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Total Thyroidectomy for Graves' Disease: Compliance with ATA Guidelines may not Always be Necessary

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Abstract

Background—Total thyroidectomy (TT) is the preferred surgical approach to Graves' disease (GD). Current American Thyroid Association (ATA) guidelines call for administration of potassium iodide (KI) and achievement of euthyroid state before operation. Small numbers and a mixture of surgical approaches spanning several decades hinder previous surgical series. We present the outcomes for TT at a single high-volume center.

Methods—A retrospective cohort study was conducted on 165 patients undergoing TT for GD from 7/2007 to 5/2012.

Results—Mean age was 43 years (Range: 17-78), and 128 patients (78%) were female. 95% of patients were on methimazole or propylthiouracil, and 42% remained hyperthyroid at time of surgery. Only 3 (2%) patients received KI. Mean operative time was 132 minutes (Range 59-271). Mean gland size and blood loss were 41 grams (Range 8-180) and 55 mL (Range 10-1050), respectively. No patient developed thyroid storm. Median follow-up was 7.5 months. Temporary and permanent hypocalcemia developed in 51 (31%) and two patients (1.2%), respectively. Temporary and permanent recurrent laryngeal nerve paresis occurred in 12 (7%) and one (0.6%) patient, respectively. Sixty-one (37%) patients experienced at least one complication. On multivariate analysis, patient age less than 45 years (OR 2.93, 95% CI 1.39-6.19) and obesity (OR 2.11, 95% CI 1.00-4.43) were associated with occurrence of complications.

Conclusion—This high-volume surgeon experience demonstrates no appreciable detriment to patient outcomes when ATA recommendations for routine use of KI and euthyroid state before thyroidectomy are not met. Transient hypocalcemia and hoarseness are frequent complications of

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TT for GD resolving within six months in most patients. Age less than 45 years and obesity are risk factors for post-operative complications.

Keywords

Graves' disease; total thyroidectomy; hyperthyroidism; thyrotoxicosis; Potassium-iodide (KI)

Introduction

Graves' disease (GD) remains one of the most common causes of thyrotoxicosis in the United States.¹ Patients and their physicians can manage GD with three modalities: anti-thyroid medications, radioactive iodine (RAI), or surgery. Making an informed decision about which therapy for GD to pursue requires an understanding of the risks and benefits of each modality. Although remission of GD can be achieved with anti-thyroid medications, remission rates are variable (ranging from 14-80%), and it is difficult to predict which patients will achieve it with medical therapy.² For these reasons, patients and physicians frequently opt for definitive treatment with either surgery or RAI. Choosing between these two modalities requires weighing anesthetic and operative risks of thyroidectomy versus symptoms, recurrence rates, and complications related to RAI therapy.

In the past, subtotal thyroidectomy was the preferred surgical approach employed in an attempt to prevent hypothyroidism and to protect both the recurrent laryngeal nerves and the parathyroid glands. However, hyperthyroidism recurred in as many as 8% of patients treated with subtotal thyroidectomy. Moreover, reoperative completion thyroidectomy in this setting is fraught with complications.³ In contrast, total thyroidectomy (TT) carries a nearly 0% risk of recurrence, avoiding complex re-operative surgery.³ Therefore, current American Thyroid Association guidelines (R24) recommend total or near total thyroidectomy as the surgical therapy of choice for GD.⁴

Most recent series on surgical treatment of GD involve either small numbers or a long time span with a mix of subtotal and total thyroidectomy.⁵⁻¹² In the last decade our center has seen an increase in the number of patients referred for surgical treatment of GD. Here we evaluate the perioperative outcomes of a large and contemporary series of patients undergoing TT for GD at a high volume center.

Current ATA guidelines (R22 and R23) also recommend that patients be rendered euthyroid with methimazole preoperatively and that KI be given in the immediate preoperative period.⁴ The recommendation to render patients euthyroid with anti-thyroid medication is an effort to reduce the risk of thyroid storm that the stress of surgery could precipitate. KI is recommended to reduce thyroid gland vascularity with the goal of improving operative visualization and reducing operative complications. In this series we also evaluate the extent to which these recommendations were met and the extent to which failure to achieve these goals results in untoward effects.

Materials and Methods

After approval by the Institutional Review Board, a retrospective analysis of the medical records at a large, urban, academic hospital was conducted. All patients undergoing TT with a preoperative diagnosis of GD from July 1, 2007 through May 30, 2012 were included. During this time period no patients underwent subtotal thyroidectomy for GD. Information on preoperative medical history, operative characteristics, and post-operative complications was collected.

The diagnosis of GD was generally established by the referring endocrinologist or other referring provider utilizing clinical signs and symptoms, thyroid hormone and thyroid-stimulating hormone assays, radioactive iodine uptake and scan, and/or measurement of thyrotropin receptor antibodies. Patients were deemed ready for surgery based on the judgment of the surgeon in consultation with the referring endocrinologist if they were not clinically toxic and treatment had been initiated with anti-thyroidal medication and/or beta-blockers. Pre-thyroidectomy KI was not routinely used, although it was not discontinued if another provider prescribed it. Total thyroidectomy was performed at a single center by one of six endocrine surgeons. Recurrent laryngeal nerve monitoring was used in all cases. Operative site drains were not used. Patients were discharged the same day or after overnight observation unless a complication developed requiring longer inpatient hospitalization. Serum calcium levels were obtained the following morning and patients were placed on standard calcium supplements (1 gram of elemental calcium TID). Calcium levels were rechecked two weeks after thyroidectomy. Calcitriol was added when calcium levels were <7.8 mg/dL or when the patient was symptomatic. Parathyroid hormone (PTH) levels were not routinely checked unless clinically indicated.

Thyroid hormone status was defined based on the last set of laboratory values before operation. Because the rise in TSH following initiation of medical therapy lags behind the fall in thyroid hormone levels, T4 and T3 levels are used to gauge thyroid status in the early course of medical management rather than TSH values. As such, unless the TSH was frankly elevated, thyroid hormone status was defined based on T4 and T3 levels rather than TSH, consistent with clinical practice, as follows: hypothyroidism was defined as an elevated TSH level or a T4 or T3 level below the reference value; euthyroidism was defined as normal or low TSH level with normal T4 and T3 levels; mild hyperthyroidism was defined as either T3 or T4 level above the reference range but less than 1.5 times the upper limit of normal; moderate hyperthyroidism was defined as T3 or T4 level greater than 1.5 times the upper limit of normal, but not requiring hospitalization, and severe hyperthyroidism was defined as patients who were hospitalized for hyperthyroidism at the time of their operation, regardless of hormone levels.

The primary outcome of interest was any perioperative complication occurring within the first six months after TT. Post-operative hypocalcemia was defined as either a serum calcium level below the reference range or complaints of hypocalcemic symptoms requiring treatment during the immediate post-operative period. Prolonged post-operative hypocalcemia was hypocalcemia persisting beyond 6 months after TT. Permanent hypoparathyroidism was requirement for calcium supplements above a normal daily

supplement with low parathyroid hormone levels beyond 12 months. Recurrent laryngeal nerve (RLN) paresis was defined as subjective complaints of hoarseness at the first post-operative visit (2 weeks), while prolonged RLN palsy was defined as hoarseness and documented RLN paralysis at laryngoscopy persisting beyond 6 months.

Risk factors for complications were compared in both bivariate and multivariate analyses. Statistical significance on bivariate analysis was determined with the chi-squared test, with a p value of ≤ 0.05 representing statistical significance. Given the sample size, a maximum of 6 variables was set for regression analysis to limit loss of power from multiple comparisons. A subset of the patient characteristics were chosen for multivariate analysis based on the authors' hypotheses that these were the most likely to be clinically relevant. A logistic regression of the "any complication" variable on the selected risk factors was performed with heteroskedasticity-robust standard errors using Stata (StataCorp LP, College Station, TX). In the reported regression, subjects with missing observations were dropped.

Results

Patient Factors

165 patients underwent TT for GD during the period studied (Table 1). Mean age was 43 years, and 78% of the patients were female. Mean BMI was 28 kg/m², and 39% of the patients had a history of Graves' ophthalmopathy, defined as pre-operative diagnosis of Graves' ophthalmopathy by a referring physician based on history and physical exam. Smoking history was present in 32%. Preoperatively the majority (95%) of patients were taking methimazole or propylthiouracil. Three patients (2%) received KI preoperatively, as prescribed by their endocrinologists, while 15 (9%) were on steroids at the time of operation. The majority of patients (58%) were euthyroid or hypothyroid at the time of operation based on the above definitions. Based on the anesthesiologist assessment of patient comorbidities according to the American Society of Anesthesiologists Physical Status Classification system (ASA class), almost all patients were ASA Class 2 or 3, 62% and 36%, respectively. Median length of hospital stay was 1 day (range 0-10); the patient with the 10-day stay was hospitalized for psychiatric reasons not related to her operation; the next longest length of stay was 4 days. 156 patients (95%) were discharged within 23 hours of their operation. Patients were followed for a median of 7.5 months (range 0-52).

Reasons patients chose TT, rather than RAI or medical management, are presented in Table 2. The most common reason (38%) given was patient preference without specific references to indications or contraindications for any therapy. For 6% of the patients, no reason for surgery over other therapies was given in the record. For the remaining patients, reasons included concern for the exacerbation of ophthalmopathy with RAI, allergy or intolerance to medications, failed medical therapy, large thyroid with compressive symptoms or thyroid nodule(s) in addition to GD, contraindications to RAI, failed RAI, or desire for childbearing in the near future. Some patients had more than one reason for preferring total thyroidectomy, so the numbers sum to greater than 100%.

Operative Factors and Complications

Operative characteristics were as follows. Mean procedure time was 132 minutes (SD 39, range 59-271), and the median estimated blood loss was 30 mL (mean 55 mL, SD 98, range 10-1050). Parathyroid autotransplantation was performed in 23 (14%) cases, and in 13 (8%) cases pathologic analysis demonstrated parathyroid tissue inadvertently excised with the specimen. The mean weight of the excised gland was 41 grams (SD 29, range 8-180).

Complications are presented in Table 3. Sixty-eight distinct complications occurred in 61 of the 165 patients (37%). The most common complication was hypocalcemia, occurring in 51 (31%) patients. To what extent transient hypocalcemia represented transient hypoparathyroidism versus bone hunger is difficult to determine as routine PTH levels were not available on all patients. The majority of cases were transient, with only 6 patients (4%) experiencing hypocalcemia beyond 6 months. Of these six patients, four have returned to eucalcemia off supplements at 12 months follow-up. The remaining two patients continued to require calcium and calcitriol supplements; one had PTH level below the limit of detection at 12 months, and the other had PTH level of 5 pg/ml. Permanent hypoparathyroidism was therefore seen in 2 (1.2%) patients. RLN paresis was identified in 12 (7%) patients, but in only 1 (0.6%) did hoarseness persist beyond six months. Of these 12 patients, one (0.6%) suffered a RLN transection, which was identified and repaired intraoperatively. Although this patient had post-operative hoarseness, it did not persist beyond six months, and the patient declined laryngoscopy as she felt her voice had returned to normal. One patient (0.6%) developed a post-operative hematoma requiring emergent re-exploration. Three patients (2%) developed a seroma that required drainage at the first clinic visit, and one patient (0.6%) suffered a small tracheal injury that was identified and repaired intraoperatively with no sequelae. No patient developed thyroid storm perioperatively, nor did any patients develop hypertensive, cardiovascular, or neurologic complications.

Patient and operative factors were examined via bivariate analysis to identify risk factors of any complication (Table 4). On bivariate analysis the only risk factor found to be statistically significant for any complication was age less than 45 years. On multivariate regression analysis, age less than 45 years remained a significant risk factor and obesity became significant.

Given that such a large proportion of the patients in this series were hyperthyroid at the time of operation (42%), we sought to examine the implications for thyroid hormone status on outcomes. On bivariate and multivariate analysis, thyroid hormone status was not significantly correlated with complications. In the absence of any discernable effect on outcome, we used intraoperative beta-blocker administration as a surrogate for hemodynamic instability. Of the 70 patients who were hyperthyroid (mildly, moderately, or severely) at operation, 18 (26%) received intraoperative beta-blocker, compared with 15 of the 95 (16%) euthyroid or hypothyroid patients ($p=0.12$). Comparing the moderately and severely hyperthyroid patients as a group to all other patients, the former did have a significantly higher rate of beta-blocker usage (OR 2.65, 95% CI 1.16-6.01).

Discussion

Total thyroidectomy is a safe and effective therapy for GD. In this series, the most common complication, hypocalcemia, was, in general, transient. The most feared complication, RLN paresis, was uncommon and also generally transient. Rates of both complications (transient and permanent) were comparable with those demonstrated in previous studies of total and subtotal thyroidectomy for GD and after TT for non-toxic multinodular goiter. In these studies the incidence of transient hypocalcemia ranged from 3 to 40%, with the incidence of long-term hypocalcemia ranging from 0.6 to 6%. Similarly, the incidence of transient and permanent RLN palsy ranged from 0 to 24%, and 0 to 2%, respectively.⁵⁻¹⁵ In the current series, other complications, such as hematoma, seroma, and tracheal injury, occurred at very low rates. These data reconfirm the consensus that TT is a safe and appropriate initial therapy for GD when performed by high volume surgeons.

Current ATA guidelines recommend that patients be rendered euthyroid with methimazole preoperatively and that KI be given in the immediate preoperative period.⁴ The recommendation to render patients euthyroid with anti-thyroid medication stems from a concern that the stress of surgery could precipitate thyroid storm. In this series, the majority of patients were treated with anti-thyroid medications and no patient suffered from thyroid storm, even though a large proportion (42%) remained biochemically hyperthyroid at the time of operation. While the moderately and severely hyperthyroid patients did require more intraoperative beta-blockers, there was no evidence for any other untoward cardiovascular outcomes resulting from hyperthyroidism. On bivariate analysis, association between hyperthyroidism and complications approached statistical significance, but did not reach it ($p=0.059$). Adjusting for other factors via multivariate analysis, the association between hyperthyroidism and complications still failed to reach statistical significance ($p=0.120$). Thus, while we believe preoperative medical management is absolutely justified on the basis of symptom management, these data suggest that patients who remain biochemically hyperthyroid prior to surgery can still have good surgical outcomes.

The recommendation to administer KI preoperatively arose originally from HS Plummer's observation that administration reduced the risk of thyroid storm.¹⁶ Later, KI administration was noted to decrease thyroid vascularity on histologic examination.¹⁷ Only after the introduction of thionamides was the reduction in vascularity put forward as the primary justification for KI administration since its thyrostatic properties were less clinically important.¹⁸ The evidence for the utility of KI administration has been mixed, and much of the evidence in its favor comes from imaging studies assessing thyroid blood flow.¹⁹⁻²¹ The clinical importance of these imaging studies is difficult to extrapolate. Clinical studies have not consistently demonstrated any benefit to KI administration. An older double-blinded, randomized controlled trial showed no appreciable difference in blood loss at thyroidectomy or surgeon reports of operative difficulty whether or not KI was administered.²² A slightly later retrospective study came to a similar conclusion that KI did not make an appreciable clinical difference.²³ However, a more recent un-blinded, randomized trial by Erbil *et al.* did report a difference with administration of KI. In this trial 36 patients with GD were assigned either to pre-operative treatment with KI or to no treatment. These investigators

demonstrated a statistically significant difference in intraoperative blood loss (108 mL in the control vs. 54 mL in the KI group) favoring the KI group.²⁴

In the study by Erbil *et al.*, the estimated blood loss in the KI group (mean 54 mL) is similar to the blood loss we found in our series in which KI was almost never administered (mean 55 mL). Moreover, the 0.6% rate of reoperation for hematoma in our series is comparable to an 0.8% rate reported for a large series of parathyroid and thyroid operations of all types.²⁵ The number of patients taking KI preoperatively in the current study was too small to allow statistically meaningful comparison with those who did not. Since large intraoperative blood loss can potentially lead to poor visualization, longer operating times, increased incidence of hypocalcemia, RLN injury and hematomas we can not advocate that all surgeons should stop using KI preparation. Large, blinded randomized studies may be needed to further clarify the routine use of KI. However, these data do add to the studies that show that KI administration may have less clinical importance in modern thyroidectomy by high-volume surgeons.

This series also permits investigation into risk factors for complications. Young age (< 45 years old) was significantly associated with complications on both bivariate and multivariate analysis. By far, the most common complication overall was transient hypocalcemia (Table 4). This result correlates with a large registry-based study that found younger patients have an increased incidence of hypocalcemia after thyroidectomy for GD.¹³ Since definitions of hypocalcemia in these series include (in part) the development of symptoms, this was hypothesized to be due to younger patients possibly being more sensitive to and having more symptoms of hypocalcemia in the post-operative period, consistent with a previous analysis of hypocalcemia after thyroidectomy for GD.²⁶ However, this result is not consistent across studies, and some studies have identified older age as a risk factor for post-thyroidectomy complications.^{27,28} The data suggest clinicians may need to counsel younger patients about an increased risk of hypocalcemia when they discuss treatment plans.

On multivariate analysis, obesity was also significantly associated with occurrence of at least one complication. Previous studies have demonstrated that morbidity and operative time for thyroidectomy and parathyroidectomy are higher in overweight and obese patients.²⁹ It is plausible to assume that TT is more technically challenging in an obese neck and that post-operative complications would therefore arise more frequently in obese patients. Obese patients may also have more comorbid conditions that predispose to complications, but including ASA class in the regression should partially control for such confounding.

The current study has several limitations. As with any retrospective investigation, this study is limited to the data already present in the medical record. This report reflects the results of high volume surgeons (>100 thyroidectomy procedures per year) and its findings may not be generalizable. To the authors' knowledge, the present study represents the largest contemporary, U.S. experience of TT for GD.^{8,10,12} Nevertheless, the current study remains relatively small, and statistical inference on risk factors is thus limited. Even so, this observational study does shed further light on outcomes of TT for GD. It also points to the need for further comparative studies on the efficacy of KI.

This series demonstrates that, in the hands of high volume surgeons, TT for GD can be accomplished with minimal morbidity. It rightly has a place as the initial surgical treatment for GD. As experience accumulates, recommendations for preoperative management of GD may change and potentially be simplified. With accurate information on the risks of complications, physicians can counsel their patients to choose the therapy for GD that maximizes benefit and minimizes harms and best fits the patient's wishes.

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List of Abbreviations

ASA class	American Society of Anesthesiologists Physical Status Classification
ATA	American Thyroid Association
CI	Confidence Interval
PTH	Parathyroid Hormone
GD	Graves' Disease
KI	Potassium-iodide
PTU	Propylthiouracil
RAI	Radioactive Iodine

RLN	Recurrent Laryngeal Nerve
SD	Standard Deviation
TSH	Thyroid Stimulating Hormone
TT	Total Thyroidectomy

Table 1
Characteristics of 165 Patients with Graves' Disease

Characteristic	n (%)
Mean Age (years,+/-SD)	43 +/- 14
Sex	
Male	37 (22)
Female	128 (78)
BMI Status *	
Underweight	8 (5)
Normal Weight	45 (29)
Overweight	46 (27)
Obese	56 (36)
History of Graves' Ophthalmopathy	65 (39)
Smoker	53 (32)
Pre-op Medications	
Methimazole	133 (81)
PTU	23 (14)
KI	3 (2)
Steroids	15 (9)
Beta Blocker	92 (57)
Thyroid Hormone Status	
Euthyroid (%)	87 (53)
Hypothyroid (%)	8 (5)
Hyperthyroid (%)	70 (42)
-Mildly Hyperthyroid (%)	31 (19)
-Moderately Hyperthyroid (%)	27 (16)
-Severely Hyperthyroid (%)	12 (7)
ASA Class	
1	2 (1)
2	102 (62)
3	60 (36)
4	1 (0.6)

Characteristic	n (%)
Median Follow Up (months, Range)	7.50 (0-52)

PTU=propylthiouracil; KI=potassium iodide; TSH=thyroid stimulating hormone; T4=thyroxine; BMI=body mass index; ASA class= American Society of Anesthesiologists Physical Status Classification System

* There were 10 missing observations for BMI; percentages given are calculated based on the 155 patients with BMI information

Table 2
Reasons for Choosing Total Thyroidectomy over Medical or Radioactive Iodine (RAI) Therapy

Reason for Choosing Operation	n=165
Patient Preference	62 (38%)
Large Thyroid/Thyroid Nodules	37 (22%)
Ophthalmopathy	28 (17%)
Failed RAI	14 (8%)
Failed Medical Therapy	11 (7%)
Allergy/Intolerance to Medications	10 (6%)
Desire for Childbearing	10 (6%)
Reason not Addressed	10 (6%)
Contraindications to RAI	1 (0.6%)

Total sum is greater than 100% as more than one reason could be given for each patient

Table 3
Complications after Total Thyroidectomy for Graves' Disease

Complication	n=165 (%)
Any Complication	61 (37%)
Post-operative Hypocalcemia	51 (31%)
-Transient Post-operative Hypocalcemia	45 (27%)
-Prolonged Post-operative Hypocalcemia *	6 (4%)
RLN Paresis	12 (7%)
-Transient RLN Paresis	11 (7%)
-Permanent RLN Palsy	1 (0.6%)
Post-operative Hematoma	1 (0.6%)
Seroma	3 (2%)
Tracheal Injury	1 (0.6%)

RLN=recurrent laryngeal nerve

*, see text for detail, only two patients had permanent hypocalcemia

Table 4
Bivariate Analysis of Risk Factors for Any Complication after Total Thyroidectomy for Graves' Disease

Risk Factor	Patients with No Complications (n=104)	Patients with Any Complications (n=61)	p-value
Female	76 (73%)	51 (84%)	0.121
Age<45 years	48 (46%)	42 (69%)	0.005
Obese *	32%	42%	0.189
History of Graves' Ophthalmopathy	43 (41%)	22 (36%)	0.503
Smoker	33 (32%)	20 (33%)	0.741
Hyperthyroid at Operation	39 (38%)	31 (51%)	0.095
ASA Class 3 or 4	39 (38%)	22 (36%)	0.854
Operative Time >150 minutes	28 (27%)	19 (31%)	0.562
Parathyroid Autotransplantation	11 (11%)	12 (20%)	0.103
Parathyroid Excised	8 (8%)	5 (8%)	0.908
Thyroid Weight >40g	34 (34%)	22 (38%)	0.651

* Obesity defined as BMI greater than 30 kg/m². There were 10 missing observations for BMI; percentages given are calculated based on the 155 patients with BMI information.

ASA= American Society of Anesthesiologists Physical Status Classification system; BMI=body mass index

Table 5
Multivariate Logistic Regression of Risk Factors for Any Complication after Total Thyroidectomy for Graves' Disease

Risk Factor	Odds Ratio	95% Confidence Interval	p-value
Gender			
Male	1.00	---	
Female	1.53	0.65-3.59	0.331
Age			
45 years or over	1.00	---	
Under 45 years	2.93	1.39-6.19	0.005
Obesity			
BMI 30 kg/m ² or less	1.00	---	
BMI over 30 kg/m ²	2.11	1.00-4.43	0.049
Smoking History			
Non-smoker	1.00	---	
Smoker	1.23	0.59-2.59	0.579
Thyroid Status at Operation			
Hypothyroid or euthyroid	1.00	---	
Hyperthyroid	1.75	0.86-3.53	0.120
ASA Class			
1 or 2	1.00	---	
3 or 4	0.96	0.45-2.04	0.917

ASA= American Society of Anesthesiologists Physical Status Classification system; BMI=body mass index