Fifteen years' experience in thyroid surgery

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ABSTRACT

INTRODUCTION Thyroid disease is common, thyroid cancer is uncommon. Most goitres are investigated using blood tests, fine needle aspiration cytology together with ultrasound. Surgery usually entails either lobectomy or total thyroidectomy, and for malignancy, patients may need a neck dissection. Recently, significant advances have been made regarding mechanisms involved in both thyroid growth and function (goitrogenesis) and carcinogenesis at a molecular level.

PATIENTS AND METHODS In the study cohort, 1113 patients had benign disease and 387 malignancy. For benign disease, 716 patients had lobectomy or isthmusectomy, 44 had near-total thyroidectomy and 318 a total thyroidectomy. For malignancy, patients received initial lobectomy (180) or total thyroidectomy (152). One hundred and eleven had completion surgery. Thirty patients had extensive surgery. Thyroid growth and function was investigated using 500 human thyroid cell primary cultures obtained at surgery, as well as in three animal models. The role of pituitary tumour transforming gene (PTTG), PTTG binding factor (PBF) and sodium iodide symporter (NIS) in thyroid cell function was then evaluated.

RESULTS Temporary and permanent recurrent laryngeal nerve palsy rates were 2.4% and 0.4%. Other complications included temporary (21%) and permanent (3%) hypoparathyroidism, wound infection (1.2%), haematoma (1.2%) and poor scar (0.8%). Six patients have died. Regarding thyroid growth and function, TSH represents (either directly or indirectly) the main factor mediating thyroid follicular cell growth. For carcinogenesis, over-expression of the proto-oncogenes PTTG and PBF induces tumours in nude mice, and PTTG can induce proliferation of human thyroid cells and, in addition, both repress expression and function of NIS.

KEYWORDS

Thyroid disease including cancer – Growth factors – Thyroid surgery

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John Hunter founded The Royal College of Surgeons of England, and is regarded as a forefather of modern day surgery. He set high standards for understanding both anatomy and pathology by mastering meticulous techniques of descriptive dissection. Hunter, like Shakespeare, recognised the need for private income for patronage and we sometimes underestimate the difficulties that there must have been earning a livelihood in Hunter's time.¹ Both men were keen observers and Shakespeare obviously encountered significant goitres in his travels,² so my initial perspective is to be a good thyroid surgeon, you must first be a good physician. This paper outlines my experience in thyroid surgery, covers aspects of investigation and management of thyroid disease, and makes reference to guidelines, audit, training and research.

History of thyroid surgery

Goitre (Latin for throat) has been recognised as a discreet condition since earliest recorded times. Normal thyroid

anatomy was not generally understood until the renaissance when the gland was named *glandulam thyroideam* (Latin for shield shaped). The first thyroidectomy was performed in 1646, but the 10-year-old patient died and the surgeon was imprisoned.³ In the 1850s, mortality rates remained high (about 40%) but, following key advances in anaesthesia, the discovery of antisepsis and the development of the haemostat by Spencer Wells, surgeons such as Billroth and Kocher improved mortality rates from 12.6% in the 1880s to 0.2% in 1898.⁵ Kocher was a meticulous surgeon with low complication rates. He described the incision for thyroidectomy, as well as other surgical advances and for his work, became the first surgeon to be awarded the Nobel Prize in 1909.³

Kocher trained Halstead who subsequently trained Crile, Mayo and Lahey, who in turn trained Oliver Beahrs. In the UK James Berry and Cecil Joll further championed advances, as did Sir Thomas Dunhill in Australia who pioneered one-stage near-total thyroidectomy for benign disease. Further advances

Table 1 Classification of goitre**Simple (non-toxic)**

- Diffuse
- Solitary thyroid nodule (STN)
- Multinodular goitre (MNG)
- Recurrent nodule

Toxic

- Diffuse
- Solitary thyroid nodule
- Multinodular goitre
- Recurrent nodule

Neoplastic

- Benign
- Adenoma
- Malignant – Differentiated adenocarcinoma; medullary thyroid carcinoma; lymphoma, and anaplastic carcinoma

Inflammatory

- Hashimoto's; Riedels and De-Quervains

Rare

- TB, amyloid, syphilis, HIV and lithium

regarding the anatomy of the recurrent laryngeal nerve, parathyroids (including extracapsular dissection) and the external branch of the superior laryngeal nerve allowed surgeons to further refine their techniques.⁵

Thyroid disease – investigation and management

Thyroid disease is common. Up to 15% of the population have a goitre, of which half represents nodular disease and up to 70% will have nodules on high definition ultrasonography.⁴ The majority of patients have benign disease (Table 1). All patients require thyroid function tests (TFTs), usually with antibody status and serum calcium. Benign, non-toxic disease can be treated conservatively, and the indications for surgery for benign multinodular goitre include obstructive and cosmetic symptoms, suspicion of malignancy or substernal disease.

Patients with thyrotoxicosis are usually treated initially with medical therapy (drugs or radioactive iodine), although increasingly nowadays, more opt for initial surgery (particularly with increasing restrictions on the use of radio-iodine, better informed consent and lower surgical complication rates).

Recurrent benign goitre is less common now that subtotal thyroidectomy is obsolete and investigations include TFTs and fine needle aspiration cytology (FNAC) together with appropriate imaging. Cases are individualised and often best treated conservatively, since complication rates

are higher and, in high-risk patients, radioactive iodine is an acceptable alternative. Retrosternal goitre is not that uncommon and is usually defined as having more than 50% of its volume below the thoracic inlet. Currently, there is a move to consider early elective surgery in younger symptomatic patients.⁵

Whilst thyroid disease is common, thyroid malignancy is uncommon in the UK (approximately 1200 cases per annum) although in North America it is currently the fastest rising malignancy (approximately 40,000 cases in 2009).⁶ This is probably due to over-investigation and subsequent surgery for a large number of smaller tumours.⁶ The commonest way for differentiated thyroid cancer (DTC) to present is a solitary thyroid nodule in a euthyroid patient, when the incidence of malignancy is between 7–10%.⁴ Initial investigations include blood tests, FNAC and ultrasound.^{6,7} Subsequent management is based on the THY cytology classification (Table 2) and, where malignancy is suspected, risk stratification often dictates that patients will have a total thyroidectomy. High-risk patients with DTC should be considered for central compartment (level 6) dissection, and suspicious or proven lateral neck disease requires a selective neck dissection (levels 2a–5b).⁷

The risk of malignancy is increased with an elevated TSH,⁸ and there is currently no role for routine calcitonin testing.^{6,7} The frequency of thyroid malignancy is shown in Figure 1, and the majority of patients (90%) have well-differentiated carcinoma. Of these, high-risk patients include males, those over 45 years; those in the extremes of life, those with neck disease and patients with tumours > 1 cm as well as widely invasive follicular pathology.^{6,7} Some low-risk patients can be treated with lobectomy alone with MDT supervision, but most will have a total thyroidectomy (with or without central neck dissection) which means with increasing postoperative risk stratification, less low-risk patients require radioactive iodine ablation.⁶

Medullary thyroid cancer (MTC) is rare, sometimes familial and associated with multiple endocrine neoplasia

Table 2 Management of thyroid nodules according to the THY cytology classification

Diagnostic category	Meaning
THY 1	Non-diagnostic
THY 2	Non-neoplastic
THY 3	Follicular lesion/suspected follicular neoplasm
THY 4	Suspicious of malignancy
THY 5	Diagnostic of malignancy

Adapted from the British Thyroid Association's guidelines.^{4,6,7}

syndromes types MEN 2a and MEN 2b. Positive diagnosis prompts immediate referral to the regional centre. Patients should be tested for the RET proto-oncogene and, if positive, the family further investigated with genetic backup.^{7,9} A pheochromocytoma should be excluded and further investigations include TFTs, serum calcium and calcitonin, parathormone levels, urinary catecholamines and whole body computed tomography (CT).^{7,9} Minimum treatment (after surgery for pheochromocytoma) includes a total thyroidectomy with central compartment clearance (levels 6 and 7) together with an ipsilateral selective neck dissection (levels 2–5) in high-risk patients (tumours > 2 cm, familial disease and proven central compartment nodes).^{7,9} Bilateral neck dissection in high-risk patients has been popular, but there is now a move back to unilateral neck dissection and subsequent follow-up with serum calcitonin (and staged further surgery), since patients with three zone disease are incurable.^{7,9}

Guidelines

Writing on guidelines has been enjoyable,^{7,10} and they can improve both standards, audit and outcomes.¹¹ Critics say they can introduce bias¹⁵ and lead to overtreatment, exclusion of difficult cases while making the treatment of cancer read a bit like a shopping list; however, for standardisation of treatment, multidisciplinary team (MDT) discussion and ease of follow-up, I believe they are essential.

Surgery

Techniques in thyroid surgery have changed little over the last century.^{12,15} Dunhill popularised near-total thyroidectomy for patients with benign disease to minimise complications and subsequent hypothyroidism. Crile and Mayo followed suit and, by 1922, also undertook bilateral resections, although still operated in stages. The operation then developed in the 1930s to bilateral subtotal resection (the Dunhill operation), which became the accepted method to treat

Table 3 Thyroid lobectomy – basic tips

- Appropriate incision. Elevate flaps
- Deal with strap muscles; divide sternothyroid?
- Identify thyroid gutter and paracarotid tunnel
- Ligate middle thyroid vein
- Define the surgical capsule
- Find the inferior thyroid artery and recurrent laryngeal nerve (RLN) in Beahr's triangle
- Ligate superior pedicle, avoiding damage to the external branch of the superior laryngeal nerve
- Preserve parathyroids using extracapsular dissection
- Preserve RLN and divide ligament of Berry
- Transfix the isthmus

benign disease. Nowadays, difficulties in estimating amounts of residual functioning thyroid tissue, together with both recurrent goitre and thyrotoxicosis has led to a greater global use of total thyroidectomy.^{6,7}

Operations should be defined accurately,^{6,7} and most receive lobectomy (Table 3) to include the isthmus (extended hemithyroidectomy). The remainder have isthmusectomy alone or total thyroidectomy (with or without central compartment clearance).^{6,7} Subtotal thyroidectomy should no longer be performed.

For malignancy, a total thyroidectomy may include central compartment (level 6) lymphadenectomy preserving the recurrent laryngeal nerves and parathyroids. For suspected or proven lateral compartment neck disease in DTC, levels 2a–5b are dissected. In MTC, level 5a is also dissected and, for invasive malignancy, modified radical or radical neck dissections may be required. For patients with advanced disease involving the larynx, pharynx or trachea, extensive surgery may be required to include tracheal resection, partial or total laryngectomy together with pharyngectomy. These cases should be individualised because quality-of-life issues are important.^{6,7}

For substernal goitre, access is important, and for those glands that are palpable in the neck, a cervical approach will usually suffice (Table 4). For extensive mediastinal disease, some form of sternal split may be required. Complication rates are higher with revision surgery for recurrent goitre so many are treated conservatively. When surgery is indicated, a one-sided approach avoids a bilateral vocal cord palsy. Dissection should proceed on the pseudocapsule, the nerve approached laterally when it is often in its normal position. Patients should be consented for tracheostomy. Using a harmonic scalpel or nerve monitor makes very little difference to outcomes;^{14,15} however, in the future, the latter will probably play an ever-increasing

Table 4 Tips to remove a retrosternal goitre

- Most are benign
- The majority can be dealt with via a cervical approach
- Adequate incision. 'The lower the goitre, the higher the cut!'
- Divide the straps, and do the easy side first
- Do the upper pole first
- Stay within the pseudocapsule, and work medial to lateral
- Get into the right plane for lower pole vessels, and always get control inferiorly
- Have a good assistant

role for teaching and training, revision cases and for medicolegal reasons.

Results

A personal series of 1500 thyroidectomies (1994–2009) is presented. Data were collected prospectively on continuously updated databases. Patients were investigated with TFTs, antibodies, serum calcium, FNAC and imaging as appropriate. In the cohort, 1115 patients had benign disease, and 387 had malignancy. Patients with benign disease (197 male, 916 female; age range, 4–91 years; mean, 46 years) underwent lobectomy or isthmusectomy (716), near-total thyroidectomy (44) or total thyroidectomy (318; Fig. 2). A small number underwent other procedures. The histology is shown in Figure 3. Included in the data were patients

with both recurrent and substernal goitre.

For malignancy, 380 had DTC and MTC, three had lymphoma and four had anaplastic cancer (117 males, 270 females; age range, 2–84 years; mean, 47 years). For DTC, 13% had Stage 1 disease, 35% had Stage 2, 33% patients had Stage 3 and 19% patients had Stage 4 disease. For MTC, eight had Stage 1 disease, three had Stage 2, one had Stage 3 and 21 had Stage 4 disease. Patients underwent initially either a thyroid lobectomy (180) or total thyroidectomy (152). In addition, 111 patients had completion surgery.

Figure 3 Histology of benign (A) and malignant (B) disease.

Figure 4 Trend in neck dissections 1993–2009.

Overall, 148 patients had a central compartment clearance, the use of which has increased over the last 5 years (Fig. 4); 113 patients had lateral compartment neck dissection (levels 2a–5b for DTC, levels 2–5 for MTC). Thirty patients had extensive surgery (excluding neck dissection) for advanced disease (Table 5).

There was no significant difference in complications for benign or malignant disease, or level of surgeon. Patients' vocal cords were examined before and after surgery with a nasopharyngoscope; the rate of temporary and permanent recurrent laryngeal nerve (RLN) palsy was 2.4% and 0.4%, respectively (1952 nerves at risk). Three patients had a bilateral vocal cord palsy, all of whom recovered. Other complications included temporary (21.0%) and permanent (3.0%) hypoparathyroidism, wound infection (1.2%), haematoma (1.2%) and poor scar (0.8%). Temporary hypocalcaemia was more common following surgery for thyrotoxicosis and DTC. Minimum follow-up was 6 months. Temporary hypocalcaemia was defined as a serum calcium level below 2.0 mmol/l, and permanent hypocalcaemia as patients being on either calcium supplements or vitamin D at 6 months.¹⁶ All complication rates fell within recent nationally published audit rates.¹⁷ There were six deaths following surgery (five from disease; one from a pulmonary embolism following DVT).

The average length of stay has decreased for unilateral and bilateral surgery, from 2.8 days and 3.6 days prior to 2002, to 1.8 days and 2.8 days afterwards (Fig. 5). These results indicate 24-h ambulatory surgery is feasible for thyroid lobectomy. However, following total thyroidectomy (when the serum calcium can fall precipitously on the second postoperative day), discharging patients in less than 48 h will only be possible if they are put on calcium supplements, or a 24-h PTH measurement is within the normal range.¹⁸

Training

Training in surgery is changing rapidly. Calman Hine, Modernising Medical Careers (MMC) and the European

Table 5 Surgery for advanced malignancy

Tracheal resection	9
Partial laryngectomy	4
Total laryngectomy	7
Pharyngolaryngectomy	4
Total number of patients	30

Working Time Directive (EWTD) have undoubtedly impacted on medical training, as have the deaneries, SAC Committees, PMETB and the GMC all affected sub-specialty training. So – 'How does one get trained in thyroidectomy?' For general and endocrine surgery, this is principally a post-CCST operation and training is confined to specialised units and one post-CCST Fellow. In ENT, currently every trainee should understand the principles of thyroid disease and management, and many are exposed to thyroid surgery during their training. These disparities need to be addressed, and the current interface head and neck fellowships exclude applications from general and endocrine surgeons, so the goal should be special interface fellowships in

Figure 5 Average length of stay following thyroidectomy.

Figure 6 Percentage of operations wholly performed by trainees.

thyroid and parathyroid surgery inviting applications from both specialties. I have specifically trained juniors in thyroid surgery (Fig. 6) and, out of 1500 operations, approximately 31% were done by the trainee without any significant increase in complication rates. The third BAETS audit similarly showed that thyroid surgery in the UK is consultant led, and approximately 25% of operations were consultant supervised.¹⁷

Research

Why do people get benign goitre? TSH is clearly implicated and, in humans with an iodine-deficient diet (as well as animal models treated with goitrogens), prevention of thyroid hormone synthesis results in an elevated TSH and subsequent goitre. This is harder to demonstrate *in vitro*, and only in long-term studies is TSH a growth factor. These data prompted the hypothesis that TSH mediates thyroid follicular cell growth by promoting the synthesis of autocrine growth factors.

Established growth factors such as epidermal growth factor (EGF) and fibroblast growth factor (FGF) stimulate thyroid growth as well as inhibiting thyroid function.¹⁹ These data from primary cultures of human thyroid cells grown under serum-free, chemically defined conditions show iodide uptake is maintained in culture and thyroid hormone synthesis is iodide-dependent. Are EGF or FGF autocrine factors? There is little evidence that follicular cells normally produce EGF in the human model but FGF is produced, and the FGF receptor is also up-regulated by TSH,²⁰ providing a potential mechanism for increased growth and decreased function in human goitre.

Goitre growth requires a blood supply. Angiogenesis precedes goitrogenesis, and other relevant angiogenic factors were studied. Angiopoietins, acting through their receptors, Tie1 and Tie2 with vascular endothelial growth factors (VEGFs) acting through their receptors (VEGFRs), are the best known examples although FGF also stimulates angiogenesis. *In vitro*, thyroid cells expressed angiopoietins and also the Ties,²¹ which are normally specific for endothelial cells. Follicular cells secrete VEGF and also express VEGFRs, and an animal model was used to examine their functional significance. Adenoviral vectors were used to introduce soluble forms of the growth factor receptors. These then bind to circulating growth factors and prevent their effects. This approach was used to inhibit angiopoietins and VEGFs. For FGF, a mutant form of the FGF receptor that blocks signalling was established and its effects on the constructs of mouse goitre growth were examined. All constructs individually reduced goitre size; however, in combination, the three were completely effective in preventing goitre formation.²² These studies confirm that goitre (benign or malignant) can be prevented by limiting angiogenesis.

This probably means several different growth factors and their receptors are involved in goitrogenesis. Goitres may express different factors at different times throughout their evolution, with TSH regulating both factors' and receptor expression. Hence, the thyroid has a unique ecosystem capable of modulating both growth and function so any disturbance in iodine supply, thyroid hormone synthesis and TSH levels may disturb this and thereby promote goitrogenesis.

What about carcinogenesis? Multiple genes are implicated in thyroid cancer including RET/PTC, BRAF and RAS, and specifically our work has concentrated on the proto-oncogenes PTTG and PBF which bind together both *in vitro* and *in vivo*.²³ Over-expression of each gene individually can induce tumour growth in nude mice. Latterly, it has been shown that PTTG is overexpressed both in thyroid cancer and transformed rat thyroid cells, as well as inducing genetic instability, which is an early hallmark of cell transformation. PBF is similarly overexpressed in thyroid tumours and expression correlates with subsequent recurrence.²³

PTTG and PBF are also implicated in the promotion of transformed cell growth.²⁴ In the human thyroid, PTTG induces proliferation of thyroid cells and regulates multiple angiogenic genes in thyroid cells including thrombospondin and ID-5.²⁴ We have also demonstrated that they interact with and repress the expression and function of the sodium iodide symporter (NIS),²⁵ which has important implications for both disease treatment and progression, since radio-iodine is transported via NIS into thyroid cells. NIS is a glycoprotein on the basolateral membrane of thyroid cells and is responsible for iodide uptake. Overexpression of PBF leads to NIS relocation into intracellular vesicles and repression of function. A murine transgenic model was then constructed, overexpressing PBF specifically in the thyroid which is currently being phenotypically characterised.

Conclusions

This paper has outlined my experience in a career in thyroid surgery. Historically, this was the domain of the general surgeon, but nowadays there is an emphasis on multidisciplinary working to include both endocrinologists as well as surgeons from backgrounds in both general and endocrine surgery, as well as otolaryngology.

Initial goitre investigations include TFTs, FNAC together with imaging as appropriate. Surgery for benign goitre is based on either obstructive or cosmetic symptoms, or failed medical therapy for thyrotoxicosis. In patients with a suspected or confirmed malignant thyroid nodule, the majority will have a total thyroidectomy with central compartment clearance.²⁶ Occasionally, more extensive surgery is required and excellent outcomes are attainable.

Side by side, guidelines and audit are important together with on-going research programmes so that patients with thyroid disease can be offered both accurate diagnosis and tailored management. Gene therapy for benign disease should be investigated further, and the use of increased molecular profiling and FNA analysis may enhance identifying which patients need targeted treatment, and also which ones are likely to do well. Examining PTTG and PBF expression in thyroid tumours could be used to predict the efficacy of radio-iodine uptake, and potentially adjust dosage. Furthermore, inhibition of PTTG and PBF function in thyroid cancer may prove useful to increase the efficacy of ablative radioiodine treatment. However, despite all of the above, the majority of goitres in the foreseeable future will be treated with surgery when more and more will have a total thyroidectomy.

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New Associate Editor

The *Annals* is pleased to welcome Jyoti Shah to the new post of Associate Editor. Jyoti completed undergraduate and postgraduate training in London where she obtained an MD, an MS, a Diploma in the History of Medicine and a Diploma in Postgraduate Medical Education. She recently moved to Burton on Trent where she is a Consultant Urological Surgeon.

Jyoti was appointed to this post by competitive interview; we intend that she will learn about editing a journal, and will undertake a project to enhance the *Annals* during the next two to three years.