Objective: To examine the indications for operation and the frequency, efficacy, and outcome of surgical therapy for thyrotoxicosis.

Methods: The medical records of all patients who underwent thyroidectomy between 1990 and 1998 were reviewed. Operative indications, laboratory evaluations, extent of thyroidectomy, pathologic findings, and morbidity and mortality were determined for patients with thyrotoxicosis.

Results: Of the 347 patients who underwent thyroidectomy, 54 (16%) had thyrotoxicosis, secondary to Graves’ disease (32 patients), toxic multinodular goiter (18 patients), thyroiditis (2 patients), or amiodarone (2 patients). The indications for operation were compressive symptoms or substernal extension or both (35 patients), patient preference (12 patients), thyrotoxicosis (4 patients), or a dominant nodule (3 patients). Most patients received pharmacological preparation, followed by total (32 patients), near-total (13 patients), subtotal (8 patients), or unilateral (1 patient) thyroidectomy. The initial 8 patients with Graves’ disease underwent subtotal thyroidectomy, and after a mean 28-month follow-up, 1 was euthyroid; 2, hyperthyroid; and 3, hypothyroid. Associated carcinoma was present in 4 (7%) of the 54 patients. Symptomatic hypocalcemia occurred in 10 patients (19%), with a mean free thyroxine level of $60.49 \pm 16.09$ pmol/L vs $40.41 \pm 19.56$ pmol/L ($4.70 \pm 1.25$ ng/dL vs $3.14 \pm 1.52$ ng/dL) in 25 patients (46%) with asymptomatic hypocalcemia ($P < .05$). Vocal cord paresis and a hematoma requiring operative evacuation occurred in 1 patient each. There was 1 mortality in a patient with amiodarone-induced thyrotoxicosis.

Conclusions: Massive thyroid enlargement with compressive symptoms, a dominant nodule, and patient preference are indications for surgical treatment of thyrotoxicosis. Near-total or total thyroidectomy is safe and more effective than subtotal thyroidectomy in preventing recurrence and should be considered in most patients referred for surgical treatment of thyrotoxicosis. Transient postoperative hypocalcemia is common and is related to the severity of thyrotoxicosis.


HYRROTOXICOSIS is a syndrome characterized by signs and symptoms of hypermetabolism and increased sympathetic nervous system activity that results from excessive thyroid hormone. The most common cause of thyrotoxicosis is Graves’ disease, accounting for 60% to 90% of all cases of thyrotoxicosis. Toxic multinodular goiter and a solitary toxic nodule are less common causes of thyrotoxicosis. The treatment alternatives for thyrotoxicosis include antithyroid drugs, thyroid ablation with iodine 131 ($^{131}$I), and thyroidectomy. In the United States, $^{131}$I is the predominant modality used for treatment of thyrotoxicosis. Many clinicians have questioned the necessity of surgical therapy for thyrotoxicosis. At one large tertiary care institution, only 3 patients with Graves’ disease were treated with thyroidectomy during a 25-year period. Factors that need to be considered when deciding on an appropriate treatment plan for patients with thyrotoxicosis include patient age; associated ophthalmopathy; the size of the thyroid gland; the presence of compressive symptoms, substernal thyroid extension, or a concomitant dominant nodule; contraindications to the use of radioiodine; intolerance to antithyroid drugs; response to previous therapy; and patient preferences. The purpose of this study was to determine how often thyroidectomy is performed for treatment of thyrotoxicosis, delineate the reasons why patients with thyrotoxicosis are referred for thyroidectomy, and assess the efficacy and outcome of surgical therapy for thyrotoxicosis.

RESULTS

Of the 347 patients undergoing thyroidectomy, 54 (16%) were referred for treatment of thyrotoxicosis. Of these, 43 (80%) were women. Ages ranged from 23 to 85 years (mean age, 42 years). The cause of thyrotoxicosis was Graves’ disease in 32 patients (59%), toxic multinodular goiter in 18 (33%), relapsing thyroiditis in 2
PATIENTS AND METHODS

A retrospective review of all patients undergoing thyroidectomy between 1990 and 1998 was completed, and those who underwent thyroidectomy for thyrotoxicosis were identified. Their medical records were reviewed for demographic data, the cause of thyrotoxicosis, clinical manifestations, results of baseline thyroid function tests, alkaline phosphatase levels, and the presence of a dominant nodule or substernal extension. In patients with Graves’ disease, the presence of ophthalmopathy was noted. Whether patients underwent preoperative pharmacological preparation was determined, and the agents used were characterized. The indications for operation, extent of thyroidectomy, management of the parathyroid glands, weight of the resected thyroid gland, postoperative calcium levels, final pathologic findings, and morbidity and mortality were also identified. Operative reports were reviewed to determine success at identifying the recurrent laryngeal nerves and the frequency of parathyroid gland autotransplantation.

A comparative analysis of free thyroxine (FT$_4$) and alkaline phosphatase levels was completed for patients with symptomatic vs asymptomatic postoperative hypocalcemia. The severity of thyrotoxicosis in patients with Graves’ disease was compared with that in patients with other causes of thyrotoxicosis. The reference ranges for the laboratory indices analyzed were: FT$_4$, 9.40 to 25.87 pmol/L (0.73 to 2.01 ng/dL); thyrotropin, 0.46 to 3.59 mIU/L; calcium, 2.1 to 2.5 mmol/L (8.4 to 10.0 mg/dL); and alkaline phosphatase, 25 to 136 U/L. The statistical significance of differences was determined using a $t$ test. $P<.05$ was considered significant.

The indications for operation in the 32 patients with Graves’ disease were massive thyroid enlargement with compressive symptoms (17 patients), a dominant nodule (3 patients), and patient preference (12 patients), including 2 who had failed radioiodine treatment and 6 patients with concerns about radioiodine-induced aggravation of their ophthalmopathy. The extent of thyroidectomy in patients with Graves’ disease included 17 total, 7 near-total, and 8 subtotal thyroidectomies. The average weight of the resected thyroid gland was 72 g (range, 20-210 g). In our early experience, we performed subtotal thyroidectomy, leaving bilateral 3-g remnants of thyroid tissue in 8 patients, 1 of whom after a mean 28-month follow-up was euthyroid; 2, hyperthyroid; and 5, hypothyroid. Pathologic evaluation of the dominant nodule in 3 patients with Graves’ disease revealed a 2-cm papillary carcinoma in 1 and a follicular adenoma in 2. One patient without a dominant nodule had an incidental occult microscopic papillary carcinoma.

Eighteen patients underwent thyroidectomy for toxic multinodular goiter, with substernal extension in 11 and compressive symptoms in 13. A total thyroidectomy was performed in 12 patients, near-total thyroidectomy in 5, and a unilateral resection of a large substernal goiter in a single elderly patient with subclinical thyrotoxicosis, minimal disease in the contralateral thyroid lobe, and a markedly attenuated recurrent laryngeal nerve on the side of the substernal goiter. The average weight of the resected gland in patients with toxic multinodular goiter was 184 g (range, 34-1025 g). One patient had an incidental 2.5-cm medullary carcinoma diagnosed on final pathologic examination.

Two patients with relapsing thyroiditis experienced alternating episodes of symptomatic hyper- and hypothyroidism for 5 and 10 years’ duration. Their FT$_4$ levels were 30.37 pmol/L (2.36 ng/dL) and 55.34 pmol/L (4.3 ng/dL), and both had a low radioiodine uptake. Near-total and total thyroidectomies were performed, with excision of a 10-g and 24-g thyroid gland. The final pathologic finding was chronic lymphocytic thyroiditis in both patients, 1 of whom also had an incidental 0.4-cm papillary carcinoma.

Two patients underwent total thyroidectomy for amiodarone-induced thyrotoxicosis that was resistant to antithyroid medications. One patient, previously described,$^3$ was a 72-year-old man with significant cardiopulmonary disease and refractory ventricular arrhythmias, who had a 30.7-g thyroid resected. The second patient was an 85-year-old paraplegic man with significant cardiopulmonary disease, refractory supraventricular arrhythmias, and a massive multinodular goiter, causing shortness of breath, dysphagia, and swelling of his face and neck. He had a computed tomographic scan that showed a large substernal goiter displacing the trachea and esophagus (Figure 1). At operation, the patient was noted to have a massive substernal goiter (Figure 2). The weight of the resected thyroid gland was 292 g. On the fifth postoperative day, the patient developed acute respiratory distress, secondary to an aspiration pneumonitis. Because of his comorbid diseases and in accordance with his living will, the family allowed him to die, with comfort measures only. This was the only mortality in our series.


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Intraoperatively, the recurrent laryngeal nerves were identified in all patients. There was no incidence of nerve transection. Two or more parathyroid glands were preserved in situ in all patients. Thirteen patients (24%) had 1 or 2 parathyroid glands autotransplanted into the sternocleidomastoid muscle.

Postoperative complications included vocal cord paresis in 1 patient that resolved 1 month after a near-total thyroidectomy for Graves’ disease. One patient developed a hematoma that required operative evacuation following subtotal thyroidectomy for Graves’ disease. Two patients, both with Graves’ disease treated by subtotal thyroidectomy, developed recurrent thyrotoxicosis. Postoperative hypocalcemia occurred in 35 patients (65%), 10 (29%) of whom were symptomatic. The mean pretreatment FT$_1$ level in patients with symptomatic hypocalcemia was 60.49±16.09 pmol/L vs 40.41±19.56 pmol/L (4.70±1.25 ng/dL vs 3.14±1.52 ng/dL) in patients with asymptomatic hypocalcemia ($P<.05$). The mean pretreatment alkaline phosphatase level in patients with symptomatic hypocalcemia was 147±55 U/L vs 145±80 U/L in patients with asymptomatic hypocalcemia ($P>.05$). No patient developed permanent recurrent laryngeal nerve injury, permanent hypoparathyroidism, or thyroid storm. The average follow-up for the entire group was 22 months.

**COMMENT**

Graves’ disease, an autoimmune disorder of uncertain origin, accounted for 59% (32 patients), and toxic multinodular goiter, a disease characterized by multiple autonomously functioning thyroid nodules, accounted for 18 (33%) of the patients with surgically-treated thyrotoxicosis in our series. Patients with toxic multinodular goiter were noted to have larger thyroid glands and more frequent substernal extension and compressive symptoms. Although patients with toxic multinodular goiter were more likely to have local symptoms related to marked thyroid enlargement, patients with Graves’ disease had more severe thyrotoxicosis, as evidenced by significantly higher pretreatment FT$_1$ levels. Thyrotoxicosis from thyroiditis or amiodarone-induced thyrotoxicosis was uncommon. No patient with a solitary toxic nodule was referred for surgery in our series.

Patients with thyrotoxicosis constituted 16% (54/347) of all patients referred for thyroidectomy at our institution during the 9-year study. The most common reason for recommending surgical therapy was marked thyroid enlargement, with associated substernal extension or compressive symptoms or both. In patients with massive thyroid enlargement, multiple radioiodine treatments are often required to treat thyrotoxicosis, with little effect on the size of the thyroid gland. This was true for 2 of our patients with Graves’ disease, who opted for surgical treatment after 1 and 2 treatments with $^{131}I$ failed to ameliorate their thyrotoxicosis.

An associated dominant nodule with abnormal findings on fine-needle aspiration biopsy was the principal indication for surgery in 3 (9%) of our patients with Graves’ disease, 1 diagnosed as having a papillary carcinoma and 2 as having a follicular adenoma. This underscores the importance of obtaining an $^{123}$I thyroid scintiscan in patients with a dominant thyroid nodule and a fine-needle aspiration biopsy that is consistent with a follicular neoplasm when a serum thyrotropin level is low.$^8$ This is necessary to differentiate a hypofunctioning nodule in a patient with Graves’ disease, where the risk of malignancy varies from 10% to 50%, from a hyperfunctioning nodule, where the incidence of malignancy is less than 1%.$^6,7$

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**Figure 1.** Computed tomographic scan of a patient with amiodarone-induced thyrotoxicosis and multinodular goiter showing (A) a large substernal goiter displacing the trachea and esophagus and (B) extension of the thyroid to the level of the arch of the aorta.

**Figure 2.** Intraoperative photograph of a large substernal thyroid gland in a patient with amiodarone-induced thyrotoxicosis and multinodular goiter (the patient’s head is to the right).
The second trimester, with the use of an intravenous nario. Optimally, the surgery should be performed during
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referred for 1 or 2 radioiodine treatments, and 6 patients were concerned about the potential for radioiodine-induced aggravation of their ophthalmo-
reported a 4.7% incidence of clinically relevant and 3.3%
methods, and 6 patients were concerned about the potential
Two patients had failed either 1 or 2 radioiodine treat-
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that most patients with thyrotoxicosis. Patients with
cholesterol antagonist, if necessary. No pregnant patients with
patients treated with131I. Total thyroidectomy has been recom-
potential for worsening of Graves’ eye disease in patients
radioiodine-induced aggravation of their ophthalmopathy. Tallstedt and colleagues10 have previously reported
considering the remnant size is inherently difficult.
able outcome as it may subject patients to131I therapy, which
between 1.2% and 16.2% (*Table*).2,11,13-19 This can be ex-
results demonstrate that near-total and total thyroidectomy in patients with thyrotoxicosis can be per-
low morbidity. We attribute this to several factors. The first is the use of preoperative pharmacological
in our experience, subtotal thyroidectomy with 3-g rem-
subtraction is inherently difficult. Even if such a determination could be made, standard-
been helpful in reducing intraoperative bleeding, which
tissue to leave a euthyroid state remains controversial. Bradley and Liechle14 described their technique of leaving two 5-g remnants, each attached to an
achieved in 92% of 107 patients followed up for more than 2 years. Others have not been able to demonstrate a clear-cut relationship between the
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advocated to decrease thyrotropin receptor antibodies and
One of the major advantages of surgical treatment that appeals to many patients is the rapid
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mid-term assessment of patients’ thyroid function post-
operatively. Since more than 30% of patients with thyrotoxicosis treated by bilateral subtotal thyroidectomy be-
come hypothyroid within 20 years of surgery, close follow-up is required to prevent delay in recognition and treatment of hypothyroidism.2,13 Following near-total or total thyroidectomy, all patients are immediately started
replacement dose of thyroid hormone.
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dular goiter; a papillary carcinoma in 2 (6%) of 32
lymphocytic thyroiditis. Pellegriti and colleagues14 have previously reported a 4.7% incidence of clinically relevant and 3.3% incidence of occult differentiated thyroid carcinoma in a series of 450 patients with Graves’ disease.
Bilateral subtotal thyroidectomy has been advocated for patients with Graves’ disease to establish a eu-
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gal nerve injury and hypoparathyroidism. How much

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*NR indicates not recorded.*

Patient preference was the primary reason for opera-
tion in 12 (38%) of the 32 patients with Graves’ disease. Two patients had failed either 1 or 2 radioiodine treat-
ments, and 6 patients were concerned about the potential for radioiodine-induced aggravation of their ophthalmo-
high levels of thyrotropin receptor antibod-
ies.9 Total removal of the abnormal thyroid antigens is
advocated to decrease thyrotropin receptor antibodies and
other antibodies that are directed against the extraocular muscles and optic nerve.9 One of the major advantages of surgical treatment that appeals to many patients is the rapid
reversal of symptomatic thyrotoxicosis, whereas a 6- to 12-week delay in symptom resolution is not unusual for pa-
ients receiving radioiodine therapy. These reasons underscore the clinician’s responsibility to discuss all therapeutic
alternatives for thyrotoxicosis with the patient.

Another generally accepted indication for surgical man-
agement of Graves’ disease is for pregnant women who are
intolerant to antithyroid drugs. This is an uncommon sce-
nario. Optimally, the surgery should be performed during
the second trimester, with the use of an intravenous β-re-
ceptor antagonist, if necessary. No pregnant patients with
thyrotoxicosis and intolerance to antithyroid drugs were
referred for surgical therapy in our series.

The overall incidence of carcinoma in our surgically-
treated patients with thyrotoxicosis was 7% (4 patients).
This included an incidentally discovered 2-cm medul-
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dular goiter; a papillary carcinoma in 2 (6%) of 32
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cult microscopic lesion; and a 0.4-cm occult papillary carcinoma in 1 of our 2 patients with lymphocytic thy-
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Our results demonstrate that near-total and total thy-
roidectomy in patients with thyrotoxicosis can be per-
formed with a low morbidity. We attribute this to several
factors. The first is the use of preoperative pharmacologi-
ical preparation that has effectively eliminated thyroid storm. Iodine administration in patients with Graves’ disease has
been helpful in reducing intraoperative bleeding, which
can affect the identification and preservation of the recur-
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thyroid hormone. Amiodarone-induced thyrotoxicosis is a rare disorder, reported in fewer than 3% of patients taking this antiarrhythmic agent. Amiodarone is taken up by the thyroid gland, and its high iodine content produces an increase in iodine stores available for hormone synthesis. It has also been shown to damage thyroid cell membranes, resulting in increased release of large stores of thyroid hormone. Amiodarone-induced thyrotoxicosis has also been reported to occur in patients with preexisting thyroid disease, most commonly multinodular goiter. It is often resistant to amiodarone withdrawal and conventional pharmacological therapy. Mulligan et al demonstrated that near-total thyroidectomy is safe and effective in producing rapid resolution of symptoms in patients with amiodarone-induced thyrotoxicosis. The only mortality in our series occurred in a patient with amiodarone-induced thyrotoxicosis, emphasizing that these patients may be at higher risk for surgery related to their underlying comorbid diseases.

Transient postoperative hypocalcemia is common following thyroidectomy for thyrotoxicosis, occurring in 35% (65%) of our patients. The causative mechanism is not completely understood. Postoperative hypocalcemia has been attributed to parathyroid insufficiency due to injury, devascularization, or inadvertent excision of parathyroid glands. In patients with thyrotoxicosis, other causes of temporary hypocalcemia include calcium uptake by bone in patients with thyrotoxic osteodystrophy or parathyroid suppression from increased calcium resorbed from the bone of patients with hyperthyroidism. Transient postoperative hypocalcemia was symptomatic in only 10% (19%) of our patients, with a mean pretreatment FT 3 level that was significantly higher than that in patients with asymptomatic hypocalcemia. This supports earlier findings from our institution that the development of symptomatic postoperative hypocalcemia is related to the severity of thyrotoxicosis. In most patients, symptomatic postoperative hypocalcemia resolved within 2 weeks of surgery.

In conclusion, our results demonstrate that surgical therapy has an important role in patients with thyrotoxicosis, accounting for 54% (16%) of the 347 thyroidectomies performed at our institution during a 9-year period. Our series emphasizes that massive thyroid enlargement with compressive symptoms, a dominant nodule with abnormal fine-needle aspiration biopsy findings, failed radiiodine therapy, or patient preference, especially when there are concerns about radiiodine-induced aggravation of ophthalmopathy, are established indications for surgical treatment of thyrotoxicosis. Near-total or total thyroidectomy, when it can be performed safely, should be considered for definitive management of Graves' disease, toxic multinodular goiter, chronically remitting thyrotoxicosis secondary to thyroiditis, and amiodarone-induced thyrotoxicosis. Transient symptomatic postoperative hypocalcemia is common in patients with surgically-treated thyrotoxicosis and is related to the severity of thyrotoxicosis.

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Corresponding author and reprints: Christopher R. McHenry, MD, Department of Surgery, MetroHealth Medi-cal Center, Case Western Reserve University School of Medicine, 2500 MetroHealth Dr, Cleveland, OH 44109-1998.

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