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Total Thyroidectomy: a safe and effective treatment for Graves' disease

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Abstract

Background—Thyroidectomy as a first line treatment for Graves' disease is rarely utilized in the US. The purpose of this study was to analyze the safety and efficacy of thyroid surgery among patients with Graves' disease.

Methods—56 patients with Graves' disease underwent thyroid surgery between 05/1994 and 05/2008 at a single academic institution. Pre-operative, intra-operative, and post-operative variables were analyzed.

Results—A total of 58 surgeries were performed: 55.1% (n=32) total thyroidectomy, 41.3% (n=24) subtotal/lobectomy, 3.4 % (n=2) completion thyroidectomy. The average gland weight was 47.3 ± 10.8 gm, with 70% weighing > 30 gm. Reasons for having thyroid surgery were persistent disease despite medical therapy (46.6%), patient preference (24.1%), multinodular goiter/cold nodules (20.3%), failed RAI (radioactive iodine) treatment (16%), and ophthalmopathy (12.1%). Of those patients that failed prior RAI therapy, the only factor that was predictive of failure was disease severity, as demonstrated by a markedly elevated initial free-T4 value (11.8 ± 4.5 ng/dL, $p=0.04$). Transient symptomatic hypocalcemia occurred in 10.7% (n=6) of patients, and 1 patient (1.8%) had symptomatic hypocalcemia lasting > 6 months. There were no permanent recurrent laryngeal nerve injuries. There was no difference in overall complication rates between patients based on surgical procedure (subtotal vs. total thyroidectomy), preoperative RAI treatment, or gland size. Recurrences occurred in 6% of the subtotal thyroidectomy group and 0% of the total thyroidectomy group ($p=0.008$).

Conclusion—Thyroidectomy for patients with Graves' disease can be performed with very low complication rates and when a total thyroidectomy is performed there is almost no risk of recurrence.

Introduction

Graves' disease is an autoimmune disorder of the thyroid gland, and is the most common cause of hyperthyroidism. Treatment options for Graves' disease include anti-thyroid drugs (ATD), radioactive iodine (RAI), and surgery. The treatment modalities used vary in different parts of the world. In the United States, ATD are the most common initial treatment modality, followed by RAI when drug therapy fails¹. RAI is preferred by

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endocrinologists in the United States, whereas other European and Asian countries favor ATD followed by surgery². In the United States, thyroidectomy is rarely offered as a first line treatment option for patients with Graves' due to the fear of post-operative complications, such as permanent hypocalcemia and recurrent laryngeal nerve damage.

Recent literature supports the use of surgery as an initial treatment option for Graves' disease^{1,3,12,17}. Research shows that thyroidectomy has a lower recurrence rate than RAI or ATD,^{1,2,3,12,14,17}. In addition some patients with significant ophthalmopathy or goiter may be best served with surgical treatment². Additionally, studies have shown that in the hands of experienced surgeons, thyroid surgery can be done safely¹. This study analyzes the safety and efficacy of thyroid surgery for patients for Graves' disease, in order to determine if thyroidectomy should be considered a viable treatment option for all patients with Graves' disease.

Methods

A retrospective study of a prospective database at a single academic institution was conducted. Patients with Graves' disease who underwent thyroid surgery between May 1994 through May 2008 were identified. The majority of procedures were performed by one of four high volume endocrine surgeons, although all operative cases during this time period, regardless of surgeon experience, were included. The medical records were reviewed for preoperative variables such as thyroid function tests, use of ATD, RAI, and beta-blockers, Lugol's solution, past surgeries, and indication for surgery. The intraoperative variables for estimated blood loss, operative time, and complications were also documented. Post operative variables reviewed were gland size, weight, pathology of specimen, serum calcium level, parathyroid autotransplants, neck hematoma, recurrent laryngeal nerve damage, transient and permanent hypocalcemia. Statistical analysis for Students *t* test and chi-squared analysis were performed using SPSS (Version 16.0, Chicago, IL). A p-value less than 0.05 was considered statistically significant.

Results

Fifty-six patients were identified who underwent thyroidectomy for treatment of their Graves' disease. Family history of thyroid disease (hypothyroidism, hyperthyroidism, thyroid cancer or disease) was noted in 22 (39%) patients and eighty-six percent of patients were female, and the average age of patients was 31 ± 2 years old. None of the patients had a history of neck radiation, and 3 patients (5.4%) had a previous neck operation.

The mean baseline pre-operative TSH and free T4 values were 0.13 ± 0.38 mU/L and 7.7 ± 8.2 mcg/dL, respectively. Most patients (91%), received pre-operative antithyroid medication (72.5% PTU, 21.6% methimazole, and 5.9% both) and 12% (n=7) of patients developed allergies to these medications. Beta blockers were used in 69.6% of patients (n=39). Lugol's iodine solution was administered to 15 patients (25.4%) pre-operatively.

The most common reason for thyroid surgery was persistent disease despite medical therapy (46.6%). Patient preference was a major factor in 24.1% of the cases. Other reasons for surgery included patients having multinodular goiter/cold nodules (20.3%), failed RAI (radioactive iodine) treatment (16%), and ophthalmopathy (12.1%) (Figure 1).

We analyzed the subset of patients that had failed prior RAI therapy and compared them to the remainder of the cohort to determine if there was any factor that might be associated with the failure of RAI. The only factor that was associated with failed prior RAI treatment was disease severity, as demonstrated by a markedly elevated initial fT4 value (11.8 ± 12.8)

compared to the remainder of patients with a significantly lower fT4 value (6.8 ± 7.0 , $p=0.043$).

A total of 58 operations were performed, 41.3% (n=24) subtotal thyroidectomy/lobectomy, 55.1% (n=32) total thyroidectomy, 3.4 % (n=2) completion thyroidectomy. The average operative time was 145 ± 5 minutes, and the mean estimated blood loss (EBL) was 112 ± 17 mL. The average gland weight was 47.3 ± 10.8 gm with 70.2% of glands weighing > 30 gm. Three patients (5.1%) were found to have papillary thyroid cancer on final pathology. The largest tumor size was 30 mm and the smallest was 0.7 mm. One patient had a multifocal tumor.

Transient and permanent post-operative complications including hypocalcemia and recurrent laryngeal nerve damage were recorded prospectively in our database. The mean post-operative calcium was 8.5 ± 0.1 mg/dL (Table 1). Eleven percent (n=6) of patients experienced transient symptomatic hypocalcemia, and 1 patient (1.8%) had symptomatic hypocalcemia lasting > 6 months. There were no permanent recurrent laryngeal nerve injuries. We found no difference in overall complication rates between patients based on surgical procedure (subtotal vs. total thyroidectomy), whether or not they had received pre-operative RAI treatment, or based on gland size.

With a median follow up time of 9 (1–96) months, four patients (6%) developed recurrent disease. All recurrences occurred in patients who underwent a subtotal thyroidectomy (n=4, 16.6%), and there were no recurrences in the total thyroidectomy group ($p=0.008$). Two of the four patients who recurred subsequently underwent a completion thyroidectomy and two were treated with post-operative RAI, all were successfully treated.

Discussion

This study has shown that thyroidectomy is a safe and effective treatment for Graves' disease^{1–4}. However despite the low complication rates associated with thyroid surgery, this mode of treatment is still greatly underutilized in the United States. About 70% of the endocrinologists in the US still refer Graves' patients to I¹³¹ ablation as the first line treatment, where only 22% and 11 % of European and Asian endocrinologists prefer RAI¹⁷.

The complication rates of thyroid surgery are well established. Complications of thyroidectomy include transient hypocalcemia, permanent hypocalcemia, and recurrent laryngeal nerve damage. Bhattacharaya et al¹⁴ found that the post operative hypocalcemia is the most common immediate surgical complication (6%) after total thyroidectomy and recurrent laryngeal nerve paralysis occurs in 1%. Many physicians fear that the complication rates are higher in patients with Graves' disease due to the increase vascularity and inflammation found in these glands. Our complication rates are 11% and 2% for transient and permanent hypocalcemia and 0% for recurrent laryngeal nerve injury, which is consistent with the accepted standards. Several other studies support our results and have shown 6–20% for transient hypocalcemia and 0–3% for permanent hypocalcemia, and 0% for recurrent laryngeal nerve damage^{1, 2, 3, 16}, suggesting the thyroidectomy in patients with Graves' is safe, and is associated with a very low risk of complications. Our series is relatively small and was obtained from a high volume thyroid practice and most surgeries were performed by experienced endocrine surgeons. Therefore we cannot extrapolate our results to all surgeons performing thyroidectomy, and believe are results best reflect the practice of a high volume center, performing >50 thyroidectomies a year.

Our data suggests that the majority of patients that undergo thyroidectomy for Graves' disease only seek surgery after the failure of ATD and/or RAI. Although ATD and RAI can be effective treatment options, they are associated with much higher recurrence rates and are

not without their own complications. ATD are associated with allergies, and other side effects such as agranulocytosis, which can be life threatening. Additionally, propylthiouracil can induce severe liver failure, especially in children, with Graves' disease¹⁸. ATD have a remission rate of 50% after 1 year, and only 30 to 40 % at 10 years³, thus most patients experience recurrent Graves' disease once the medication is stopped. RAI is frequently used after initial treatment with ATD. RAI treatment has a latency period of 6 weeks to 6 months^{1, 3}. The effective dosage for RAI is often difficult to gauge, and patients often require multiple treatments. The risk of developing hypothyroidism during the first year following RAI treatment is 20–60% and it increases 3 to 5% per year after that, reaching 86% by 10 years^{1, 3, 4}. I-131 ablation is also a concern for small children and is an absolute contraindication for women who are pregnant or are lactating. There is much controversy regarding the increased risk of mortality after RAI. Studies have suggested that hyperthyroid patients who were treated with RAI have an increased cerebrovascular and cancer mortality⁷. Furthermore, Graves' ophthalmopathy is worsened by RAI and patients need to take steroids in conjunction with RAI to reduce the risk of progression^{8–11}. Subsequently, research has suggested that surgery might be a better treatment option for patients with Graves' ophthalmopathy, as ophthalmopathy has been reported to improve in 71–74% of Graves' patients after thyroid surgery¹². In addition, patients with Graves' ophthalmopathy have a higher risk of relapsing hyperthyroidism, and are less likely to go into remission, thus need to consider more definitive treatment options like surgery, instead of ATD or RAI which are less effective in preventing recurrence of disease¹³. Although RAI is still a very safe procedure, a recent paper published by Grodski et al stated that if patients were adequately educated about surgery and RAI, they develop significant fear of RAI and would rather face surgery¹. Furthermore, cost-effectiveness research has demonstrated that total thyroidectomy is more cost-effective than RAI or long-term ATD for the treatment of Graves' ¹⁹.

While surgery is an underutilized option for patients with Graves', some patients may not be good operative candidates due to co-morbid diseases or if they are unlikely to be compliant with thyroid supplementation post-operatively. Surgery may also not be the best option if they have previously undergone neck surgery as this may increase the risks of complications.

Thyroid cancer is not a rare finding in patients surgically treated for their Graves' disease. The incidence of thyroid cancer has been shown to be as high as 15–20%. In our study the risk of malignancy was only 5%, which may be related to our smaller patient population. In situations where nodules are malignant, total thyroidectomy offers a more definitive approach to Graves' patients, treating both the Graves' and the cancer simultaneously.

The estimated blood loss of 112 ± 17 mL is comparable to other study of Graves' patients receiving thyroidectomy, but is significantly greater than non-Graves' patients². Since about 70% of the patients had a goiter, the increased blood loss is mostly likely caused by hypervascularity of an enlarged thyroid gland. Multiple studies have indicated that the pre-operative use of lugol's solution can help reduce blood loss during surgery^{2–4}. This adjunct was only used in 20% of cases and has only been adopted routinely in our practice recently. Therefore, the beneficial effect of Lugol's solution may not be reflected in our data. When comparing subtotal vs. total thyroidectomy, total thyroidectomy is associated with less blood loss (135 ± 152 vs. 83 ± 118 mL). Interestingly, another study has reported similar findings in patients who underwent a total vs. subtotal (100.6 ± 268 vs. 202.1 ± 489.4 mL) resection. The higher blood loss in a subtotal resection is likely due to bleeding from the cut surface of a highly vascular thyroid gland. In addition, there was a shorter hospital stay for patients who received a total thyroidectomy¹⁶.

There is still substantial debate regarding whether subtotal vs. total thyroidectomy is the best operation for patients with Graves' disease. However from our study, all recurrences were observed in patients who underwent a subtotal and none in patients who underwent a total thyroidectomy. In addition, the complication rates were low in both groups. Although total thyroidectomy renders patients permanently hypothyroid, this is anticipated and can be easily treated with thyroid hormone replacement immediately post-operatively in order to avoid transient hypothyroidism. Most other treatment options also cause patients to become hypothyroid³, although this is less predictable and patients are more likely to become symptomatic before it is recognized and appropriate replacement is initiated.

Conclusion

This series has demonstrated that thyroid surgery (both subtotal and total thyroidectomy) are associated with a low rate of transient and permanent complications. While both surgical approaches provide rapid remission of disease, total thyroidectomy is associated with a much lower risk of developing recurrence of disease and hence is the surgical treatment of choice for Graves' disease. In the hands of experienced surgeons, total thyroidectomy is a safe and effective treatment modality that offers rapid and long-lasting results. In high volume centers (performing ≥ 50 thyroidectomies per year), surgery should be offered as a first line treatment option for patients with Graves' disease.

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Figure 1.
Reasons for patients with Graves' disease to undergo thyroidectomy

Table 1

Operative variables and postoperative complications

Surgery	Total	Subtotal	<i>p</i> -value
N (%)	32 (59)	24 (44)	
Estimated blood loss (mL)	83 ± 118	135 ± 152	0.045
Mean Operative time (min)	140 ± 40	157 ± 36	.023
Complications			
Transient hypocalcemia	4 (7)	2 (4)	NS
Permanent hypocalcemia	1 (2)	0	NS
Recurrent Laryngeal Nerve Injury	0	0	NS
Recurrence	0	4 (7)	0.008