

# Surgery for Graves' disease. A review of 378 cases

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## ABSTRACT

Surgery for Graves' disease is usually reserved for patients who have failed conservative treatment, which consists chiefly in antithyroid drugs in Europe and in radioiodine therapy in the United States. Either total or subtotal thyroidectomy can be used.

**Study objectives:** To compare adverse event rates with total and subtotal thyroidectomy. Our working hypothesis was that rates would be similar.

**Patients and methods:** We retrospectively reviewed the medical charts of 378 patients with Graves' disease who underwent thyroidectomy in our department between 1973 and 2002; thyroidectomy was subtotal in 312 patients and total in 66 patients. Reasons for surgery, postoperative thyroid function, surgery-related complications, and cancer rates were studied in the overall population and compared between the two thyroidectomy groups.

**Results:** The most common reason for surgery was failure of pharmacotherapy (ineffectiveness, side effects, or recurrence after drug discontinuation). Thyroid function was normal in 59.8% of patients after subtotal thyroidectomy; 6.9% of patients treated with this procedure experienced recurrent Graves' disease. Permanent recurrent laryngeal nerve palsy and permanent hypocalcemia were noted in 1% and 2.3% of patients, respectively, with no significant difference between total and subtotal thyroidectomy. The cancer rate was low (1.8%), and all cancers were micropapillary carcinomas.

**Conclusion:** Thyroidectomy provides excellent outcomes with a very low adverse event rate and no significant differences between total and subtotal thyroidectomy. The current tendency of endocrinologists to request total thyroidectomy can be expected to reduce the rate of recurrences, which are difficult to treat. (*Fr ORL - 2005 ; 86 : 10-16*)

**Keywords:** Hyperthyroidism, Graves' disease, Total thyroidectomy, Subtotal thyroidectomy, Thyroidectomy, Adverse events.

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Submitted for publication: March 2004

Accepted for publication: January 2005

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### INTRODUCTION

A triad of hyperthyroidism, goiter, and exophthalmos combined with palpitations and occurring chiefly in women was described in 1835 by Robert James Graves of Ireland and in 1840 by Karl Adolph Basedow of Germany. Graves' disease is a manifestation of an underlying autoimmune disorder in which antibodies bind to thyroid-stimulating hormone (TSH) receptors on the thyroid cell membrane, stimulating both the function and the growth of thyroid cells [1]. If left untreated, Graves' disease can cause life-threatening cardiac manifestations and sight-threatening ophthalmopathy.

The treatment of Graves' disease seeks to suppress thyroid function. This can be achieved with antithyroid drugs, radioactive iodine, or surgery. Antithyroid drugs are used as the first-line treatment in Europe. Either a mercapto-imidazole derivative (carbimazole or methimazole) or a thiouracil derivative (propylthiouracil or benzothiourecil) [2] is given orally for 18 months. Although these drugs are rapidly effective, they carry a risk of agranulocytosis requiring close monitoring of blood cell counts. Furthermore, 50% of patients experience a relapse upon treatment discontinuation.

Radioactive iodine ( $^{131}\text{I}$ ) acts more slowly, after about 2 months. Iatrogenic events are uncommon, although the initial release of thyroid hormone may precipitate the occurrence of thyroid storm. A brief course of antithyroid drug therapy is given both to prevent thyroid storm and to alleviate the symptoms during the time needed for the radioactive iodine to destroy the thyroid gland. No adverse effects on fertility have been documented. Radioactive iodine treatment cannot be used during pregnancy. The dose of  $^{131}\text{I}$  is calculated on the basis of estimated thyroid weight and radioiodine

uptake [3]. The patient remains in an isolation room for 24 to 48 hours to protect against radioactive contamination. Thyroidectomy is used in only about 1% of patients, in Europe, Japan, and the United States [4]. Total or subtotal thyroidectomy can be performed. In both cases, pharmacotherapy to normalize thyroid function must be given prior to surgery to protect against thyroid storm. Subtotal thyroidectomy seeks to cure the disease without inducing hypothyroidism but may be followed by a relapse, requiring removal of the thyroid remnants, a procedure fraught with difficulty. Total thyroidectomy

consistently induces hypothyroidism requiring life-long hormone replacement therapy.

The objective of this study was to compare outcomes after total and subtotal thyroidectomy. Our working hypothesis was that adverse events would be similar with these two procedures.

### PATIENTS AND METHODS

We retrospectively reviewed the medical charts of 402 patients who underwent thyroidectomy for Graves' disease in our department between 1973 and 2002. Data were incomplete for 24 patients, who were excluded. This left 378 patients for the study. There were 322 (85.2%) women and 56 (14.8%) men with a mean age of 38 years (range, 16-68 years). Of the 378 patients, 312 underwent subtotal thyroidectomy (usually leaving the posterior surface of the right lobe) and 66 underwent total thyroidectomy.

For each patient, the following data were abstracted from the medical charts: reason for surgery, complications, postoperative hormonal status, and whether cancer was found. The total thyroidectomy and subtotal thyroidectomy groups were compared for these data. Over the study period, we noted an increase in the number of requests for total thyroidectomy made by endocrinologists and patients for reasons that were formerly uncommon, i.e., nodules, side effects of medical treatment, and ophthalmopathy; consequently, we conducted a separate analysis of the 118 patients treated during the last 11 years (1992-2002), of whom 72 underwent subtotal thyroidectomy and 46 total thyroidectomy.

Preoperative preparation to prevent thyroid storm consisted of treatment with an antithyroid drug (carbimazole) and a beta-adrenoceptor antagonist. When faster preparation was required, we used iodine as Lugol solution daily for 15 days. Mean postoperative stay length was 4 days. Patients were evaluated at our department's outpatient clinic at least once, 2 months after surgery, for a physical examination and serum assays of TSH and calcium. Subsequently, follow-up was delivered by the referring endocrinologists. Permanent recurrent laryngeal nerve palsy was defined as palsy persisting after 1 year. Permanent hypocalcemia was defined as a need for calcium and vitamin D supplements for longer than 6 months after surgery.

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### Statistics

Comparisons were done using the chi-square test. When required by sample sizes, Yates' correction and Fisher's test were used. P values smaller than 0.05 were considered statistically significant

### RESULTS

The reasons for surgery in the overall study population (n=378) were

- one or more recurrences after pharmacotherapy (54.7%)
- adverse reactions to pharmacotherapy (7.6 %)
- ineffectiveness of pharmacotherapy (10.3 %)
- planned pregnancy (6.4 %)
- presence of thyroid nodules (3.9 %)
- recurrence after radioiodine therapy or surgery (3.1 %)
- large goiter (5.5 %)
- exophthalmos or cardiac disease (5.5 %).

A similar distribution of reasons for surgery was found among the 118 most recent patients (Table I). In this subgroup, factors that were more common in patients who underwent total as opposed to subtotal thyroidectomy were presence of nodules, side effects of pharmacotherapy, ophthalmological complications, and recurrence after subtotal thyroidectomy; however, only for presence of nodules was the difference statistically significant ( $P<0.05$ ). The main reasons for subtotal thyroidectomy were recurrence after pharmacotherapy and ineffectiveness of pharmacotherapy (Table I).

**Thyroid hormone status after surgery** in the overall population and the subgroup of recently treated patients is reported in Table II. Among the 118 recent patients, 59.8% of those treated with subtotal thyroidectomy had normal thyroid function, whereas all those treated by total thyroidectomy had hypothyroidism.

The recurrence rate in this subgroup after subtotal thyroidectomy was 6.9%; however, this may be an underestimation, as follow-up was short for some of these patients and recurrences may develop several years after subtotal thyroidectomy.

The lower rate of euthyroidism after subtotal thyroidectomy in the recent patients as compared to the overall population is probably ascribable to the introduction of the ultrasensitive TSH assay, which is more likely to detect hypothyroidism than were earlier tests.

**The rate of complications** in the overall population and in the recent patients is reported in Table III. In the recent population, a comparison of complication rates with subtotal vs. total thyroidectomy found no statistically significant differences.

- Thyroid storm occurred in only 1% of patients; no cases were recorded after 1992.
- *Hematoma* responsible for compression was rare also (1.8%).
- Temporary unilateral recurrent laryngeal nerve palsy occurred in 1.8% of patients overall and 1.4% of recent patients; in this last group, all cases occurred after subtotal thyroidectomy.
- *Hypocalcemia* was the most common postoperative complication. Temporary hypocalcemia occurred in 7.6 % of patients overall; in the recent subgroup, this complication was significantly more common after total thyroidectomy (10.8 %) than after subtotal thyroidectomy (1.4 %). The higher rate of temporary hypocalcemia after total thyroidectomy is consistent with the difficulties encountered in dissecting the posterior surfaces of the thyroid lobes, which may result in transient vascular supply deficiencies responsible for abnormal parathyroid function. The rate of permanent *hypocalcemia* was far lower, 2.3 % overall, and was similar in the recent patients after total and subtotal thyroidectomy, pointing out the functional aspect of dysfunction rather than anatomical .

**Cancer** was found in 7 (1.8 %) patients overall and in 5 (4.3 %) recent patients. All 5 recent patients had *micropapillary carcinoma*.

### DISCUSSION

The treatment of Graves' disease seeks to restore normal thyroid function as rapidly as possible, while minimizing the risk of recurrence and of hypothyroidism.

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**Table I: Reasons for thyroidectomy in the 118 patients treated during the last third of the study period (1992-2002) The main reasons for total thyroidectomy were presence of nodules, side effects of pharmacotherapy, exophthalmos, and recurrence after subtotal thyroidectomy.**

	Subtotal thyroidectomy (n=72)	Total thyroidectomy (n=46)	value p
Recurrence after pharmacotherapy	58.3%	30.4%	n.s.
Recurrence after subtotal thyroidectomy	0%	8.7%	n.s.
<b>Nodules</b>	<b>5.5%</b>	<b>23.9%</b>	<b>p&lt; 0.05</b>
Side effects of pharmacotherapy	8.3%	17.4%	n.s.
Ineffectiveness of pharmacotherapy	15.3%	15.2%	n.s.
Exophthalmos	1.3%	4.4%	n.s.

*n.s.: not statistically significant (P≥0.05).*

**Table II: Postoperative thyroid function**

	1973-200(n=378)		1992-2002 (n=118)	
	Overall population (n=378)	Subtotal thy- roidectomy (n=312)	Total thyroidectomy (n=46)	Subtotal thyroidectomy (n=72)
Hypothyroidism	39.1%	23.7%	100%	33.3%
Hyper-thyroidism	8.2%	6.0%	0%	6.9%
Euthyroidism	52.6%	70.3%	0%	59.8%

**Tableau III: Complications**

	1973-2002 (n=378)	1992-2002 (n=118)		
		Total (n=46) thyroidectomy	Subtotal (n=72) thyroidectomy	p value
Temporary hypocalcemia	7.6%	10.8%	1.4%	0.03
Permanent hypocalcemia	2.3%	2.1%	1.4%	n.s.
Temporary recurrent laryngeal nerve palsy	1.8%	0.0%	1.4%	n.s.
Permanent recurrent laryngeal nerve palsy	1.0%	0.0%	1.4%	n.s.
Hematoma with compression of neighboring structures	1.8%	2.1%	0.0%	n.s.
Thyroid storm	1.0%	0.0%	0.0%	n.s.

*n.s.: non significatif (P≥0.05).*

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The first-line treatment of typical Graves' disease is an antithyroid drug in 88% of patients in Japan and 77% of those in Europe, as compared to only 30% of those in the US [4]. Radioiodine ( $^{131}\text{I}$ ) is the preferred first-line treatment in the US (69% of patients) [4] but is used in Europe and Japan as a second-line treatment (22% and 11% of patients, respectively [4]). Although radioactive iodine can provide a definitive cure for the hyperthyroidism, the results are unpredictable and slow to develop. The rate of hypothyroidism after radioactive iodine therapy is 12% after 1 year and increases gradually over time to 76% after 11 years [5]. Recurrent or persistent hyperthyroidism has been reported in 33.5% of patients after 1 year. This requires additional doses of radioactive iodine therapy, each of which must be followed by strict isolation in a hospital for several days to avoid leakage of radioactivity. In addition, an antithyroid drug must be given as long as the hyperthyroidism persists [3-6], so that exposure of the patient to the side effects of therapy is increased. Finally, an additional burden associated with recurrent or persistent hyperthyroidism is the need for close follow-up to monitor hormone levels and blood cell counts.

Surgery is used in about 1% of patients with Graves' disease in Europe, Japan, and the US [4]. Surgery is a radical and fast-acting treatment. The reasons for surgery reported in the literature are similar to those found in our study: recurrence after pharmacotherapy, side effects of antithyroid drugs (mainly hematological toxicity), poor compliance with antithyroid drug therapy, presence of nodules with a need to rule out cancer; cardiac or ophthalmologic complications of Graves' disease, recurrence after radioiodine therapy or subtotal thyroidectomy, and patient preference. Inadequate effectiveness of antithyroid drug therapy is usually due to poor compliance.

When the decision to perform surgical treatment is taken, a choice must be made between total and subtotal thyroidectomy. In our study, 70.3% of the patients who underwent subtotal thyroidectomy ( $n=312$ ) had normal thyroid function, but 23.7% had hypothyroidism requiring hormone replacement therapy. In the recent patients, the recurrence rate was 6.9%, in keeping with earlier studies [7-8]. Whether one or both posterior lateral surfaces or one or both superior poles are left in place seems less relevant than the weight of the thyroid remnants: several stu-

dies [9-10] have found a positive correlation between the recurrence rate and the weight of the thyroid remnants. There is general agreement that 4 g to 8 g of tissue should be left in place [11-12]. Below 2 g, hypothyroidism seems to occur consistently. Thus, the challenge resides in estimating the amount of tissue left. The most accurate method may be to perform total lobectomy on one side and subtotal lobectomy on the other, comparing the weights of the two specimens [13-15]. Leaving a few cubic centimeters on either side of the trachea [16] or leaving an amount similar in size to the second phalanx of the surgeon's thumb [17] has been reported to yield good results. There is a consensus that remnant weight estimation by the surgeon is heavily dependent on subjective factors. Because hypothyroidism is easier to treat than recurrent hyperthyroidism, excessive resection is usually felt to be preferable over leaving large remnants. We share this opinion.

The risk of surgery-related adverse events also influences the choice between total and subtotal thyroidectomy. Lesions of the parathyroid glands and recurrent laryngeal nerves are the main complications. In one study [18], no difference was found between total and subtotal thyroidectomy. Of the 346 patients treated with subtotal thyroidectomy, 2.6% experienced temporary recurrent laryngeal nerve palsy and none had permanent palsy; of the 34 patients treated with total thyroidectomy, 1 had permanent palsy. The rate of temporary hypocalcemia was 1.82% after subtotal thyroidectomy and 1.3% after total thyroidectomy [18]; corresponding rates for permanent hypocalcemia were 0.78% and 0.26%, respectively.

We conducted a separate analysis of the 118 patients treated during the last third of our study period (1992 to 2002). Temporary hypocalcemia was significantly more common among the 46 patients who underwent total thyroidectomy (10.8%) than among the 72 patients treated with subtotal thyroidectomy (1.4%) ( $P=0.03$ , Fisher's test). However, permanent hypothyroidism occurred in similar proportions of patients in these two groups (2.1% vs. 1.4%) (NS). Temporary hypocalcemia was less common when the inferior part of a thyroid lobe was left in place. This is consistent with the fact that the inferior thyroid artery supplies the inferior parathyroid glands and often the superior parathyroid glands also [19]. A study comparing bilateral subtotal thyroidectomy

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to total lobectomy on one side with subtotal lobectomy on the other found no differences in adverse event rates [13]. In our experience, endocrinologists increasingly request total thyroidectomy for patients with side effects of antithyroid drugs, ophthalmopathy, or thyroid nodules (significant difference for this last reason, Table I). Total thyroidectomy in patients with thyroid nodules is warranted by the risk of cancer.

Recurrent hyperthyroidism after surgery for Graves' disease is due to persistence of the underlying pathophysiologic mechanism, which can act on thyroid remnants if these are sufficiently large. Recurrent hyperthyroidism after subtotal thyroidectomy can be treated by total thyroidectomy. In one study, the early recurrence rate was 14.6%, and risk factors included not only a larger amount of residual thyroid tissue, but also higher preoperative levels of TSH binding inhibitory immunoglobulin and of antithyroid microsomal antibodies [20]. Thus, high levels of these two antibodies prior to surgery may warrant removal of a larger proportion of thyroid tissue.

Of the 118 patients who underwent surgical treatment during the last third of our treatment period (1992-2002), 5 (4.3%) had micropapillary cancer discovered only upon histological examination of the operative specimen. Total thyroidectomy was the only cancer treatment used in these 5 patients. Similarly, in a 1985 study [20], 5.1% of patients with Graves' disease had papillary cancer. The antibody that stimulates thyroid-cell function in Graves' disease may also stimulate the genesis and proliferation of thyroid cancer cells. However, autopsy studies in patients without Graves' disease found occult thyroid cancer in 5% to 30% of individuals [21]. We believe these micropapillary cancers discovered upon histological examination are incidental tumors that carry little risk of further progression.

### CONCLUSION

Thyroidectomy is a definitive, fast-acting, and highly effective treatment for Graves' disease. In addition, adverse events are uncommon provided the surgeons are experienced and the patients are given medical treatment to normalize thyroid function prior to surgery.

The relative merits of total and subtotal thyroidectomy remain debated. Total thyroidectomy should be recommended in patients with thyroid nodules, ophthalmological complications, side effects of pharmacotherapy, or high levels of immunological markers for Graves' disease. Given the risk of recurrence due to stimulation of thyroid remnants and the effectiveness of hormone replacement therapy, endocrinologists are increasingly requesting total thyroidectomy as the first-line surgical procedure. In addition, patients often prefer a definitive treatment.

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