Treatment of patients with Graves' disease and the appropriate extent of thyroidectomy

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Graves' disease is an autoimmune disorder caused by thyroid stimulating auto-antibodies directed against the thyrotropin receptor on thyroid follicular cells. It is the most common cause of hyperthyroidism and is associated with cardiovascular, ophthalmologic and other systemic manifestations. Three treatment options are available for Graves' disease: anti-thyroid drugs, radioactive iodine and thyroidectomy. While thyroidectomy is the least common option used for treatment of Graves' disease, it is preferentially indicated for patients with a large goiter causing compressive symptoms, suspicious or malignant thyroid nodules or significant ophthalmopathy. The best operation for Graves' disease has been a matter of debate. The standard operation was a subtotal thyroidectomy for much of the twentieth century, however, over the past 20 years total thyroidectomy has been increasingly performed. Herein, we provide a historical perspective and review the current literature, including randomized controlled trials, systematic reviews and meta-analyses and conclude that total thyroidectomy is the preferred option for the surgical treatment of Graves' disease, with a nearly 0% recurrence rate, predictable postoperative hypothyroidism and a low complication rate comparable to subtotal thyroidectomy when performed by high-volume thyroid surgeons.

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Introduction

Graves' disease (GD) is a systemic autoimmune disorder caused by thyroid stimulating auto-antibodies directed against the thyrotropin (TSH) receptor on thyroid follicular cells that results in follicular cell hypertrophy, thyroid enlargement, increased synthesis of thyroid hormone and hyperthyroidism. GD affects approximately 0.5% of the population, and is the most common cause of hyperthyroidism, accounting for 50−80% of all cases [1]. Hyperthyroidism due to GD is associated with an increased risk of atrial fibrillation, cardiomyopathy and congestive heart failure [2]. Clinical manifestations of GD include a diffuse goiter (Fig. 1), ophthalmopathy, pretibial myxedema and proximal muscle weakness. Approximately half of patients with GD develop Grave's ophthalmopathy (GO), an inflammatory eye disease caused by the cross-reactivity of antibodies to the thyroid-stimulating hormone (TSH) receptors that are also found on retro-ocular fibroblasts and adipocytes. Five percent of GD patients suffer from severe GO [3].

The diagnosis of GD is established based on clinical evaluation, laboratory studies and selective measurement of radioiodine uptake and thyroid imaging. Laboratory evaluation typically reveals a suppressed TSH level, a high free triiodothyronine (T3) level with or without a high free thyroxine (T4) level. Elevated levels of TSH-receptor antibodies or thyroid-stimulating immunoglobulins (TSI) are highly sensitive and specific for GD [4]. Radioiodine uptake and thyroid scintigraphy is selectively used in patients with thyrotoxicosis to differentiate between toxic multinodular goiter, solitary toxic thyroid nodule, thyroiditis and GD [5]. It may also help identify hypofunctioning nodules in the background of GD that have an increased risk of malignancy. Ultrasound is used to evaluate concomitant thyroid nodules, which are more common in patients with GD than previously appreciated [6].

Treatment options for Graves' disease: anti-thyroid drugs, radioactive iodine and thyroidectomy

In patients with GD, the goals of treatment are to provide rapid resolution of hyperthyroidism and its symptoms and prevent its sequalae, resect goiters that are causing compressive symptoms, diagnose and manage associated thyroid cancer, prevent progression of ophthalmopathy and dermopathy and prevent recurrence. There are three therapeutic options for management of GD, anti-thyroid drugs (ATDs), radioactive iodine (RAI) and thyroidectomy. Each therapeutic option has its advantages and disadvantages. Published guidelines for management of hyperthyroidism from The American Thyroid

Fig. 1. A diffuse symmetrically enlarged thyroid gland that was producing mass effect on the trachea excised from a patient with GD who was experiencing dyspnea, dysphagia and hoarseness.

Association in 2011 and 2016 emphasize the importance of patient preference and physician input in the selection of a treatment modality for GD [3,7]. The 2018 European Thyroid Association GD guidelines recommend initial medical management of newly diagnosed GD with 12−18 months of ATDs, after which patients with persistent hyperthyroidism and high TSH receptor antibodies have the option for an additional 12 months of ATDs, RAI or thyroidectomy [4].

Antithyroid drugs

Most patients with GD are initially treated with ATDs (methimazole or propylthiouracil), which inhibit thyroid hormone synthesis and re-establish a euthyroid state in 3−8 weeks. Some patients are continued on ATDs for 12−18 months, while others undergo RAI or surgery once a euthyroid state is achieved, with the goal of a faster cure of hyperthyroidism. Remission of GD occurs in 20−50% of patients after 12−18 months of treatment with ATDs, typically in patients with smaller goiters and lower anti-TSH receptor antibody titers [8,9]. An advantage of ATDs is the potential for remission in a select group of patients without development of hypothyroidism or the potential complications that can occur with RAI or thyroidectomy. Disadvantages of ATDs alone include a lower rate of remission compared to RAI and surgery, a high rate of relapse in patients with large goiters or high antibody titers, as well as side effects associated with the medications, such as pruritus, exanthemas, arthralgia, myalgia, dysgeusia, agranulocytosis and hepatotoxicity [10].

Radioactive iodine

In the United States, RAI treatment with iodine-131 rapidly became the first-line treatment for GD after its introduction in 1942. Iodine-131 emits beta particles which destroy the follicular cells of the thyroid gland. Higher doses of RAI have been recommended to induce hypothyroidism in order to prevent recurrence of GD [1]. The cure rate of RAI is approximately 80%, resulting in euthyroidism or hypothyroidism. RAI takes a median of 3 months and sometimes requires multiple doses to resolve hyperthyroidism [8]. RAI is preferentially used in patients without ophthalmopathy, patients who are poor surgical candidates, patients who have a contraindication to ATDs or have failed ATD treatment. RAI is contraindicated in women who are pregnant or breastfeeding and in patients with moderate to severe GO, as it has the potential to worsen GO [1,8,10].

Thyroidectomy

Thyroidectomy was introduced for treatment of GD in the 1800s, but it was not until the early 1900s that thyroidectomy was performed with acceptable morbidity. After its introduction as a treatment option for GD in the 1940s, RAI therapy quickly replaced thyroidectomy as the preferred option for definitive treatment of GD due to the higher risk of complications associated with surgery [11]. However, the safety of thyroidectomy for hyperthyroidism has dramatically improved over the last century. With the introduction of ATDs and beta blockers and the evolution of modern surgical technique, thyroidectomy has become a much safer option for definitive treatment of GD. Experienced, high volume surgeons are reporting rates of complications from thyroidectomy in patients with GD of less than 3% [2,12].

The surgical procedures most often performed for the treatment of GD are total thyroidectomy and less commonly subtotal thyroidectomy. Subtotal thyroidectomy consists of two distinct operations: a bilateral subtotal thyroidectomy (Enderlen-Hotz procedure) leaving a 2−4 g thyroid remnant bilaterally, and unilateral total and contralateral subtotal thyroidectomy with a remnant less than 7 g (Dunhill procedure) [8,13,14]. While historically subtotal thyroidectomy was the standard surgical treatment for GD, over the past two decades total thyroidectomy has become the preferred surgical option for management of GD [3,7,15].

Although thyroidectomy should be discussed as a treatment option with all patients with GD, surgery is preferentially indicated for a large goiter especially with mass effect on the trachea or symptoms related to compression of the other structures in the neck; a concomitant thyroid nodule that is suspicious for malignancy or malignant; co-existent hyperparathyroidism; pregnant patients

with a contraindication or intolerance to ATDs; patients with moderate to severe GO; women who plan pregnancy in <6 months; high anti-TSH-receptor antibody titers; failure of RAI; and patient preference for surgery [3,7,8]. There are disparities that exist in the management of GD and special consideration for surgical treatment should be considered in patients with poor compliance, lack of access to healthcare and sporadic follow-up [11]. Subtotal thyroidectomy may be preferable to total thyroidectomy in patient populations that do not have ready access to thyroid hormone replacement medications [16].

Advantages of thyroidectomy for GD include prompt and definitive control of hyperthyroidism, concomitant treatment of thyroid nodules and incidental thyroid carcinoma, improvement or prevention of progression of eye manifestations of GD, avoidance of exposure to radioactivity and minimization of the potential side effects of ATDs [7]. The disadvantages of surgery for GD include the need for lifelong thyroid hormone replacement and the risk of complications, such as hypoparathyroidism, recurrent laryngeal nerve injury and neck hematoma.

Geographic variability

There is geographic variability in the preference and selection of each of the three treatment modalities for GD. In the Unites States, RAI has been the preferred therapy, however more recently there has been an increase in ATD use and a decline in the use of RAI [3,7,10,17]. In Germany, surgery is the preferred definitive treatment for GD, potentially due to high incidence of co-existant thyroid nodules along with GD occurring in areas of iodine deficiency resulting in decreased use of RAI [14]. In addition, some countries such as Germany and New Zealand have specific legislation concerning radiation protection, and RAI is much less commonly used than ATDs or surgery [14,18]. In other parts of Europe, Japan and South America, there has been an increase in the preferential use of ATDs and/or surgery [3,7,19]. Surgery remains the least commonly selected option for the initial management of GD, used only in 1−2% of patients as the first-line treatment in Europe and America [20,21]. A 2011 survey of clinical practice patterns in the treatment of GD and GO in the United States showed a decline in the use of RAI with a simultaneous increase in ATDs compared to a 1991 survey. Members of three US endocrine societies took a web-based survey dealing with treatment preferences of GD. This study showed that the preferred mode of treatment of uncomplicated GD was ATDs for 54% of physicians surveyed, while 45% preferred RAI and only 1% preferred surgery. In patients with GO, ATDs were the preferred first-line treatment modality by 63% of practitioners, while 18% preferred surgery, 17% preferred RAI in addition to corticosteroids and 2% preferred RAI alone [21].

Comparing therapy options for Graves' disease

Comprehensive studies comparing the effectiveness of the three different treatment modalities for GD are limited by the fact that surgery is less commonly used as a treatment modality for GD compared to ATDs and RAI. Furthermore, in most of the comparative studies, subtotal thyroidectomy was the surgical treatment that was compared to RAI and ATDs. It is only in the last 2 decades that total thyroidectomy has become the procedure of choice for treatment of GD. There are no randomized controlled trials to date that directly compare outcomes of RAI vs. total thyroidectomy for definitive treatment of GD.

A prospective randomized study by Torring et al., in 1996 analyzed the benefits of three treatment options: ATDs for 18 months, RAI and subtotal thyroidectomy in patients ages 20−55 years treated between 1983 and 1990. Patients were divided in two groups based on age: young adults 20−34 years of age and older adults 35−55 years old. Follow-up was 3 years or longer and only the older adults received RAI treatment. The risk of relapse was highest in the medically treated groups: 42% relapse in young adults and 34% relapse in older adults. The relapse for older adults treated with RAI was 21%. The lowest relapse rates were seen in young and older adults treated with subtotal thyroidectomy, 3% and 8%, respectively. In all three treatment groups, the highest risk of relapse was seen in patients who had elevated TSH receptor antibodies at the end of medical or surgical therapy [22].

A systematic review by Genovese at al in 2013 [2] compared RAI and thyroidectomy as definitive treatment for GD. The study analyzed retrospective and prospective studies between 2001 and 2011

that evaluated RAI or ST and/or TT as a treatment modality for GD. A total of 14,245 patients and 70 studies were included, 51 studies that evaluated RAI therapy and 19 studies that evaluated ST and/or TT. The study found that over 20% of patients treated with a single dose of RAI remained hyperthyroid at 6 months after treatment. In addition, surgery was 3.4 times more likely to be successful in curing hyperthyroidism than RAI. ST and TT were 2.3 and 94 times more likely than a single RAI dose to result in successful resolution of hyperthyroidism, respectively [2].

Another systematic review performed by Sundaresh et al., in 2013 [23] evaluated the relapse rate of hyperthyroidism due to GD after treatment with ATDs, RAI or ST. The study included 1 randomized controlled trial and 7 comparative cohort studies that compared 2 or more treatment options and were published between 1979 and 2006. The study found relapse rates of GD after treatment with ATDs, RAI or ST to be 52.7%, 15%, and 10%, respectively [23]. Similar conclusions were obtained in a meta-analysis by Ren at al in 2015, which included 4 RCTs and compared RAI, RAI + prednisone, ATDs and ST, although this study was limited by the small number of surgical patients included [24]. A systemic review and meta-analysis by Li et al., in 2016 evaluated the effect of treatment of GD on the development and progression of GO. It compared treatment with ATDs, RAI or thyroidectomy and showed that RAI is a significant risk factor for development or worsening of GO, but progression of GO can be prevented by administration of glucocorticoids prior to RAI treatment [25].

A randomized trial evaluating the treatment of GD with ATDs, RAI or surgery from 1983 to 1990 found that the long term quality of life was the same for all three groups [26]. A survey study of patients who had treatment with surgery or RAI from 2011 to 2013 for GD found that surgery was associated with higher levels of patient satisfaction compared to RAI, in part due to patient involvement in the decision-making process [27]. Cost analysis in a study by In et al., in 2009 showed that thyroidectomy is more cost-effective than either RAI or ATDs and offers patients a better quality of life [9].

Surgical treatment options for Graves' disease: bilateral subtotal thyroidectomy, Dunhill procedure, and total thyroidectomy

Bilateral subtotal thyroidectomy

In 1917, Bartlets, and also Enderlen and Hotz described bilateral subtotal resection of the thyroid gland [14]. Results of total thyroidectomy for GD were published by Pearsons in 1920 and Parks in 1936. Total thyroidectomy was considered too radical of an operation for a benign disease, due to postoperative complications and challenges in postoperative management [14]. Thus, bilateral subtotal thyroidectomy (BST) was the surgical treatment of choice for GD for most of the 20th century. The operation consisted of removing the majority of the thyroid gland, but leaving a 2- to 4-g remnant of thyroid tissue on either side of the trachea with the goal of establishing a euthyroid state and avoiding injury to the recurrent laryngeal nerves and the parathyroid glands. The challenge with this operation is the difficulty in standardizing the size of the remnant, thus resulting in a wide range of hypothyroidism, euthyroidism and recurrent hyperthyroidism. The reported rates of hypothyroidism range from 3 to 48% based on the size of the remnant, thyroid antibody titers and the definition of hypothyroidism [28,29]. Thyroid remnants greater than 8 g have a decreased risk of hypothyroidism, but persistent or recurrent hyperthyroidism occurs in approximately 15%. A remnant smaller than 3 g has a 2−10% risk of recurrence, but a 40% chance of developing hypothyroidism [28]. In some countries, bilateral subtotal thyroidectomy remains the preferred surgical option because of the limited access to thyroid hormone replacement medications [8,16]. Prolonged follow-up of patients who undergo BST for GD has revealed that a majority eventually become hypothyroid and require thyroid hormone replacement even when they were euthyroid in the first few years following surgery [8].

The Dunhill procedure

Unilateral subtotal thyroidectomy with contralateral hemithyroidectomy was described by Dunhill in 1912. He was an Australian surgeon who pioneered safe surgery and anesthesia for GD, which

decreased the mortality rate to <2% by performing a subtotal thyroidectomy under local anesthesia [30]. He wrote: "We have to remove enough to cure the disease and we must leave enough for physiological purposes" [13]. In his early experience, he only performed a hemithyroidectomy, but found that many patients were not cured and required additional thyroid tissue to be removed. He found the optimal amount to remove was "one lobe and half the other," which resulted in improved symptoms of thyrotoxicosis and ophthalmopathy in most patients. Some patients required multiple reoperations to remove more thyroid tissue from the thyroid remnant to cure hyperthyroidism and achieve a euthyroid state [13]. The remnant in the Dunhill procedure (DP) is typically 4–7 g in size, and the dissection on the side of the remnant spares the exposure of the recurrent laryngeal nerve and parathyroid glands. If patients had recurrence after the Dunhill operation, one advantage of this procedure was the option for reoperation on only one side of the neck for additional resection of thyroid tissue [28].

Total thyroidectomy

Total thyroidectomy (TT) for GD involves removing all macroscopically visible thyroid tissue. Near total thyroidectomy refers to leaving less than 1 g of thyroid tissue to avoid recurrent laryngeal nerve injury, and sometimes these terms are used interchangeably in the literature. Removing all visible thyroid tissue in GD eliminates the risk of persistent or recurrent hyperthyroidism. All patients are rendered hypothyroid postoperatively and require thyroid hormone replacement. The predictability of curing hyperthyroidism and postoperative hypothyroidism in all patients have made total thyroidectomy the procedure of choice in the treatment of GD in many regions of the world where thyroid hormone replacement is readily available [3,4,8]. In recent randomized controlled trials and meta-analysis, risks of postoperative complications for ST and TT have been found to be similar when thyroidectomy is performed by experienced surgeons [31–33].

Current surgical procedure of choice for Graves' disease: total thyroidectomy

Until approximately 2000, ST was the procedure of choice for the surgical management of GD. However, there has been considerable debate over whether ST or TT is the optimal approach for treatment of GD. The controversy presumably arose because of the previously reported higher prevalence of permanent complications following TT [34]. More recent data has called this conclusion into question, with similar complication rates published for ST and TT if performed by a high-volume surgeon [33–36]. The primary goal of thyroid surgery for GD is to avoid persistent or recurrent hyperthyroidism, because it can be more difficult to induce remission of recurrent GD via ADTs or RAI. Persistent or recurrent hyperthyroidism is a particularly bad outcome because it may subject patients to RAI, which they may have initially declined, or reoperation, which is associated with higher complications rates [8,30]. The randomized controlled trials, systematic reviews and meta-analysis discussed below and summarized in Tables 1 and 2 provide the rationale that established TT as the preferred procedure for the surgical treatment of GD.

Five randomized controlled trials that compared at least two of the three surgical options for the treatment of GD have been published to date, with one ongoing study without published data available (Table 1) [14,31,34,37,38]. The only prospective randomized trial that compares all three surgical techniques was a single-center study from Germany published in 2000 by Witte et al. [37]. It included 150 patients with GD randomized to one of three surgical groups: BST, DP or TT. Follow-up was 6–36 months and the primary endpoints evaluated included the effect of thyroidectomy on GO, postoperative TSH-receptor antibody titers and postoperative complication rates. The goal remnant size for BST and DP was less than 4 ml, although 12% of the patients had a remnant larger than 4 ml on postoperative ultrasound measurements. Results of the study revealed no difference in the rate of GO improvement or progression and no difference in postoperative TSH receptor antibody titers between the three groups. GO improved in 72%, 74% and 71% of patients undergoing BST, DP or TT, respectively, while 6.5% of TT patients and 7.1% of ST patients had worsening eye symptoms. The mean TSH receptor antibody level decreased in all three groups, with a wide variation in individual levels, but no significant differences between the three groups. Postoperative serum TSH antibody titers did not correlate

Table 1
RCTs evaluating different surgical techniques in the treatment of GD and/or GO.

RCT	Procedures compared	Time period	Country	Number of patients	follow up	Primary endpoints	Key Results	Study conclusion/recommendation
Witte 2000	BST vs. DP vs. TT	1993–1995	Germany	150 (50 each group)	6–36 months	1. Postop GO change 2. Postop TSH-R ab levels 3. Complication rates	1. No difference 2. No difference 3. Higher early transient hypoparathyroidism in TT group 4. Recurrence: 2% in ST, 0% in TT, p = NS	Due to increased risk of hypoparathyroidism in TT and no difference in other outcomes, the authors recommend subtotal thyroidectomy with remnant <4 g for GD[1]
Muller 2001	BST vs. DP	1988–1992	Germany	152 (67 vs. 85)	6 years	1. Complications 2. Recurrence rates	1. No difference 2. No difference (7.5% BST, 8.7% DP)	Dunhill procedure is preferred for GD, because if reoperation is necessary for a recurrence, lower complications expected as only one side of neck has to be re-explored.
Chi 2005	BST vs. DP	1998–2002	Taiwan	340 (166 vs. 174)	26 months	1. Complications 2. Recurrence rates	1. No difference 2. Higher in BSE (9% vs. 2%)	Dunhill procedure has better outcomes compared to BSE
Jarhult 2005	ST vs. TT		Sweden	44	3 yrs	1. GO change 2. complications	1. No difference, GO improved in both groups 2. Complications higher in TT than ST	ST with small remnant <2 g has similar improvement in GO but less complications compared to TT
Barczynski 2012	BST vs. TT	2000–2004	Poland	200	5 yrs	1. Recurrence rates 2. Change in GO 3. Complications	1. Higher recurrence in BST (9.5% vs. 0%) 2. No difference in GO progression (9.5% vs. 7%) 3. No difference in permanent hypoparathyroidism or RLNs injury	TT for GD prevents recurrent hyperthyroidism, similar complications as BST

BST: bilateral subtotal thyroidectomy; DP: Dunhill procedure, unilateral subtotal with contralateral hemithyroidectomy; TT: total thyroidectomy.

Table 2
Meta-analysis and/or systematic reviews of surgical techniques for GD and GO.

Study	Study type	Comparison	Types of studies/ patients included	Hyperthyroidism persistence or recurrence	GO progression	Permanent RLN injury	Permanent hypoPTH	Conclusion
Palit et al., 2000	Meta-analysis	ST vs. TT (6703 vs. 538 pts)	35 retrospective studies published between,1965 −1996, 7241 pts	ST: 8% TT: 0%		ST:0.7% TT: 0.9% P = NS	ST: 1% TT: 1.6% P = NS	TT more effective at curing GD without increased complications
Feroci et al., 2013	Systemic review and meta-analysis	BST vs. TT (1577 vs. 1665 pts)	4 RCTs, 19 NRCTs published between 1996 and 2012, 3242 pts	TT vs. BST OR 0.10 P<0.00001	TT vs. BST OR 0.90, P = 0.58	TT vs. BST OR 0.91 P = 0.92	TT vs. BST OR 2.91 P = 0.005	TT more effective at curing GD with small increase risk of temporary/permanent hypoPTH
Guo et al., 2013	Meta-analysis of RCTs	BST vs. TT (332 vs. 342 pts)	4 RCTs published between 2000 and 2012, 674 pts	TT vs. BST RR 0.14 P < 0.01	TT vs. BST RR 0.92 P = 0.8	TT vs. BST RR 1.54 P = 0.52	TT vs. BST RR 2.30 P = 0.13	TT associated with decreased recurrent hyperthyroidism, increased temporary hypoPTH, no difference in permanent complications.
Liu et al., 2015	Cochrane review of RCTs	TT vs. BST vs. DP (172 vs. 383 vs. 309 pts)	5 RCTs published 2000−2012, 886 pts	TT vs. ST OR 0.14 P = 0.001 (0.8% vs. 5.5%) TT vs. BSE OR 0.13 P = 0.001 BSE vs. DP OR 2.73 P = 0.01	GO regression TT vs. ST OR 1.15 P = 0.64	TT vs. ST OR 1.45 P = 0.59	TT vs. ST OR 4.79 P = 0.01 5.9% vs. 1.4%	TT is more effective than both BST and DP at preventing recurrent hyperthyroidism. The type of surgery performed does not affect regression of GO. Increased risk of permanent hypoPTH with TT vs. ST.

RCT − randomized controlled trial; NRCT − non-randomized comparative studies; OR − odds ratio; TT − total thyroidectomy; BST − bilateral subtotal thyroidectomy; DP − dunhill procedure; ST − subtotal thyroidectomy, includes BST and DP; hypoPTH - hypoparathyroidism.

with symptoms of GO. Eight patients had increased postoperative antibody titers, but only one developed new or progressive GO. The rate of recurrent hyperthyroidism was 2% and occurred in the ST groups. Transient hypoparathyroidism was higher in the TT group but there was no difference in rates of permanent hypoparathyroidism or other complications between the three groups. This study concluded that there are minimal differences in the overall cure rate for GD and the rate of GO between the three groups and advocated for ST with a remnant <4 ml for treatment of GD.

Two randomized controlled trials compared BST and DP. Muller et al. published a study in 2001 performed in at a single institution in Germany of 152 patients randomized to BST or DP. Remnant size was approximately 3 g on both sides for BST and 3 g on the subtotal side for DP. The primary endpoints evaluated were postoperative complication rates and rates of recurrent hyperthyroidism, and no significant difference was found between the two groups. The rate of recurrent hyperthyroidism was 7.5% for BST group and 8.7% in the DP group [14]. In a similar study by Chi et al. that randomized 340 patients with GD to BST or DP and followed them for 2 years found no difference in postoperative complication rates, but there was a higher rate of recurrence in the BST group compared to DP group (9% vs. 2%) [31]. Remnant size was 2.5 × 1.0 × 1.0 cm on both sides for the BST group and a similar size remnant on only on one side for the DP group. This study concluded that there were better outcomes in patients undergoing the Dunhill operation compared to bilateral subtotal thyroidectomy for GD.

A prospective randomized study from Sweden published by Jarhult et al., in 2005 focused on the long term results of surgery in patients with GD and moderate to severe ophthalmopathy [38]. Forty-four patients were randomized to subtotal thyroidectomy with a 2 g remnant vs. total thyroidectomy. At 3 years, there was no difference in the rate of improvement of GO between the two groups, but there were higher rates of complications in the TT group (permanent vocal cord palsy 14% vs. 5%, permanent hypoparathyroidism 9% vs. 0%). Subjective and objective evaluation of eye symptoms before and after thyroid surgery showed an improvement in all parameters, with the exception of proptosis and no differences were observed between the two groups.

One of the largest randomized studies to evaluate TT in comparison to BST was performed in Poland and published by Barczynski et al., in 2012 [34]. It included 200 patients who were followed for 5 years after surgery and were evaluated for rates of recurrent hyperthyroidism, progression of GO and postoperative complications. The BST remnant was 2 g on each side. The recurrence of hyperthyroidism was 9.5% in the BST group vs. 0% in the TT group. There was no difference in the rate of progression of GO (9.5% in BST group vs. 7% in TT group) or permanent postoperative complications. The study authors concluded that TT is the preferred surgical technique for GD, as it prevents recurrence of hyperthyroidism and has similar complication rates to BST.

Data from randomized controlled trials and many other non-randomized comparative studies was synthesized in several meta-analysis and systematic reviews and was used to make practice recommendations for the optimal surgical treatment of GD and GO based on larger number of patients (Table 2). The first published meta-analysis focusing on the surgical options for GD by Palit et al. synthesized published data from 35 retrospective studies published from 1965 to 1996 and included 7241 patients [35]. Of those, 6703 patients underwent ST and 538 patients underwent TT. The rate of recurrent or persistent hyperthyroidism was 8% in the ST group and 0% in the TT group. While there was great variability in the ST technique used, remnant size and follow-up duration, 60% of patients who underwent ST achieved euthyroidism and 26% became hypothyroid. Complications rates were low for both groups (<1% permanent recurrent laryngeal nerve injury, <2% permanent hypoparathyroidism) without a significant difference between the groups. This important study concluded that TT is more effective at curing GD and can be performed safely, without increased complications compared to ST.

A systematic review and meta-analysis by Feroci et al. [30] in 2013 included 4 randomized controlled trials [31,34,37,38] and 19 non-randomized comparison studies published between 1996 and 2012 that addressed comparative outcomes of BST and TT for GD. This study had a robust number of patients, including 1577 patients that underwent BST and 1665 patients that underwent TT. An increase recurrence rate was observed for BST patients in both randomized and non-randomized studies (8.1% vs. 0.4%, Odds radio 0.10, 95% CI 0.06−0.18, p < 0.00001). There was no significant difference in progression of GO and permanent recurrent laryngeal nerve injury between the two groups. However, there was a higher rate of permanent hypoparathyroidism in the TT group compared to BST (OR 2.91, 95% CI 1.59−5.21, p = 0.005). The authors concluded that TT has the highest rate of cure of GD

with a small increase in the risk of temporary and permanent hypoparathyroidism, and should be the preferred method of operative treatment of GD in areas where thyroid hormone replacement is available.

Guo et al. [32] published a meta-analysis of 4 randomized controlled trials [31,34,37,38] in 2013 that compared TT vs. BST for GD. Gou and coauthors' conclusions were similar to those by Palit et al. [35] and Feroci et al. [30]. TT was associated with a much lower rate of recurrent hyperthyroidism compared to ST (0.8% vs. 7.8%), and there was no difference in progression of GO or postoperative permanent hypoparathyroidism, bleeding or recurrent laryngeal nerve injury (Table 2). One of the studies included in this meta-analysis, Chi et al., is called into question as truly meeting the inclusion criteria, as the patients in this study underwent DP, not TT, but were included in the meta-analysis as if they underwent TT [39]. The authors comment that the analysis and conclusion do not differ with or without the data from Chi's study.

Lastly, a Cochrane review was published by Liu et al., in 2015 that included all 5 randomized controlled trials discussed in Table 1 and compared all three surgical techniques of GD [33]. TT was the most effective surgical technique to cure GD, followed by the Dunhill procedure, which has significantly lower hyperthyroidism recurrence rates than BST (Table 2). There was no difference in GO regression rates between the three techniques. The rate of permanent hypoparathyroidism was significantly higher in TT vs. ST (5.9% vs. 1.4%, OR 4.79, 95% CI 1.36–16.83, p = 0.01).

Taken together, the conclusion of the meta-analysis and systematic reviews that compare the three surgical techniques for GD is that TT is the preferred surgical option for treatment of GD when performed by experienced surgeons. It may be associated with a slightly higher rate of temporary and permanent hypoparathyroidism compared to ST, although this was not a uniform finding in all studies. Randomized controlled trials have not found a difference in regression or progression of GO in patients undergoing TT or ST. TT is always associated with permanent hypothyroidism, so in areas where thyroid hormone replacement is not readily available, ST should still be considered as a surgical option for GD with the aim of trying to achieve a euthyroid state but recognizing the higher risk of recurrent hyperthyroidism.

Preoperative preparation and postoperative managements of Graves' disease patients undergoing thyroidectomy

When surgery is selected as the treatment option for GD, patients should be referred to a high-volume thyroid surgeon to optimize surgical outcomes [7,40]. Pretreatment with ATDs to achieve a euthyroid state is essential in the preoperative period to prevent thyroid storm during or after surgery [4,7]. A beta-blocker such as propranolol can be added for treatment of tachycardia and adrenergic symptoms. Once the patient's free T3 and free T4 levels have normalized, a potassium iodine solution, either in the form of a saturated solution of potassium iodide or Lugol's solution, may be administered for 10 days prior to surgery to reduce thyroid hormone release and thyroid gland vascularity, decreasing intra-operative blood loss [8,41]. Vitamin D deficiency can be corrected in the preoperative period to reduce postoperative risk of hypocalcemia [4]. Post-operatively, serum calcium should be measured and oral calcium and calcitriol replacement should be supplemented based on those results. Because of a higher risk of profound post thyroidectomy hypocalcemia in patients with GD, preemptive calcium and vitamin D therapy can be started 2 weeks preoperatively in order to help reduce the length of hospital stay postoperatively to treat hypocalcemia [42]. ATDs should be stopped immediately after thyroidectomy. Beta blockers can either be stopped or gradually weaned. Levothyroxine should be started postoperatively at a dose of 1.6 μg per kg, and TSH should be measured 5–6 weeks postoperatively.

Conclusion

Surgery is the most effective definitive treatment of GD. Advantages of thyroidectomy for GD include prompt and definitive control of hyperthyroidism, concomitant treatment of thyroid nodules and incidental thyroid carcinoma, improvement or prevention of progression of eye manifestations of GD, avoidance of exposure to radioactivity and minimization of the potential side effects of ATDs [7].

Total thyroidectomy performed by a high-volume thyroid surgeon is the preferred surgical therapy for GD in areas where thyroid hormone replacement is readily available, as it has the highest rate of cure and complication rates that are comparable to subtotal thyroidectomy.

Practice points

- The advantages and disadvantages of anti-thyroid drugs, radioactive iodine and thyroidectomy should be reviewed for all patients with GD.
- Patients with GD and large goiters, suspicious thyroid nodules or ophthalmopathy, or those who have failed or wish to avoid side effects of anti-thyroid drugs or radioactive iodine may be best managed by thyroidectomy.
- TT is the preferred surgical technique for patients with GD, as it has the highest cure rate and similar complication rates to ST.
- Patients should be rendered euthyroid with the use of anti-thyroid medications prior to undergoing TT for GD.

Research agenda

- Randomized trials comparing cure rates, complication rates, quality of life and patient satisfaction for GD treated with radioactive iodine versus TT.
- Studies that further elucidate the immune mediated mechanism of Graves' ophthalmopathy to guide better preventative and treatment options.
- Studies focusing on improving surgical technique and adjuncts that can minimize the risk of recurrent laryngeal nerve injury and hypoparathyroidism after TT for GD.

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