POSTOPERATIVE ENDOCRINE FUNCTION IN PATIENTS WITH SURGICALLY TREATED THYROTOXICOSIS

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Abstract: *Background.* Endocrine function after surgery for thyrotoxicosis is difficult to predict. The operative morbidity and long-term thyroid function of patients surgically treated for thyrotoxicosis is presented, and factors postulated to affect long-term function are correlated with outcome.

Methods. The clinical records of 289 consecutive patients who underwent surgery for thyrotoxicosis were reviewed. Indications for surgery, intraoperative findings, postoperative complications, and endocrine status 1, 2, and 5 years after surgery were analyzed. Sex, age, duration of medical treatment, weight of thyroid removed and preserved, and antimicrosomal/antithyroglobulin antibody status were correlated with outcome 5 years after surgery.

Results. The incidence of permanent recurrent laryngeal nerve injury and hypocalcemia were 0.7% and 1.7%. The cumulative hypothyroid and hyperthyroid rates for the first, second, and fifth postoperative years were 13.8% and 3.5%, 14.5% and 4.8%, and 15.6% and 8.0%. All the prognostic variables analyzed did not achieve a significant correlation with outcome at 5 years by univariate and multivariate age- and sex-adjusted relative risk.

Conclusions. Failure from hypothyroidism develops early; recurrent hyperthyroidism increases with the number of years of follow-up. Patients undergoing subtotal thyroidectomy warrant long-term follow-up because of the inability to accurately predict postoperative function with consistently reliable prognostic factors. © 2004 Wiley Periodicals, Inc. *Head Neck* **26:** 331–337, 2004

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Antithyroid medication, radioactive iodine (RAI) ablation, and surgery are all established modalities in the treatment of thyrotoxicosis. Treatment policies, although largely empirical, are influenced primarily by the patient profile, physician preference, and the geographic region. Medical management is still widely accepted as the first-choice modality in Europe, Japan, China, and New Zealand,[1–3] whereas RAI remains the mainstay of treatment in the United States.[4] Medical management of thyrotoxicosis consists of antithyroid medication for a duration of 12 to 18 months, with the expectation of remission on cessation of therapy. The main disadvantage of medical treatment, however, is the high relapse rate of between 20% and 75%.[5] The use of radioactive iodine in the treatment of thyrotoxicosis is associated with delayed onset, a high cumulative hypothyroid

incidence of greater than 70% over 10 years,[6] and a theoretic mutagenic risk in the young patient. Recent reports have also alluded to the aggravation of ophthalmopathy on commencement of RAI.[7]

Surgery as the initial modality of treatment is infrequently recommended.[8] Surgery offers the advantage of quick control and in experienced hands carries extremely low morbidity. Endocrine function after surgery, however, can be unpredictable; it is often difficult to estimate exactly how much tissue to remove or preserve and to predict which patients regain their euthyroid status, relapse, or become hypothyroid. Some patients continue to exhibit unstable function many years after surgery. Factors that may affect postoperative outcome have been studied, but no single factor has proven conclusive and consistently reliable in predicting the postoperative endocrine status.

We evaluate the results of patients undergoing a subtotal thyroidectomy for thyrotoxicosis in our institution to determine the postoperative status 1, 2, and 5 years after surgery. In addition, we analyze postulated prognostic factors to see if they might significantly influence postoperative outcome at 5 years in our patients.

MATERIALS AND METHODS

The clinical records of 289 consecutive patients who underwent surgery for thyrotoxicosis in the Department of Surgery, Singapore General Hospital, over a 5-year period from January 1990 to December 1994 were reviewed. Indications for surgery, intraoperative findings, and histologic reports were retrieved, and postoperative complications and long-term thyroid status were documented. All patients in this review underwent a bilateral subtotal thyroidectomy, preserving approximately 4 g of thyroid on either side. The capsule of the remnant gland was reapposed and sutured to the trachea with a running absorbable suture for both hemostasis and anchor. The amount of thyroid to preserve was estimated by the surgeon at the time of surgery by assuming a volume equivalent of 1 cm^3 to 1 g. An effort was made to identify both recurrent laryngeal nerves and all parathyroid glands routinely, and documentation was made in the clinical records when this was successfully done. Parathyroid glands thought to be compromised during surgery were autotransplanted into the ipsilateral sternocleidomastoid after histologic confirmation. Patients were assessed postoperatively clinically and biochemically with free thyroxine (fT4) and thyroid-stimulating hormone (TSH) titers. Patients were routinely, although not invariably, placed on 3-month follow-up for the first postoperative year and 4-month follow-up for the second year. The subsequent follow-up schedule was variable, determined largely by the patients' postoperative endocrine control and physician preference. Evaluation of function for this study was performed 1, 2, and 5 years after surgery. Recurrent thyrotoxicosis was diagnosed both by positive signs on clinical assessment and confirmatory biochemical evidence of elevated fT4 and suppressed TSH. Hypothyroidism was similarly diagnosed when the patient was clinically symptomatic and exhibited low fT4 and raised TSH levels. Euthyroid patients were divided into three categories: patients who were both clinically and biochemically euthyroid, patients clinically euthyroid with normal fT4 but raised TSH (subclinical hypothyroidism), and patients clinically euthyroid with normal fT4 but depressed TSH (subclinical hyperthyroidism).

Variables studied against postoperative outcome at 5 years were sex, age at diagnosis, age at surgery, duration of medical treatment, weight of thyroid removed, weight of thyroid preserved, and antimicrosomal and antithyroglobulin antibody status. In univariate analysis, χ^2 and Fischer's exact probability test were used for binary data. The level of significance was taken at $p < .05$, and SPSS (version 10.0) was used as the statistical software.

RESULTS

Of the patients studied, 82.7% were women, with a median age of 27.4 years at diagnosis and 31.8 years at surgery. The median interval from the commencement of medical therapy to surgical intervention was 4.4 years. The median follow-up was 71.3 months, with a range of 48 to 106 months.

Indications for Surgery. Failure of medical therapy was the main indication for surgery. This included noncompliance and drug-related problems. Miscellaneous reasons included personal choice, obstructive symptoms, and fear of malignancy (Table 1).

Preoperatively, a clinical diagnosis of Graves' disease was made in 90.6% of patients and toxic multinodular goiter in 9.3%; 78.6% of patients had raised levels of antimicrosomal antibodies, whereas 47.1% had raised antithyroglobulin antibodies.

Histopathologic findings correlated well with clinical assessment, with 87.5% exhibiting diffuse

Table 1. Indications for surgery.

Indication for surgery	% patients
Failed medical therapy	81.0
Noncompliance	24.6
Drug-related problems	10.0
Desire to conceive	5.2
Cosmesis	3.8
Miscellaneous	10.0

Table 2. Surgical morbidity.

Complication	No. patients (%)
Hemorrhage	8 (2.8)
Hypocalcemia	5 (1.7)
Tracheomalacia	3 (1.0)
Permanent hoarseness	2 (0.7)
Wound-related problems	12 (4.4)

hyperplasia and 9.1% nodular hyperplasia. Incidental well-differentiated papillary carcinoma, all less than 1 cm in diameter, was discovered in 3.4%. These patients were given suppressive thyroxine regardless of postoperative status.

Intraoperative Findings. The median weight of thyroid tissue removed was 69.5 g, with a range of 10 to 280 g. The median weight of thyroid tissue preserved, estimated by the surgeon at the time of surgery, was 6.6 g, with a range of 4 to 16 g.

Of operative records, 69.8% documented the preservation of at least one parathyroid, and 59.3% had complete documentation of preservation of all four. Both recurrent laryngeal nerves were identified and preserved in 94.5%.

Surgical Complications. Postoperatively, 284 patients (98.3%) had normal vocalization; five (1.7%) noticed a persistent subjective difference in voice quality, but only two (0.7%) had documented unilateral cord palsy on nasopharyngoscopy. One of these patients had emergency reoperation for primary hemorrhage (Table 2).

Eight patients (2.8%) required reexploration for hemostasis within 24 hours of surgery. All three patients with tracheomalacia had more than 200 g of thyroid removed. They were managed with mechanical ventilation postoperatively for between 1 and 3 days and were subsequently extubated without event. Permanent hypocalce-

mia, defined as clinical symptoms and biochemical hypocalcemia requiring oral replacement therapy more than 6 months after surgery, was documented in five patients (1.7%).

Wound problems, consisting of subcutaneous hematoma, infection, or keloid formation, were seen in 12 patients (4.4%). There was no incidence of a thyroid crisis or storm, and there was no surgical mortality.

Postoperative Outcome. Complete information was available in 274 patients (94.8%) in the first and second postoperative year, and in 213 (73.7%) in the fifth postoperative year. Patients lost to follow-up by the fifth year were either euthyroid at the time of discharge or defaulted from further follow-up after achieving a period of normal thyroid function (Table 3).

Forty patients became hypothyroid within the first year, whereas 10 had recurrent hyperthyroidism develop. The number of patients with hypothyroidism increased only marginally in the second postoperative year to 42, but the number who relapsed continued to increase steadily to 14. By the fifth year, there was only a small further increase in patients with overt hypothyroidism to 45 but a significant increase in the number of patients with recurrent thyrotoxicosis to 23.

Reviewing the failure trends over 5 years, it seems that most patients who become hypothyroid tended to do so early, with 77.8% of the total number declaring within the first postoperative

Table 3. Endocrine status first, second, and fifth postoperative year.

Postoperative year	First year (n = 274)	Second year (n = 274)	Fifth year (n = 213)
Euthyroid	226 (78.2)	218 (75.4)	145 (50.2)
Clinical/biochemical	168 (58.1)	162 (56.1)	121 (41.3)
Subclinical hypothyroid	37 (12.8)	36 (12.5)	15 (5.2)
Subclinical hyperthyroid	19 (6.6)	20 (6.9)	9 (3.1)
Hypothyroid	40 (13.8)	42 (14.5)	45 (15.6)
Hyperthyroid	10 (3.5)	14 (4.8)	23 (8.0)

Note. Values are number patients (%).

Table 4. Failure trend over 5 years.

	First year (%)	Second year (%)	Third year (%)
Hypothyroid *(n = 45)*	35 (77.8)	42 (93.3)	45 (100)
Hyperthyroid *(n = 23)*	10 (43.5)	14 (60.9)	23 (100)

year. The number of patients with recurrent hyperthyroidism, however, continued to increase with the number of years of follow-up. Only 43.5% of the total number of recurrences were seen in the first postoperative year (Table 4).

Of the total number of patients with recurrent hyperthyroidism, 56.5% exhibited prior biochemical evidence of "subclinical" disease (normal fT4, low TSH) before overt clinical and biochemical manifestations of recurrence developed. In the hypothyroid group, however, only 22.2% exhibited early biochemical evidence of "subclinical" disease, a reflection of the short duration it took before they were rendered overtly hypothyroid.

Correlation with Postoperative Outcome. Characteristics of patients who had surgery fail from hypothyroidism or recurrent hyperthyroidism were studied. Univariate analysis of risk ratio for sex, age at diagnosis, age at surgery, number of years of medical treatment, weight of thyroid removed, weight of thyroid preserved, and antimicrosomal and antithyroglobulin antibody status were conducted by logistic regression, and corresponding two-tailed *p* values were calculated. Significance for the two-tailed *p* value was placed at $p < .05$. Age at diagnosis and at surgery was compared between those 30 and younger and those older than 30. The weight of thyroid removed was compared between 60 g and less and greater than 60 g removed, and the weight of thyroid preserved was compared between 6 g and less and greater than 6 g preserved. These values were based on the medians of age at diagnosis, weight of gland removed, and weight of gland preserved, respectively. Antibody status was compared between those that were serologically positive preoperatively for antimicrosomal and antithyroglobulin antibodies with those that were negative. Multivariate analysis of age- and sex-adjusted risk ratio was conducted for the duration of medical treatment, weight of thyroid removed and preserved, and antibody status.

None of the variables studied achieved a statistically significant correlation with clinical outcome at 5 years both in univariate and age- and sex-adjusted analysis (Tables 5 and 6).

DISCUSSION

Three well-established treatment modalities exist for the management of thyrotoxicosis. The current trend in Europe, Japan, China, and New Zealand is for medical therapy as the first-line modality of treatment.[1-3] Carbimazole, its active metabolite methimazole, and propylthiouracil all inhibit thyroid peroxidase and hence thyroid hormone synthesis. Only 30% to 40% of patients treated with antithyroid medication achieve long-term remission,[8] but whether this is spontaneous because of amelioration of hyperthyroidism or because of an immunomodulatory action of the drugs remains unclear. Attempts to consistently predict outcome with reliable indicators, including HLA typing, have been unsuccessful,[9] although young patients with large goiters, significant ophthalmopathy, or high antibody titers are unlikely to have permanent remission.[10] Prospective studies comparing different drug regimens, including low- and high-dose thionamides with and without thyroxine replacement, have not revealed any significant difference in outcome.[11] A prospective randomized trial has also established that prolonging treatment beyond 18 months confers no additional benefit on the titration regimen, contrary to earlier studies that

Table 5. Univariate analysis of risk ratio with postoperative outcome at 5 years.

	Hypothyroid	Hyperthyroid
Sex	1.23 (0.40–3.77), *p = .71*	0.79 (0.16–3.90), *p = .77*
Age at diagnosis	0.7 (0.25–1.96), *p = .50*	0.16 (0.02–1.29), *p = .08*
Age at surgery	0.92 (0.36–2.35), *p = .85*	0.28 (0.07–1.1), *p = .06*
Years of medical treatment	0.98 (0.88–1.08), *p = .79*	0.98 (0.87–1.12), *p = .77*
Thyroid removed	2.87 (0.79–10.44), *p = .11*	0.67 (0.20–2.27), *p = .52*
Thyroid preserved	1.81 (0.67–4.86), *p = .24*	2.71 (0.69–10.61), *p = .15*
Antimicrosomal Ab	0.84 (0.25–2.86), *p = .52*	1.37 (0.41–4.62), *p = .61*
Antithyroglobulin Ab	0.74 (0.28–1.90), *p = .53*	1.37 (0.41–4.62), *p = .61*

Table 6. Multivariate analysis of age- and sex-adjusted risk ratio for postoperative outcome at 5 years.

	Hypothyroid	Hyperthyroid
Years of medical treatment	0.94 (0.82–1.08), $p = .40$	0.95 (0.80–1.12), $p = .54$
Thyroid removed	2.71 (0.73–10.03), $p = .14$	0.53 (0.15–1.88), $p = .52$
Thyroid preserved	1.81 (0.67–4.89), $p = .24$	2.51 (0.63–10.04), $p = .19$
Antimicrosomal Ab	0.84 (0.25–2.86), $p = .77$	2.52 (0.68–9.31), $p = .17$
Antithyroglobulin Ab	0.73 (0.28–1.90), $p = .52$	1.45 (0.42–5.00), $p = .61$

reported failure rates being inversely proportional to the duration of treatment.[12] The most serious complications of medical therapy are agranulocytosis, with an incidence of 3 per 10,000 patient-years,[13] and acute hepatotoxicity, which may progress and result in fatality despite discontinuation of the drugs.[14]

RAI is the preferred initial treatment for patients in North America.[4] It is safe and cost-effective[15] but is contraindicated in pregnancy and for those who are breast feeding. It has also been reported to worsen ophthalmopathy.[7] Standardized mortality rates after RAI are slightly increased,[16] and although an increased risk of benign thyroid tumors has been reported,[17] the total incidence of cancer is unchanged[18] or reduced.[19] Various methods of dose selection have been used, the most common being a formula based on estimated thyroid size and 24-hour RAI uptake. Hypothyroidism rates vary, from early reports of 2% to 3% per year to more than 70% at 10 years[6] to 95% within 3 months for advocates of a high single-dose cure protocol.[20] Regardless of the manner of dose selection, however, hypothyroidism can occur weeks, months, or years after treatment.[21] In fact, present thinking is that hypothyroidism is an almost inevitable eventual result and not necessarily a complication if the patient has adequately consented. Radioactive ablation is also recommended for failure from recurrent thyrotoxicosis after surgery.[22]

Surgery as the first-choice treatment modality in a moderate uncomplicated case of thyrotoxicosis is recommended in only about 1% of patients in the United States, Europe, and Japan.[4,23,24] Surgery offers a definite therapeutic advantage of rapid control and low morbidity. Absolute indications include patients with clinically suspicious nodules, compressive symptoms, pregnancy, or contraindications to either antithyroid medication or RAI. A young patient with a diffusely enlarged gland is ideally suited for surgery.[25] The reluctance to offer surgery has traditionally been due to the complications associated with surgical intervention. With improve-

ments in perioperative control and surgical technique, however, complication rates have been reduced dramatically, and mortality has been virtually negated. The incidence of the two most important complications, permanent recurrent laryngeal nerve injury and permanent hypocalcemia, has been reduced to less than 1%.[26,27] Surgical options include a subtotal thyroidectomy in the form of either a bilateral subtotal thyroidectomy or unilateral total lobectomy and contralateral subtotal lobectomy (Hartley-Dunhill operation), preserving 4 to 8 g of thyroid, or a total surgical ablation in the form of a total thyroidectomy for definitive cure and a predictable postoperative outcome.[28,29] Most studies do not show significant differences in complication rates between a subtotal or total thyroidectomy.[30,31] Our preference is to perform a bilateral subtotal thyroidectomy. Our cumulative failure rate (both hypothyroidism and recurrent thyrotoxicosis) of approximately 24% suggests that up to three fourths of our patients can be medication free 5 years after surgery.

Hypothyroid rates after surgery range from 3% to 48%,[32] and recurrent hyperthyroidism occurs in between 1% and 28%.[33,34] Our incidences of hypothyroidism of 15.6% and of recurrent hyperthyroidism of 8% at 5 years reflect our principle of resecting more than less gland, accepting that failure from hypothyroidism is preferable to that from relapse, which is often more difficult to treat. An interesting observation in our series is that patients who have hypothyroidism develop tend to do so early, with more than three fourths being seen within the first postoperative year. Patients who have recurrent disease, however, continue to declare even up to 5 years after surgery. Sugino et al[35] suggest that early and late recurrences might be due to different factors.

The ability to be able to accurately predict postoperative outcome after a subtotal thyroidectomy continues to elude us. Because surgery requires long-term follow-up to determine treatment failures, it does not offer a therapeutic benefit over the other treatment modalities in this respect. In an

effort to prognosticate postoperative treatment failures, various authors have studied preoperative factors that might correlate with postoperative outcome. No single factor has been proven to be consistently reliable. The factor most frequently reported to have a significant correlation with postoperative outcome is the weight of thyroid preserved.[36–39] Other positive significant correlations have been drawn with the degree of lymphocytic infiltration[37,39,40] and with antithyroid antibody titer.[37,39,41] Many of these findings, however, remain unsubstantiated in other literature on the subject, and the only factor that has possibly gained some degree of universal acceptance is the weight of thyroid remnant. Undermining all methods of prognostication is the natural history of an autoimmune disease, encompassing a wide spectrum of morphologic, histopathologic, and functional abnormalities and an over simplistic attempt to predict outcome by simple binary parameters. In a practical context, however, the weight of thyroid preserved is indeed the only factor under the direct control of the surgeon and hence most relevant to the surgeon, regardless of reported significance or otherwise.

All the variables that we studied in our series of patients, both by univariate and by age- and sex-adjusted multivariate relative risks, did not achieve a statistically significant outcome with postoperative outcome.

CONCLUSION

Surgery continues to have an important role in the management of thyrotoxicosis, although as an established modality of treatment it is probably underused. Definite indications as the primary modality of treatment exist, although in present-day practice, it often remains an adjunct to medical therapy or to RAI ablation. Surgical morbidity is low, and long-term postoperative function is acceptable. A reliable means of predicting postoperative outcome accurately and consistently, however, still eludes us, and until such a means is developed, its usefulness as a primary modality of treatment for thyrotoxicosis remains limited to selected patients.

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