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Patient outcomes following thyroid surgery for thyrotoxicosis

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Abstract

Objective. Total thyroidectomy can be used as a definitive treatment modality for thyrotoxicosis. This study assessed the outcomes of patients treated with surgery at a single secondary care site.
Method. A retrospective cohort study was conducted analysing consecutive patients who underwent thyroid surgery for thyrotoxicosis between 24 November 2000 and 26 April 2019 ($n = 595$).
Results. Total thyroidectomy was performed in 95.4 per cent of patients. Two-thirds of patients had Graves' disease histology. Of patients, 22.8 per cent became transiently hypothyroid whilst on levothyroxine (thyroid hormone replacement therapy). Transient and persistent hypocalcaemia was present in 23.3 per cent and 2.8 per cent of patients respectively. Recurrent laryngeal nerve palsy was transient and persistent in 3.6 per cent and 0.3 per cent respectively. Of patients, 2.5 per cent developed post-operative haematomas that required surgical evacuation in the operating theatre.
Conclusion. The overall complication rate for thyroid surgery is higher in thyrotoxic than in euthyroid patients. Compared to other treatment modalities, total thyroidectomy appears to be the most effective, definitive means of managing Graves' disease.

Main Article

Mr D Selwyn takes responsibility for the integrity of the content of the paper

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Introduction

Thyrotoxicosis is a disease characterised by inappropriately high levels of thyroid hormone acting at the tissue level.[1] This can be due to activation at any level of the hypothalamic–pituitary–thyroid axis. It predominantly affects women, and is most commonly associated with Graves' disease or autoimmune hyperthyroidism.[2]

Thyrotoxic patients can be treated medically in the first instance, with thionamide therapy unless contraindicated, to achieve remission. Once in remission, patients can be treated definitively by means of: surgery, a time-limited course of thionamide therapy or radioiodine treatment. The American Thyroid Association published guidelines in 2016, which stated that any three of those modalities may be considered as a first-line treatment depending on the patient's circumstances and values.[3]

Surgery in the thyrotoxic patient can be challenging for several reasons. This is reflected by a higher complication rate than for those who are euthyroid. In a metabolically overactive gland, an increased blood supply can lead to more intra-operative bleeding as well as an increased post-operative haematoma risk. Pankhania *et al.* analysed 1280 patients undergoing thyroid surgery at a single tertiary centre.[4] They found a 1.35 per cent return-to-theatre rate for post-operative haematoma in non-Graves' disease patients, but an overall 2.11 per cent return-to-theatre rate when Graves' disease patients were included, associated with an almost four times higher return rate in Graves' disease patients.[4] Other anaesthetic considerations include an increased risk of cardiac arrhythmias and thyroid crisis. Additionally, post-operatively thyrotoxic patients are at increased risk of hypocalcaemia due to hypoparathyroidism.

Thionamide medication can achieve long-term remission rates of 35 per cent; however, thionamide therapy has a significant side effect profile and remission is only achievable in cases of Graves' disease.[5] A single cycle of radioiodine can achieve excellent results (over 90 per cent) in the long-term control of thyrotoxicosis.[6] Hence, thyroid surgery is frequently reserved for selected patients. These are typically patients who cannot be rendered euthyroid by other means, have significant ophthalmopathy, or have contraindications for radioiodine such as women planning pregnancy.

The multidisciplinary thyroid clinic in Hull Royal Infirmary comprises a joint clinic run by endocrinologists and ENT surgeons together. All patients who present with thyrotoxicosis, where possible, are initially controlled with thionamide therapy. They are then given the option of each of the three definitive treatment modalities (surgery, a time-limited course of thionamide medication or radioiodine treatment), as well as the option of lifelong thionamide therapy. The audited risks and benefits of each option are explained to the patients.

In our experience, when given the option, a large number of patients will opt for surgery as first-line definitive treatment over the other treatment modalities. Hence, we believe our case series is one of the largest of thyrotoxic patients undergoing thyroid

surgery. We aimed to compare outcomes and complication rates to reports in the literature.

Materials and methods

This study and manuscript adhere to the Strengthening the Reporting of Observational Studies in Epidemiology ('STROBE') reporting guidelines for observational studies.[7]

Data were collected retrospectively and entered into Excel workbooks (Microsoft Office 365; Microsoft, Redmond, Washington, USA).

Patients were pseudo-anonymised and given a unique study number. Demographic data such as age at operation, sex and family history were recorded.

Data were gathered using the electronic medical record solution, Evolve 3 (Kainos, Belfast, Northern Ireland) and Lorenzo patient record systems (DXC Technology, Tysons, Virginia, USA). For laboratory data, an integrated clinical environment platform was used (EMIS Health, Leeds, UK).

We recorded the referral source, any relevant clinical findings, the type of operation (mainly total thyroidectomy or hemithyroidectomy), histology of the gland, and the presence or absence of post-operative complications. Complications included: recurrent laryngeal nerve palsy (post-operatively and at three months follow up), hypocalcaemia, wound infection and haematoma.

Biochemical markers were recorded pre- and post-operatively. These included thyroid-stimulating hormone (TSH), free thyroxine (T4) and adjusted serum calcium.

Results

A total of 595 patients underwent hemithyroidectomy or total thyroidectomy for thyrotoxicosis between 24 November 2000 and 26 April 2019 at a single secondary care site in the Yorkshire and Humber Deanery of Health Education England. All operations were performed by the same surgeon.

The patients' mean age was 44 years. As expected, there was a female preponderance, with a female to male ratio of 4.5:1.

Operation type

The majority of patients (95.4 per cent, $n = 568$) underwent total thyroidectomy. Two of those patients had an additional parathyroidectomy and one case was a revision total thyroidectomy. Hemithyroidectomies were performed in 4.5 per cent of patients ($n = 27$), including two revision hemithyroidectomies. None of the patients in this cohort had subtotal thyroidectomies.

Histology

The histology findings were accessible in 87.7 per cent of patients ($n = 522$). Similar to reports in the literature,[2] two-thirds of patients (66.7 per cent; 348 out of 522) had autoimmune hyperthyroidism or Graves' disease. Of the patients, 7.7 per cent (n = 40) had histologically confirmed Hashimoto's thyroiditis. A full breakdown of the remaining histological subtypes is shown in Table 1. We found that 6.1 per cent of patients ($n = 32$) had evidence of microcarcinoma, usually papillary thyroid cancer. One of the patients whose histology showed Graves' disease had a rare case of struma ovarii.

Thyroid-stimulating hormone and free thyroxine

Biochemical markers were measured at the point of referral to ENT and again pre-operatively. Our dataset contained these values from 2007 onwards ($n = 338$); the historical data were unavailable electronically.

As expected, at the point of presentation or referral to ENT for consideration of surgery, most patients (72.5 per cent, $n = 245$) had maximally suppressed TSH, defined as less than 0.05 milli-international units per litre (mIU/l). Only 1.5 per cent of patients ($n = 5$) had raised TSH levels of more than 5 mIU/l. Of the patients, 39.3 per cent ($n = 133$) had suppressed levels of TSH at the point of surgery compared to levels at initial presentation.

A known consequence of thyroid surgery is hypothyroidism; lifelong L-thyroxine was used to replace deficient thyroid hormones in those who underwent total thyroidectomies. Of patients, 22.8 per cent ($n = 77$) became transiently hypothyroid post-operatively whilst on T4 replacement therapy, with TSH levels ranging from 5.3 mIU/l to 83 mIU/l. Of note, the patient with the highest TSH level in the cohort had been non-compliant with their medication for over one year. Our T4 replacement dosage is calculated on an individual patient basis using the following regression equation: weight (kg) – age + 125 mcg/day.[8] Dose alteration or education in the avoidance of simultaneous polypharmacy when taking thyroxine was required in these patients.

Post-operative adjusted calcium levels

All patients undergoing total thyroidectomy underwent routine post-operative calcium monitoring. Based on the British

Table 1. Histological findings of thyroid glands post-operatively

Histology	Cases (*n*)
Papillary thyroid cancer + hyperplasia	1
B-cell lymphoma	1
Follicular adenoma	11
Nodular hyperplasia	7
Nodular hyperplasia + papillary thyroid cancer	1
Follicular carcinoma	2
Follicular adenoma + multi-nodular goitre	5
Follicular adenoma + papillary thyroid cancer	1
Follicular adenoma + multi-nodular goitre + papillary thyroid cancer	1
Graves' disease	326
Graves' disease + papillary thyroid cancer	12
Graves' disease + nodular hyperplasia	1
Graves' disease + Hurthle cell cancer	1
Graves' disease + follicular adenoma	8
Hashimoto's disease + papillary thyroid cancer	5
Hashimoto's disease	40
Hurthle cell cancer	1
Hurthle cell cancer + papillary thyroid cancer	1
Multi-nodular goitre	87
Multi-nodular goitre + follicular adenoma	4
Multi-nodular goitre + papillary thyroid cancer	6

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Association of Endocrine and Thyroid Surgeons algorithm,[9] hypocalcaemia was defined as a serum-adjusted calcium level of less than 2.10 mmol/l. Post-operative calcium level checks were performed at 9:00 am and again at 3:00 pm on the day after surgery. Both levels were accessible on the electronic records in 288 cases.

The initial mean post-operative serum-adjusted calcium level was 2.21 mmol/l (range, 1.63–2.55 mmol/l). Of patients, 20.8 per cent ($n = 60$) had initial post-operative hypocalcaemia (serum-adjusted calcium level range of 1.63–2.09 mmol/l, and mean of 1.99 mmol/l).

The second check of calcium level revealed a lower mean, of 2.19 mmol/l (range, 1.75–2.60 mmol/l), and an additional seven patients ($n = 67$) were hypocalcaemic on the second check. Follow-up calcium levels were available in 135 patients – the levels were typically recorded at a three-month follow up. These values were only available in patients still requiring calcium and/or vitamin D supplementation. Only eight patients remained hypocalcaemic at this point. The rate of transient hypocalcaemia, therefore, was 23.3 per cent (67 out of 288) and the rate of persistent hypocalcaemia was 2.8 per cent (8 out of 288).

Post-operative recurrent laryngeal nerve palsy

A recognised complication of thyroid surgery is recurrent laryngeal nerve palsy, which may be temporary or permanent. In our cohort, 3.6 per cent of patients (12 out of 329) had an early recurrent laryngeal nerve palsy on flexible laryngopharyngoscopy. Of these, only 0.3 per cent ($n = 1$) still had a palsy at the three-month follow up; the remaining cases were transient and had recovered.

Post-operative haematomas and seromas

In our cohort, 2.5 per cent of patients ($n = 15$) had documented post-operative haematomas that required drainage in the operating theatre. Three patients developed seromas and two separate patients underwent scar excision for scar hypertrophy.

Other complications

One patient had a laryngeal tear and a concurrent early recurrent laryngeal nerve palsy that had recovered at three months post-surgery. The patient with struma ovarii had a subsequent hysterectomy.

Discussion

The common demographics for thyrotoxic patients in our study are similar to those reported in the literature. Our most prevalent histology finding was Graves' disease, followed by multi-nodular goitre and Hashimoto's thyroiditis.

Our overall rate of malignancy was 15.3 per cent, with papillary thyroid cancer being the most common. The same observation was made in a systematic review of the incidence of thyroid carcinoma in patients undergoing thyroidectomy for thyrotoxicosis, where the overall rate of malignancy was 8.5 per cent and the most common histology was micropapillary carcinoma.[10] Careful pre-operative assessment of any nodules is important, as they are associated with an increased risk of thyroid cancer in patients undergoing thyroidectomy for thyrotoxicosis.[11]

The overall complication rate for thyroid surgery is higher in thyrotoxic than in euthyroid patients. Whilst transient post-operative complications such as hypocalcaemia or recurrent laryngeal nerve palsies were present in 23.3 per cent (67 out of 288) and 3.6 per cent (12 out of 329) of patients respectively, the documented persistence of these symptoms was much lower at out-patient follow up.

In a systematic review and meta-analysis of the predictors of post-thyroidectomy hypocalcaemia, two factors associated with transient hypocalcaemia were Graves' disease and female sex.[12] These factors are prominent in our study too, as 67.1 per cent of those with hypocalcaemia had Graves' aetiology and 87.7 per cent were female.

Graves' disease is a known risk factor for neck hematoma requiring surgical intervention.[13,14] Consequently, given that most of our population had Graves' disease and underwent total thyroidectomy, our 2.5 per cent rate of post-operative haematoma was expected.

Comparison with other studies

Whilst several larger studies have assessed the incidence of thyroid carcinoma in patients undergoing total thyroidectomy for hyperthyroidism,[10] we aimed to compare our data with the literature, assessing whether surgery remains a safe modality for the treatment of thyrotoxicosis.

Shinall *et al.* assessed 165 patients undergoing total thyroidectomy for Graves' disease where 42 per cent of the cohort remained hyperthyroid at the time of surgery.[15] They found temporary and permanent hypocalcaemia rates of 31 per cent and 1.2 per cent in their cohort respectively. Temporary and permanent recurrent laryngeal nerve palsies were present in 7 per cent and 0.6 per cent respectively. Multivariate analysis was performed, which demonstrated that patient age of less than 45 years and obesity were associated with the occurrence of complications.[15]

- Thyrotoxic patients can initially be treated medically, unless contraindicated, to achieve remission
- Patients can then be treated definitively by surgery, a time-limited thionamide course or radioiodine
- One radioiodine cycle can help achieve excellent long-term thyrotoxicosis control; surgery is often reserved for selected patients
- Complications such as post-operative haematoma, hypocalcaemia and recurrent laryngeal nerve palsy are more common in thyrotoxic than euthyroid patients
- Long-term complications rates for hypocalcaemia and recurrent laryngeal nerve palsy remain relatively low
- This large cohort study confirms the importance of total thyroidectomy for refractory hyperthyroidism and appears most effective for Graves' disease

Ali *et al.* assessed complications and outcomes in patients undergoing total thyroidectomy following the rapid control of thyrotoxicosis compared to those with well-controlled disease.[16] A total of 266 patients were included with similar demographic data to those in our study. Nineteen patients had poorly controlled disease after rapid optimisation. Long-term hypoparathyroidism occurred in 4.9 per cent and recurrent laryngeal nerve palsy in 0.38 per cent. Our cohort, whilst larger, experienced fewer proportional complications of hypocalcaemia and recurrent laryngeal nerve palsies than both of the aforementioned comparative studies.

Despite the drawbacks of retrospective analysis, the findings of our large cohort still indicate that thyroid surgery has a useful role in the management of refractory hyperthyroidism. In particular, total thyroidectomy compared to other treatment modalities appears to be the most effective, definitive means

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of managing Graves' disease.[17] Moreover, a meta-analysis suggested higher relapse rates with anti-thyroid medications than surgery in Graves' disease patients.[18]

Competing interests. None declared

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