Total thyroidectomy replaces subtotal thyroidectomy as the preferred surgical treatment for Graves' disease

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Short title: Total thyroidectomy for Graves' disease

Key words: Graves' disease, total thyroidectomy, subtotal thyroidectomy, complication, follow-up, recurrence.

Summary

Total thyroidectomy was introduced as the procedure of choice for patients with Graves' disease requiring surgical treatment in a single endocrine surgical unit. The outcome of subtotal thyroidectomy in treating Graves' disease was compared with that of total thyroidectomy. Total thyroidectomy was found to be as safe as subtotal thyroidectomy in terms of the occurrence of permanent hypoparathyroidism and recurrent laryngeal nerve palsy. A stable thyroid function can be maintained with thyroxine replacement without any risk of recurrence.

Abstract

Objective: Total thyroidectomy is increasingly adopted for patients requiring surgical treatment for Graves' disease based on a comparable surgical risk and the lack of recurrence as well as the questionable ability of subtotal thyroidectomy to maintain euthyroidism. We evaluate its safety and efficiency in our endocrine surgical unit. **Methods:** Total thyroidectomy has been adopted routinely during surgical treatment for Graves' disease from 2000. Patients (n=119) who underwent subtotal thyroidectomy (STT) from 1995-1999 were compared with those (n=98) who underwent total thyroidectomy (TT) from 2000-2003 with respect to immediate postoperative morbidity and long-term outcome. **Results:** Fourteen (11.8%) and 22(22.4%) patients required calcium supplement on discharge in the STT and TT groups respectively ($p<0.05$). One (0.8%) and 3(3.1%) patients developed permanent hypocalcaemia respectively. Transient recurrent laryngeal nerve palsy occurred in 9.2% (n=11) and 5.1% (n=5) of patients or 5.0% and 2.6% of nerves at-risk after STT and TT respectively. None of the patient had permanent nerve palsy. The estimated blood loss was less and hospital stay shorter after TT. During a mean follow-up of 64 months, 86 (72.3%) patients in the STT group required thyroxine replacement and 7 (5.9%) developed relapse. **Conclusion:** STT was associated with relapse as well as hypothyroidism in a significant proportion of patients during long-term follow-up. TT can be performed as safe as STT and should be recommended as the procedure of choice for patients requiring surgical treatment for Graves' disease.

Introduction

Graves' disease can be treated by antithyroid medication, radioactive iodine and surgery. When surgical treatment is indicated or selected for patients with Graves' disease, bilateral subtotal thyroidectomy (STT) has been recommended as the standard surgical procedure. The goal is to obtain rapid control of thyroid function by removing the pathological gland and leaving behind a small remnant of thyroid tissue to maintain adequate amount of thyroid hormones production, while being a relatively safe operation associated with low complication rates. However, recurrent hyperthyroidism from the remnant thyroid tissues occurred during long-term follow-up. From 1960's, a group of surgeons began to adopt a more radical approach to treat Graves' disease by total thyroidectomy (TT) in order to eliminate recurrence while maintaining an acceptable complication rate.[1] Since then, the surgical strategies adopted for Graves' disease has been a controversial issue with an increasing number of endocrine surgeons adopting total instead of subtotal thyroidectomy as the procedure of choice for patients requiring surgical treatment for Graves' disease. The aim of this study is to evaluate the safety of employing TT instead of STT as the procedure of choice for patients requiring surgical treatment for Graves' disease in an endocrine surgical unit by adopting a standard operative strategy as well as perioperative care over a consecutive time period. Patients who underwent surgical treatment by STT was compared with those by TT with reference to the occurrence of postoperative morbidity and the functional outcome during long-term follow up.

Patients and Method

Graves' disease was diagnosed based on the clinical presentation of thyrotoxicosis, usually in the presence of a diffuse goiter with or without thyroid eye signs. It was confirmed by hormonal and/or immunologic assays. Radioactive iodine scan would be performed for selected patients in case of diagnostic difficulty. Antithyroid medications were prescribed to patients routinely to achieve euthyroidism and, in addition, β-blocker was added for symptomatic control. Lugol's iodine was not administered.

STT was traditionally adopted as the procedure of choice in our institution because of the belief that long-term euthyroidism can be achieved and that complications may potentially increase with the adoption of TT. During STT, an estimated thyroid remnant of up to 2-3 grams was left on each thyroid lobe. Since 2000, total thyroidectomy was adopted as the procedure of choice and 5 STT were performed based on patients' wish. Patients who underwent near-total thyroidectomy with remnant of <1 grams based on intraoperative decision were analyzed in the TT group. During thyroidectomy for Graves' disease, bilateral recurrent laryngeal nerves were routinely identified and preserved. Routine perioperative laryngoscopy was performed within 1 week before and after the operations. All patients found to have recurrent laryngeal nerve palsy after the operations were referred to otorhinolaryngologist specialists for assessment and speech therapy. Repeated laryngoscopy was performed at regular interval during follow-up and permanent nerve palsy was defined as persistent palsy for >12 months after operations. Identification of all parathyroid glands was attempted

but extensive dissection would be avoided. Inadvertently removed or unequivocally devascularized parathyroid glands were removed routinely for immediate autotransplantation into the neck muscle.[2,3] Routine measurement of serum calcium was performed within 6 hours after surgery and at least once daily until stabilization during hospital stay. Replacement with calcium and/or vitamin D analogue was given when serum calcium level was less than 1.70 mmol/L (. normal 2.1-2.55 mmol/L) or patient developed symptoms of hypocalcaemia. Those who could discontinue the calcium and vitamin D analogue supplement in the presence of normocalcaemia within 12 months after operation were classified as temporary hypocalcaemia. Permanent hypocalcaemia was defined as the requirement of calcium supplement for >12 months during follow-up and was associated with a subnormal serum parathyroid hormone level (normal, 11-54 pg/ml).

Routine measurement of serum free thyroxine (T_4) and thyroid stimulating hormones (TSH) levels were done in all patients 3-6 months' interval for 2 years and then at 6-12 months' interval subsequently during follow-up visits. Patients with two consecutive persistent subnormal T_4 (normal 12-23 pmol/L) and/or elevated TSH (normal 0.35-5-5 mIU/L) levels during follow-up blood tests were regarded as having post-operative hypothyroidism and thyroxine replacement would be prescribed. Post-operative or recurrent hyperthyroidism was defined as persistently elevated T_4 or suppressed TSH requiring additional treatment during follow-up.

Data of all patients undergoing thyroidectomy by one endocrine surgical unit was prospectively entered into a thyroid database from 1995 and all patients surgically treated for Graves' disease up to June, 2003 were retrospectively reviewed. Patients who had history of partial thyroidectomy prior to the present operation were excluded. Complete follow-up data with respect to postoperative hypothyroidisim and recurrence was retrieved and all patients had a minimum follow-up of 6 months. Patients who underwent STT were compared with those who underwent TT with respect to demographics, operative details, postoperative complications and long-term outcome.

Statistical analysis was performed with the Student t test (continuous variables) and chi-square or Fischer's exact test when relevant (categorical variables). Recurrence was estimated using the Kaplan-Meier estimation method. $P < 0.05$ was regarded as statistically significant.

Results

There were 119 patients and 98 patients in the STT and TT groups respectively. Patients in both groups were comparable with reference to gender, weight of thyroid tissue resected and operative time except that patients who underwent TT (mean age$\pm$S.D.)(34.7$\pm$24.8 yrs) were older than those who underwent STT (27.9$\pm$13.8 yrs) ($p<0.001$). Patients who underwent TT had significantly less estimated blood loss (100.6$\pm$268.6 ml vs 202.1$\pm$489.4ml; $p<0.001$) during the operations compared with those who underwent STT. The hospital stay for patients who underwent TT (3.2$\pm$2.4 days) was significantly

shorter compared to those who underwent STT (4.2±3.0 days) ($p<0.001$) (Table I).

Eleven (9.2%) and 5 patients (5.1%) in the STT and TT groups respectively developed transient vocal cord palsy after the operations. One patient in the STT group was found to have bilateral cord palsy during routine laryngoscopy. However, the airway was adequate and tracheostomy was not required. Bilateral cords function recovered spontaneously within 3 months after the operation. There was no permanent recurrent laryngeal nerve palsy in all patients and vocal cord function recovered over a mean duration of 3.6 months (range, 1-8 months) after the operations. The incidence of transient recurrent nerve palsy according to the number of nerves at risk was calculated to be 5.0% (12 of 238) and 2.6% (5 of 196) for STT and TT group respectively. The difference in the incidence of nerve palsy between STT and TT was not statistically significant.

On the other hand, the incidence of postoperative hypocalcaemia was significantly higher for patients who underwent TT compared to those who underwent STT ($p=0.044$). Fourteen of 119 (11.8%) compared with 22 of 98 patients (22.4%) in the STT and TT group respectively developed hypocalcaemia in the postoperative period. During follow-up, 1 of 119 patients (0.8%) had persistent hypocalcaemia in the STT group compared with 3 of 98 patients (3.1%) in the TT group and the incidence of permanent hypoparathyroidisim was not statistically different between these 2 groups (Table II).

During a mean follow-up of 65 months (range 6-104 months), 86 patients (72.3%) in the STT group developed post-operative hypothyroidism and required thyroxine replacement. All patients in the TT group received thyroxine replacement on discharge and remained dependent on thyroxine to maintain euthyroid status during follow-up. Seven patients (5.9%) in the STT group developed recurrence within 10 to 60 months (mean 36 months). The recurrent hyperthyroidism rates were 2.6% and 6.0% at 3 and 5 years respectively (Figure 1). For the 7 patients having recurrence after STT, 5 received radioactive iodine ablation, 1 completion thyroidectomy and 1 medical treatment.

Discussion

The goal of treating Graves' disease is to control hyperthyroidism and to restore euthyroidism. There are three major treatment modalities available for Graves' disease, and each option has its advantages as well as potential problems or side effects. Surgery has been the main treatment option in the past until the mid 20th century when antithyroid medications and radioactive iodine became available. In addition, there has been a great geographical difference in the adoption of different treatment modalities for Graves' disease. Radioactive iodine ablation is now the preferred treatment in North America, while Europeans physicians favor antithyroid medication[4]. Surgery remains indicated for selected patients with nodules suspicious to be malignant, with large goitre in the presence of compressive symptoms, requiring rapid control, planning for

pregnancy, who fear radioactive treatment, with poor compliance and often for those who develop side effects or recur after antithyroid medication[5].

Subtotal thyroidectomy has been the gold standard for patients requiring surgical treatment for Graves' disease. It is believed that by leaving a small remnant of functioning gland behind, euthyroidism can be achieved without the need of life long thyroxine replacement. In addition, limited dissection is performed in the tracheo-esophageal grooves with minimal potential risk to both damaging the recurrent laryngeal nerves as well as the parathyroid glands. Therefore, it is thought to be a safer operation compared to TT with respect to postoperative recurrent laryngeal nerve palsy and hypoparathyroidism. However, this concept is being challenged by the excellent results achieved by an increasing number of endocrine surgeons who are adopting TT as the surgical treatment of choice for Graves' disease[6,7,8,9]. Total thyroidectomy for benign thyroid disease is likely to become an accepted component of the endocrine surgeon's armamentarium[10]. The only randomized control trial comparing TT and STT showed a significant difference in the incidence of transient hypoparathyroidism rate of 12% vs 28% in favor of STT. In addition, there was a tendency toward a higher permanent hypoparathyroidism in the TT (6% vs 10% with p=0.06)[11]. In a meta-analysis by Palit *et al*[12] on >7000 patients treated by either TT or STT, there was no statistical difference with respect to the incidence of two major complications, namely hypoparathyroidism and recurrent laryngeal nerve injury. Although we demonstrated a statistically significant difference in the incidence of transient hypoparathyroidism rate that favors STT, there was neither

any difference in the incidence of permanent hypoparathyroidism nor recurrent laryngeal nerve injury. For patients who underwent TT, the estimated blood loss and hospital stay were significantly less compared with those who underwent STT.

In addition, in contrary to the belief that STT is associated with additional advantage of achieving euthyroidism compared with TT, thyroid dysfunction is not uncommon after STT. A significant proportion of patients become hypothyroid during long-term follow-up after STT and post-operative hypothyroidism ranges from 4% to 75% in various reported series[13-20] (Table 1). In addition, it is not infrequent for recurrent hyperthyroidism to occur after STT and up to 20% of patients develop recurrence during long-term follow-up[21]. Majority of patients requiring surgical treatment has already rejected or had relative contraindications for other treatment modalities. Recurrent hyperthyroidism demands these patients to return back to other original declined treatment modalities or subjects patients to re-operations that carry a considerable surgical risk[22,23].

Different factors including the size of thyroid remnant, the presence of thyroid-stimulating hormone binding inhibitory immunoglobulin, antimicrosomal antibodies or antithyroglobulin antibodies, and the number of lymphoid infiltration in the thyroid gland have been studied to predict thyroid function after surgery. The size of the remnant remained the most consistent predictive factor for post-operative thyroid function with respect to both hypothyroidism and recurrent hyperthyroidism[8,16]. While Palit *et al*[12] in his meta-analysis showed that remnant size was negatively correlated with hypothyroidism, with an 8.9% decline in the

rate of hypothyroidism for each gram of thyroid remnant left. Euthyroidism was also positively and significantly correlated with remnant size, with a 6.9% increase in the rate of hyperthyroidism per additional gram of thyroid remnant left. As a result, there is no optimal remnant size during STT that guarantees euthyroidism after surgery. The chance of hypothyroidism becomes lower if more thyroid tissue is left behind, but the risk of recurrent hyperthyroidism becomes substantial. However, in retaining less thyroid tissue to reduce the chance of recurrent hyperthyroidism, it will be associated with higher risk of hypothyroidism. There is no consensus on how much thyroid should be left and it is reflected by the big variation of the post-operative thyroid status after STT. At the end, a small proportion of patients can achieve euthyroidism at the expense of a significant number of patients ending up in either hypothyroidism or hyperthyroidism.

In addition, the definition of hypothyroidism or hyperthyroidism affects the reported incidence of post-operative thyroid function. Some argue that latent hypothyroidism (normal T_4/T_3 levels with elevated TSH level) or latent hyperthyroidism (normal T_4/T_3 with suppressed TSH) are subclinical problems and should be counted as normal and reported as euthyroidism. The great variation in the duration of follow-up also contributes to the different results among various studies. The longer the follow up period is, the more likely patients with abnormal thyroid function will be detected. Dominello *et al*[14] showed a progressive onset of both hypothyroidism and recurrent hyperthyroidism with time. The proportion of patients with hypothyroidism increased from 48.5% at 6 months to 69.3% at 15 years after STT[14]. In addition, instability of thyroid function

is a common phenomenon after STT[14,18,24] and a significant proportion of patients cannot achieve euthyroidism after STT. For those who are euthyroid in the early post-operative period after STT, they still have a continuous risk of developing abnormal thyroid function. Therefore, long term monitoring of thyroid function is required. On the other hand, thyroid function is more predictable after TT and can be easily maintained with thyroxine replacement. In facts, hypothyroidism should be regarded as an end point of surgical treatment rather than a complication of total thyroidectomy. In our current study, a 72.3% incidence of hypothyroidism after STT seems to be relatively high compared to other studies. However, it can be attributed to the inclusion of latent or subclinical hypothyroidism during a relatively long follow-up period. And recurrent hyperthyroidism developed in 5.9% of patients. As a result, only 21.8% of patients remained euthyroid after STT.

In conclusion, despite the adoption of STT as the surgical treatment for Graves' disease, there remain a significant number of patients requiring thyroxine replacement apart from a small or substantial proportion developing recurrence. In experience hands, TT has been shown to be as safe as STT for surgical treatment of Graves' disease with respect to the occurrence of postoperative complication rates. However, it can provide a much more predictable thyroid functional outcome immediately after surgical treatment and during long-term follow-up with thyroxine replacement. Therefore, TT has replaced STT as the procedure of choice for patients requiring surgical treatment for Graves' disease.

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Table I. Comparison of demographics and operative details between the subtotal and total thyroidectomy groups

	Subtotal (n=119)	**Total (n=98)**	**p value**
Mean age (yrs)	27.9 (±13.8)	34.7(±24.8)	p<0.001
Sex ratio (M:F)	1:7	1:3.5	n.s.
Mean thyroid resected (grams)	66.7(±70.8)	63.5(±93.6)	n.s.
Mean operative time (mins)	153.2(±61.6)	148.2(±84.6)	n.s.
Mean blood loss (ml)	202.1(±489.4)	100.6(±268.6)	p<0.001
Mean hospital stay (days)	4.2(±3.0)	3.2(±2.4)	p<0.001

n.s: not significant

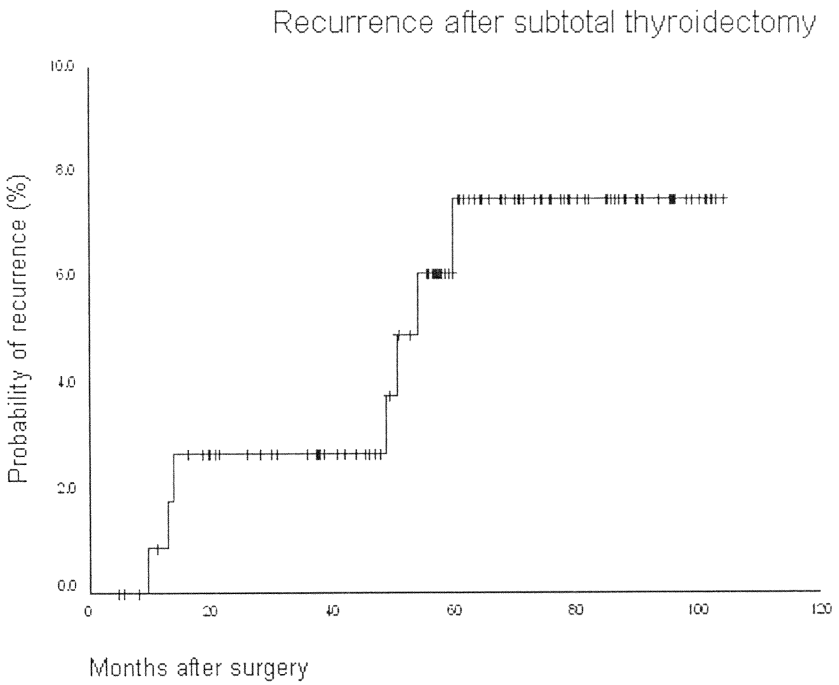
Table II. Comparison of complications after subtotal and total thyroidectomy

	Subtotal (n=119) No. (%)	Total (n=98) No. (%)	p value
Transient hypocalcaemia	14(11.8)	22(22.4)	0.04
Permanent hypocalcaemia	1(0.8)	3(3.1)	n.s.
Transient recurrent nerve palsy according to no. of patients	11*(9.2)	5(5.1)	n.s.
Transient recurrent nerve palsy according to nerve at-risk	12(5.0)	5(2.6)	n.s.

*: one patient with transient bilateral recurrent nerve palsy

n.s: not significant

Figure I.


Recurrence after subtotal thyroidectomy
Probability of recurrence (%)
10.0
8.0
6.0
4.0
2.0
0.0
0
20
40
60
80
100
120
Months after surgery