuries were recorded.

Postoperative hypocalcaemia, defined on the basis of the above-mentioned parameters, appeared in 244 patients. In 241 cases (40.6%) this was transient hypocalcaemia, resolved with a calcium replacement within 8–12 weeks after surgery in > 200 cases; only a few cases resolved hypocalcaemia within 12 months after surgery. Hypocalcaemia persisted in 3 patients (0.5%) 12 months after thyroidectomy with a PTH serum level below the normal limits. Finally, 11 patients (1.8%) developed a seroma, which required one or more percutaneous drainages on postoperative examination. No patient developed a tracheal injury or a perioperatively thyroid storm, and no patient had neurological, hypertensive or cardiovascular complications (Table 3).

Table 3
Complications after total thyroidectomy.

Complication	n (%)
Patients presented complications	261 (43.8)
Post operative hypocalcemia	
Transient	241 (40.6)
Persistent	3 (0.5)
Unilateral RLN palsy	
Transient	31 (5.2)
Persistent	1 (0.16)
Bilateral RLN palsy	0
Postoperative hematoma	3 (0.5)
Seroma	11 (1.8)

Table 4
Bivariate analysis of risk factors for any complication after thyroidectomy.

Risk factor	No complications (333 patients) n (%)	Any complications (261 patients) n (%)	*P value*
Age			
< 50 yrs	175 (52.5)	186 (71.2)	0.006
> 50 yrs	140 (42.1)	93 (35.6)	
Sex			
Male	67 (20.1)	71 (27.2)	0.330
Female	242 (72.7)	214 (81.9)	
Smoking history			
Smokers	153 (45.9)	98 (37.5)	0.04
Nonsmokers	180 (54.1)	163 (62.5)	
Obesity*			
BMI > 30 Kg/m^2	88 (26.4)	97 (37.2)	0.005
BMI ≤ 30 Kg/m^2	245 (73.6)	164 (62.8)	
Thyroid status at TT			
Hyperthyroid	82 (24.6)	68 (26.1)	
Euthyroid	233 (69.9)	176 (67.4%)	0.669
Hypothyroid	22 (6.6%)	13 (4.9%)	
Operative time			
> 180 min	79 (23.7)	52 (19.9)	0.268
< 180 min	254 (76.3)	209 (80.1)	
Thyroid weight			
> 40 g	201 (60.3)	196 (75.1)	0.0001
< 40 g	132 (39.6%)	65 (24.9)	

* Obesity defined as BMI > 30Kg/m^2.

On bivariate analysis, four risk factors were found to be statistically significant with respect to complications. They were in order of importance: a thyroid weight > 40 g, a BMI ≤ 30 Kg/m^2, age below 50 years and a history of smoking (Table 4). On multivariate regression analysis, a history of smoking became non-significant; age below 50 years became the main risk factor for complications, followed by a BMI ≤ 30 Kg/m^2 and thyroid weight respectively (Table 5).

At a median follow-up of 16.7 months (range 0–118 months), no patients had developed recurrent hyperthyroidism. In all cases, surgical treatment resulted in hypothyroidism, requiring substitution treatment with L-Thyroxin and an improvement in the quality of life. In none of the patients a worsening GO was recorded after thyroidectomy, while in 119 patients (60.7%) a regression of GO was observed.

Discussion

GD is an autoimmune disorder, accompanied by several symptoms due to an excess of circulating thyroid hormones, which can be triggered by environmental factors in genetically predisposed individuals [12]. In several countries, particularly in Europe, the recommended first-line treatment in rendering euthyroid the patient with GD is a

Table 5
Multivariate logistic regression of risk factors for any complication after thyroidectomy.

Risk factor	Odds ratio	95% Confidence Interval	*P value*
Age			
< 50 yrs	1	–	< 0.00001
> 50 yrs	0.871	0.843–0.901	
Smoking history			
Smokers	1	–	0.261
Nonsmokers	1.011	0.992–1.031	
Obesity*			
BMI > 30 Kg/m^2	1	–	0001
BMI ≤ 30 Kg/m^2	1.129	1.050–1.215	
Thyroid weight			
> 40 g	1	–	0.007
< 40 g	0.911	0.852–0.974	

* Obesity defined as BMI > 30Kg/m^2.

course of ATDs lasting for 12–18 months. However, the long-term remission rate does not exceed 40–50% of patients, and it was not improved even after > 8 months of therapy. Therefore, those patients with relapsing hyperthyroidism can be managed either with RAI therapy or surgery.

RAI therapy is a safe and effective treatment, but it is associated with a latency period, which can vary widely from between 4 weeks to 6 months. Although approximately 70% of patients become euthyroid within 4–8 weeks, the administration of ATDs can be used awaiting the beneficial effects of ablation therapy. Moreover, 5–15% of patients require a second administration of RAI [13–15]. Furthermore, the most common adverse effect of RAI therapy is the onset or the worsening of GO, which may develop in 15–33% of patients, particularly smokers [16,17]. In the present study, no patient showed a worsening in GO after thyroidectomy, on the contrary in a large percentage of cases (60.7%) a regression of symptoms was observed.

The role of surgery as a definitive treatment for GD has recently been emphasized, and thyroidectomy versus RAI is recommended in many centers. Surgical treatment has the advantage of correcting thyrotoxicosis more rapidly than RAI, reducing the recurrence rate of hyperthyroidism to approximately 0%, and offering a potential improvement in the development of GO. In a recent retrospective study involving 720 patients, Sundaresh et al. [18] have reported that ATDs had an overall failure rate of 48.3%, compared with 8% for RAI (hazard ratio = 7.6; p < 0.0001), whereas surgery had a 100% success rate. In the present study, all patients became hypothyroid after the surgery and all required substitution treatment with L-Thyroxin. It is also worth noting that, after a long-term follow-up, no cases of recurrent hyerthyroidism were observed.

Several studies have reported that the complication rate of surgery is higher when compared to the administration of RAI. However, these are transient complications in the majority of cases and the most frequent of these is transient hypocalcaemia. Guo et al. [19] have reported that the complications of TT were: hypocalcaemia (32.5% temporary, 2.6% permanent), recurrent laryngeal nerve injury (3.43% temporary, 1.46% permanent), and immediate postoperative bleeding (< 1%). Moreover, surgery can provide effective treatment for coexistent thyroid carcinomas, whose incidence rate ranges from 2% to 17% [20–28]. One papillary thyroid carcinoma was found in this study among 42 patients (7.1% of the cases), although it was a microcarcinoma in > 50% of the cases; a very low number of patients had a tumour > 1 cm.

Regarding the extent of thyroidectomy, TT has gained favour over sub-total thyroidectomy (ST) over recent decades after many studies have demonstrated no difference in complication and permanent hypothyroidism rate. Moreover, the risk of hyperthyroidism recurrence is greater for ST.

In a previous study of ours [29], no difference in terms of the complication rate, when comparing TT versus ST for GD, was observed, while an incidence rate of 16.7% of recurrent hyperthyroidism was detected in patients who had undergone ST versus 0% of those who had undergone TT. This result is consistent with others, which have been reported in various reviews on ST, in which the recurrences rate of hyperthyroidism range from 3% to 15% [30–32]. In a *meta*-analysis regarding 35 studies, comprising 7,241 patients, Palit et al. [33] observed a 7.9% rate of recurrent or persistent hyperthyroidism in patients who had undergone ST, whereas a 0% rate was observed in those who had undergone total and/or near-total thyroidectomy. Moreover, the permanent RLN palsy rate was 0.9% after TT and 0.7% after ST. Remarkably, permanent hypo-parathyroidism occurred in 0.9% of patients after TT and in 1% of patients after ST. In a recent article analyzing the long-term outcomes of thyroid function after subtotal thyroidectomy for GD, Lyn et al. [34] observed a persistent or recurrent hyperthyroidism in 28.7% of patients and hypothyroidism in over 50% of patients.

This study involved a large series of 594 patients in which TT had been chosen as the definitive treatment for GD. The most frequent complication was transient hypocalcaemia, registered in approximately 40% of the patients, while a definitive hypoparathyroidism was recorded in 0.5% of cases. Similarly, the most feared complication, i.e. RLN paresis, proved to be transient in 5.2% of patients and definitive in 1.16% of patients. Rates relating to both complications (transient and permanent) were similar to those registered in our experience on TT for non-toxic multinodular goitre. Similarly, the incidence rate of postoperative hematomas requiring an emergency reoperation was very low (0.5% of the cases). All these patients were preoperatively treated with ATDs, they were euthyroid or mildly hyperthyroid at the time of surgery and no patients experienced a thyroid storm.

At multivariate analysis, the age < 50 years was found to be the main risk factor for complications of TT. This result appears to contradict those of other studies, which have identified an older age as a risk factor for post-thyroidectomy complications [35,36]. However, a large multicenter study has confirmed that post-thyroidectomy hypocalcaemia has an increased incidence in younger patients who underwent TT for GD [37]. Other significant risk factors for the onset of post-thyroidectomy complications were the weight of the thyroid > 40 g and a BMI ≤ 30 Kg/m^2. These latter results were unexpected and strongly contrast not only with those expected by the authors of this paper, but also with various data, previously reported in literature [38,39].

Conclusion

Despite the large number of patients involved in this study, its main limitation remains its retrospective nature. However, the presented results have led us to conclude that TT can be considered as the safest and most effective cure to be offered to patients with GD. In high-volume centers, as is the case in Palermo where approximately 300 operations are performed every year (40–50 of which relate to patients with GD), TT is associated with a very low incidence rate of post-operative complications. The latter ones are often transitory, with TT offering rapid and definitive control of hyperthyroidism and its related symptoms.

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Conflict of interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

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References

[1] Klein I, Becker DV, Levey GS. Treatment of hyperthyroid disease. Ann Intern Med 1994;121:281–8.
[2] Cooper DS. Antithyroid drugs in the management of patients with Graves' disease: an evidence-based approach to therapeutic controversies. J Clin Endocrinol Metab 2003;88:3474–7.
[3] Vitti P, Rago T, Chiovato L, Pallini S, Santini F, Fiore E, et al. Clinical features of patients with Graves' disease undergoing remission after antithyroid drug treatment. Thyroid 1997;7:369–75.
[4] Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, Rivkees SA, Samules M, Sosa JA, Stan MN, Walter MA. American thyroid association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid 2016;26:1343–421.
[5] Alsanea O, Clark OH. Treatment of Graves' disease: the advantages of surgery. Endocrinol Metab Clin North Am 2000;29:321–37.
[6] Watson AB, Brownlie BE, Frampton CM, Turner JC, Rogers TG. Outcome following standardized 185 MBq dose ^{131}I therapy for Graves' disease. Clin Endocrinol (Oxf) 1988;28:487–96.
[7] Melcescu E, Horton WB, Kim D, Vijayakumar V, Corbett JJ, Ceowder KW, et al. Graves' orbitopathy: update on diagnosis and therapy. South Med J 2014;107:34–43.
[8] Elfenbein DM, Schneider DF, Havlena J, Chen H, Sippel RS. Clinical and socioeconomic factors influence treatment decisions in Graves' disease. Ann Surg Oncol 2015;22(4):1196–9.
[9] Jin J, Sandoval V, Lawless ME, Sehgal AR, McHenry CR. Disparity in the management of Graves' disease observed at an urban county hospital: a decede-long experience. Am J Surg 2012;204:199–202.
[10] Haejin I, Pearce EN, Wong AK, Burgess JF, McAneny DB, Rosen JE. Treatment options for graves disease: a cost-effectiveness analysis. J Am Coll Surg 2009;209:170–219.
[11] Khan AA, Koch CA, Van Uum SHM, Baillargeon JP, Bollerslev J, Brandi ML, Marcocci C, Rejnmark L, Rizzoli R, Shrayyef MZ, Thakker RV, Yildiz BO, Clarke B. Eur J Endocrinol 2018 Dec 1. pii: EJE-18-0609.R1 doi: 10.1530/EJE-18-0609. [Epub ahead of print].
[12] Vita R, Lapa D, Trimarchi F, Benvenga S. Stress triggers the onset and recurrence of hyperthyroidism in patients with Graves' disease. Endocrine 2015;48:254–63.
[13] Ross DS. Radioiodine therapy for hyperthyroidism. New Eng J Med 2011;364:542–50.
[14] Braga M, Walpert N, Burch HB, Solomon BL, Cooper DS. The effect of methimazole on cure rates after radioiodine treatment for Graves' hyperthyroidism: a randomized clinical trial. Thyroid 2002;12:135–9.
[15] Alexander EK, Larsen PR. High dose of (131)I therapy for the treatment of hyperthyroidism caused by Graves' disease. J Clin Endocrinol Metab 2002;87:1073–7.
[16] Bartalena L, Marcocci C, Bogazzi F, Manetti L, Tanda ML, Dell'Unto E, et al. Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. N Engl J Med 1998;338:73–8.
[17] Tallstedt L, Lundell G, Torring O, Wallin G, Ljunggren JC, Blomgren H, et al. Occurrence of ophthal- mopathy after treatment for Graves' hyperthyroidism. The Thyroid Study Group. N Engl J Med 1992;326:1733–8.
[18] Sundaresh V, Brito JP, Thapa P, Bahn RS, Stan MN. Comparative effectiveness of treatment choices for Graves' hyperthyroidism: a historical cohort study. Thyroid 2017;27:497–505.
[19] Guo Z, Yu P, Liu Z, Si Y, Jin M. Total thyroidectomy vs bilateral subtotal thyroidectomy in patients with Graves' diseases: a meta- analysis of randomized clinical trials. Clin Endocrinol (Oxf) 2013;79:739–46.
[20] Weber KJ, Solorzano CC, Lee JK, Gaffud MJ, Prinz RA. Thyroidectomy remains an effective treatment option for Graves' disease. Am J Surg 2006;191:400–5.
[21] Yano Y, Shibuya H, Kitagawa W, Nagahama M, Sugino K, Ito K, et al. Recent outcome of Graves' disease patients with papillary cancer. Euro J Endocrinol 2007;157:325–9.
[22] Phitayakorn R, McHenry CR. Incidental thyroid carcinoma in patients with Graves' disease. Am J Surg 2008;195:292–7.
[23] Bradley DP, Reddy V, Prinz RA, Gattuso P. Incidental papillary carcinoma in patients treated surgically for benign thyroid diseases. Surgery 2009;146:1099–104.
[24] Vita R, Ieni A, Tuccari G, Benvenga S. The increasing prevalence of chronic lymphocitic thyroiditis in papillary microcarcinoma. Rev Endocr Metab Disord 2018. https://doi.org/10.1007/s11154-018-9474-z. [Epub ahead of print].
[25] Melcescu E, Horton WB, Pitman KT, Vijayakumar V, Koch CA. Euthyroid Graves' orbitopathy and incidental papillary thyroid carcinoma. Hormones (Athens) 2013;12:298–304.
[26] Koch CA. How can environmental factors contribute to the incidence of thyroid cancer? Horm Metab Res 2017;49:298–304.
[27] Koch CA. A journey from brain to muscle across the thyroid continent. Rev Endocr Metab Disord 2016;17:465–9.
[28] Benvenga S, Antonelli A, Vita R. Thyroid nodules and thyroid autoimmunity in the context of environmental pollution. Rev Endocr Metab Disord 2015;16:319–40.
[29] Latteri MA, Cipolla C, Graceffa G, Amato C, Pantuso G, Bottino A, et al. Surgical therapy of Basedow's disease. A comparison between total and subtotal thyroidectomy. Chirurgia 1996;9:225–30.
[30] Torring O, Tallstedt L, Wallin G, Lundell G, Ljunggren JG, Taube A, et al. Graves' hyperthyroidism: treatment with antithyroid drugs, surgery, or radioiodine—a prospective, randomized study. J Clin Endocrinol Metab 1996;81:2986–93.
[31] Chi SY, Hsei KC, Sheen-Chen SM, Chou FF. A prospective randomized comparison of bilateral subtotal thyroidectomy versus unilateral total and contralateral subtotal thyroidectomy for Graves' disease. World J Surg 2005;29:160–3.
[32] Miccoli P, Vitti P, Rago T, Iacconi P, Bartalena L, Bogazzi F, et al. Surgical treatment of Graves' disease: subtotal or total thyroidectomy? Surgery 1996;120:1020–4.
[33] Palit TK, Miller 3rd CC, Miltenburg DM. The efficacy of thyroidectomy for Graves' disease: a meta-analysis. J Surg Res 2000;90:161–5.
[34] Lin YS, Lin JD, Hsu CC, Yu MC. The long-term outcomes of thyroid function after subtotal thyroidectomy for Graves' hyperthyroidism. J Surg Res 2017;220:112–8.
[35] Thomusch O, Machens A, Sekulla C, Ukkat J, Lippert H, Gastinger I, 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.
[36] Erbil Y, Barbaros U, Temel B, Turkoglu U, Issever H, Bozbora A, et al. The impact of age, vitamin D (3) level, and incidental parathyroidectomy on postoperative hypocalcemia after total or near total thyroidectomy. Am J Surg 2009;197:439–46.
[37] Hallgrimsson P, Nordenström E, Almquist M, Bergenfelz AO. Risk factors for medically treated hypocalcemia after surgery for Graves' disease: a Swedish multicenter study of 1,157 patients. World J Surg 2012;36:1933–42.
[38] Shinall MC, Broome JT, Nookala R, Shinall JB, Kiernan C, Parks L, Solorzano CC. Total thyroidectomy for Graves' disease: compliance with american thyroid association guidelines may not always necessary. Surgery 2013;154:1009–15.
[39] Buerba R, Roman SA, Sosa JA. Thyroidectomy and parathyroidectomy in patients with high body mass index are rare safe overall: analysis of 26,864 patintes. Surgery 2011;150:950–8.