Surgical management of Graves’ disease: historical context and single institution experience

Michael J Russell, Simon Young, Richard Martin, Richard Harman

ABSTRACT

BACKGROUND: Graves’ disease is the commonest cause of hyperthyroidism. For patients with Graves' hyperthyroidism, antithyroid medication is the most common first-line treatment option. Radioiodine and surgery are reserved for specific indications. Subtotal thyroidectomy was the preferred surgical approach historically, but total thyroidectomy has been the established procedure of choice for the last 20 years.

AIM: To describe indications and outcomes of total thyroidectomy for Graves’ disease in a large New Zealand endocrine surgery unit, and to compare these results to international studies

METHODS: We analysed a prospectively collected database to describe the indications and outcomes of surgery for Graves’ disease between December 2001 and January 2021.

RESULTS: Among 64 patients who underwent total thyroidectomy at our tertiary centre for Graves’ hyperthyroidism, Graves’ ophthalmopathy and patient preference/aversion to radioactive iodine were the most common indications for surgery. Total thyroidectomy resulted in long-term control of thyrotoxicosis in all patients. There were no incidences of recurrent laryngeal nerve injury. One patient (1.6%) suffered permanent hypoparathyroidism.

CONCLUSION: Total thyroidectomy is a safe and effective treatment for Graves’ disease. In our population, total thyroidectomy functions as a second-line treatment for Graves’ disease.

Graves’ disease, an autoimmune condition characterised by the presence of autoantibodies against the thyroid stimulating hormone (TSH) receptor, is the most common cause of hyperthyroidism. Graves’ disease is more common in women, with a ratio of 5:1. Typical symptoms include clinical and biochemical evidence of hyperthyroidism, Graves’ ophthalmopathy and goitre. Management options include biochemical control with antithyroid drugs (ATD), thyroid ablation with radioactive iodine (RAI) and thyroid surgery. Options for surgery have included bilateral subtotal thyroidectomy, Dunhill procedure (unilateral lobectomy and contralateral subtotal lobectomy) and total or near-total thyroidectomy. For most of the twentieth century, subtotal options were preferred in order to preserve a thyroid remnant of approximately 5g, which offers the possibility of avoiding long-term thyroid hormone replacement. But in the 1990s there was a shift in practice towards total thyroidectomy. A growing body of evidence indicated a significant rate of recurrence of hyperthyroidism with the subtotal approach. Total thyroidectomy, on the other
hand, provides more predictable control of Graves’ disease. It also reduces the chance of recurrent hyperthyroidism. Between the two there is no difference in terms of recurrent laryngeal nerve injury or post-operative haematoma in experienced surgical units, although with total thyroidectomy there is a slightly increased rate of permanent hypoparathyroidism. Further studies have established total thyroidectomy as a cost-effective option with no significant difference in quality of life compared to subtotal.

In recent years, our institution has performed around 100 thyroid and parathyroid cases annually, including approximately 60 thyroid cases. This study reports our local experience with routine total thyroidectomy for Graves’ disease in a New Zealand population.

Methods

Consecutive patients undergoing thyroid surgery at a specialist endocrine surgery unit were recorded in a prospective database between December 2001 and January 2021. Institutional approval for the management of this database using deidentified patient information is ongoing. Surgery was performed under the direct supervision of one of two specialist endocrine surgeons. All patients undergoing surgery for Graves’ disease received multidisciplinary pre-operative review and counselling by both the endocrinology and endocrine surgery services. Patient characteristics and indications for surgery were recorded, as well as pre- and post-operative TSH, thyroxine (T4), calcium and parathyroid hormone (PTH). The immediate and long-term requirements for post-operative calcium supplementation were recorded and the electronic record was reviewed to identify recurrence of thyrotoxicosis. Post-operative complications were also recorded.

All patients undergo pre-operative assessment with endocrinology with adjustment of antithyroid medication, beta blockade and the use of Lugol’s iodine. All patients undergo total thyroidectomy using routine nerve monitoring. Following total thyroidectomy, routine serum calcium and PTH measurements are performed the evening of surgery and again at 0600 the next day.

Patients with signs or symptoms of hypocalcaemia, and those with a post-operative adjusted calcium level less than 2.0mmol/L or with an intraoperative PTH level less than 2pmol/L, are prescribed post-operative calcium and 1,25 OH vitamin D supplementation. Our local protocols outlining management of post-thyroidectomy hypocalcaemia have recently been published. Patients are routinely followed-up in the surgical outpatient clinic six weeks following surgery. Their serum PTH, calcium and thyroid function are tested prior to this appointment. Patients then had ongoing follow-up with their general practitioner.

Results

Sixty-four patients underwent total thyroidectomy for Grave’s disease between December 2001 and January 2021. Fifty-eight (89.2%) were female. Median (range) age was 35.5 (17–69). Median (range) follow up was 76.2 (4–241) months. All but one patient (who had a concurrent papillary thyroid cancer) had symptoms of thyrotoxicosis. Thirty-five patients (54.7%) were European/Pākehā, 14 (21.9%) were Māori, 11 (17.2%) were Asian, three (4.7%) were Pasifika and one (1.5%) was classified as other.

Ten patients chose RAI due to having young children at home. One was pregnant in their second trimester. Four had suspicious nodules within the thyroid.

The most common indication for surgery (n=24) was personal preference or a refusal to take RAI. Further indications were ophthalmopathy (n=16), compressive symptoms (n=7) and failed RAI (n=2). Indications for surgery are outlined in Table 1.

In patients with ophthalmopathy as the indication for surgery, eight of the 16 were reviewed in the ophthalmology clinic prior to surgery. Of these, ten were felt to have moderate to severe ophthalmopathy, and two required specific management for this in the form of decompressive surgery or radiotherapy. The remaining six patients with mild eye disease had additional indications for surgery, such as failed RAI or large goitre. Median time from diagnosis of Grave’s disease to surgery was two years, with all patients having an attempt at control with antithyroid medication prior to surgery.
All patients had histological changes consistent with Graves' disease. Six patients (9.3%) had papillary thyroid cancer noted on final histology (this was known for one patient pre-operatively) and subsequently required radioactive iodine. The other patients had an incidentally noted microcarcinomas requiring no further treatment. All patients remained fully treated at follow-up and no patient had a recurrence within the follow-up period. All patients continued thyroxine.

Table 2 outlines post-operative outcomes. Twenty-one (32.8%) patients had post-operative hypocalcaemia (less than 2.1mmol/L) or hypoparathyroidism (PTH less than 1.5pmol/L). Mean (SD) post-operative calcium (albumin adjusted) was 2.12mmol/L (0.15). Mean (SD) PTH level was 4.11pmol/L (3.71). Twenty-four (37.5%) patients were prescribed calcium and 1,25 OH vitamin D supplements on discharge, and a total of four (6.2%) patients remained on long-term calcium supplementation at follow-up. One did not have further PTH testing and maintained a normal calcium post-surgery. Two patients had low post-operative PTH, but on follow-up these were in the normal range. Only one (1.6%) patient documented permanent hypoparathyroidism at follow-up.

Four patients (6.7%) had post-operative voice changes, although no patients suffered true recurrent laryngeal nerve injury as seen on direct laryngoscopy. All patients had normal voice at follow-up.

Two patients (3.1%) were had a post-operative haematoma, one of whom required a return to theatre. One patient had a wound infection requiring antibiotics. No patients died within 90 days of surgery.

Discussion

Grave's disease is a relatively common autoimmune disorder that predominantly occurs in young women of reproductive age. It tends to be a relapsing remitting condition, although a large goitre or very high T4 at presentation predicts a lower long-term likelihood of remission.

Typically, antithyroid drugs, usually in a tapering course over 12–18 months, are used to treat an attack of Graves' disease. In New Zealand, surgery is firmly a second-line treatment modality. In one survey of New Zealand endocrinologists, a course of antithyroid drugs was the preferred first-line treatment modality in the majority of patients (92%); early RAI was recommended in only 5% of cases; thyroidectomy as first-line treatment for Graves' disease was preferred by only a single specialist (2.7%)9.

The widespread preference in New Zealand for the use of ATD over RAI as first-line treatment differs from international results. New Zealand has very low rates of early RAI treatment.9 Some possible explanations include New Zealand's nuclear-free policy and the difficulty of accessing radioactive iodine isotopes.9 There is also a degree of fear of radiation exposure among patients, when this is discussed. Recent liter-

<table>
<thead>
<tr>
<th>Indication for surgery</th>
<th>Number (%)</th>
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<tbody>
<tr>
<td>Patient preference/refusal of RAI</td>
<td>24 (37.5%)</td>
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<tr>
<td>Graves' ophthalmopathy</td>
<td>16 (25%)</td>
</tr>
<tr>
<td>Childcare considerations</td>
<td>10 (15.6%)</td>
</tr>
<tr>
<td>Compressive symptoms</td>
<td>7 (10.9%)</td>
</tr>
<tr>
<td>Suspicious nodule</td>
<td>4 (6.3%)</td>
</tr>
<tr>
<td>Failed RAI</td>
<td>2 (3.1%)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>1 (1.6%)</td>
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</tbody>
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nature, which has raised the possibility of a slight increase in the long-term risk of malignancy following RAI treatment, has also influenced both specialists and patients, an experience that our results support: all patients had attempted to control ATD prior to referral, and the median time from diagnosis of Graves' to surgery was two years.

While RAI is safe and efficacious in the vast majority of patients, the choice of surgery over RAI as a second-line treatment option is made for varying reasons. Most commonly is that patients prefer surgery or are concerned about RAI treatment. Significant eye disease is another reason. In our unit, patients with mild ophthalmopathy are considered for RAI with steroid cover. This is supported by previous studies showing that steroids can prevent progression of eye disease. Surgery is preferred as a second-line treatment modality in patients with more severe eye symptoms; this remains a common indication for surgery in our cohort. Although use of RAI as a first-line treatment is relatively low in New Zealand, the rate of patient preference/refusal of RAI (37.5%) among patients deciding on surgery as a second-line treatment option remains comparable with other international audits. This suggests that, although patients may be reluctant to pursue RAI as primary treatment, they will generally be open to this modality as a second-line option. Childcare considerations are an important factor in deciding on surgery over RAI, reflecting the epidemiology of Graves' disease commonly affected younger female patients. Perhaps we can expect this indication for surgery to decrease in future as social norms around gender roles change.

Our results support the assertion that total thyroidectomy is a safe and effective treatment for Graves' disease. Recurrent laryngeal nerve injury and permanent hypoparathyroidism are uncommon complications. Although 37.5% of patients in our study were discharged on calcium supplementation, only one patient had true permanent hypoparathyroidism. A Cochrane review quoted a rate of permanent hypocalcaemia in total thyroidectomy for Graves' disease of 59 per 1,000 patients, and a large meta-analysis found a rate of 1.6%. Although these rates are low, remember that the impact on quality of life for these patients can be significant. They need daily calcium and vitamin D supplementation.

Table 2: Patient outcomes.

<table>
<thead>
<tr>
<th>Outcomes of surgery</th>
<th>Number (%)</th>
<th>Cochrane review</th>
<th>Meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent hyperthyroidism</td>
<td>0</td>
<td>0.8%</td>
<td>0</td>
</tr>
<tr>
<td>Hypocalcaemia/hypoparathyroidism</td>
<td>21 (32.8%)</td>
<td>5.9%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Temporary Hypocalcaemia/hypoparathyroidism</td>
<td>24 (37.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharge on calcium supplementation</td>
<td>1 (1.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Permanent hypoparathyroidism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent laryngeal nerve injury</td>
<td>4 (6.7%)</td>
<td>1.3%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Post-operative voice change</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Permanent voice change</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Permanent nerve injury (on laryngoscopy)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematoma</td>
<td>2 (3.1%)</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Infection</td>
<td>1 (1.6%)</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Return to theatre</td>
<td>1 (1.6%)</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
and have an ongoing risk of nephrocalci-
nosis and renal dysfunction associated with
long-term treatment of hypocalcaemia.Permanent recurrent laryngeal nerve injury
is a rare event, with one meta-analysis
quoting a rate of 0.9%. More generally, in
Key Performance Indicator (KPI) results
for thyroid surgery for any indication that
our unit recently published, the rate of
permanent RLN injury was 0.3%, the rate
of permanent hypocalcaemia was 2.5% and
the rate of return to theatre was 1.1%. These
results suggest that complication rates
are not significantly higher than for other
indications for thyroid surgery, and are in
line with a prior study from New Zealand
that primarily looked at the rate of thyroid
cancer in patients with Graves’ disease but
reporting rates of permanent hypoparathy-
roidism <2% and nerve injury <1%. Total thyroidectomy is an effective
treatment for Graves’ disease. In our popu-
lation, all patients achieved long-term
control of their thyrotoxicosis. A Cochrane
review quotes the risk of recurrent/
persistent hyperthyroidism at eight per
1,000 patients. All patients required
long-term thyroid supplementation,
although this has previously been demon-
strated to be a cost-effective approach with
comparable quality-of-life outcomes.

Conclusion

Total thyroidectomy has been established
as the most common surgical approach for
the management of Graves’ disease. In our
unit, thyroidectomy for Graves’ disease
makes up a relatively small component of
our practice. Our results show that it is a
safe procedure to perform and results in
excellent long-term control of thyrotoxicosis.
It is particularly useful in patients with
significant ophthalmopathy or in patients
with aversion to RAI treatment.
Competing interests:
Nil.

Acknowledgements:
The authors would like to acknowledge the Endocrine Multidisciplinary team at Waitematā District Health Board who have been involved in the management of these patients.

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REFERENCES
