State budgetary educational institution of higher professional education

"North Ossetian State Medical Academy" of the Ministry of health of the Russian Federation

Department of surgical diseases No. 2

Kalitsova M. V., Totikov Z.V.

Disorders of the thyroid gland

Textbook for students of 5 - 6 courses

medical faculty of hospital surgery

Vladikavkaz
2020

UDC-616.34

K46

Kalitsova M. V., Totikov Z.V.

Disorders of the thyroid gland textbook, North Ossetian State Medical Academy.-Vladikavkaz, 2020 - p. 32

This tutorial is devoted to Disorders of the thyroid gland. The authors present current data on the etiology, pathogenesis, clinic, diagnosis, preoperative and intraoperative tactics of management and treatment of patients with disorders of the thyroid gland. The views on controversial and unresolved issues relating to the current state of this problem are Reflected.

The manual is developed in accordance with the requirements of the Federal state educational institution, is intended for senior students of medical Universities and faculties enrolled in the specialty 31.05.01 Medical business.

UDC-616.34

K46

R e c e n s e n t s:

Kulchiev A. A.-doctor of medical Sciences, Professor, head of the Department of surgical diseases No. 3 SBOU VPO SOGMA Ministry of health of Russia

Beslekoev U. S.-associate Professor, candidate of medical Sciences, head of the Department of General surgery SBOU VPO SOGMA Ministry of health of Russia

Approved and recommended for printing by the Central coordinating educational and methodical Council of the Ministry of health of the Russian Federation (Protocol No. 8 of december 1, 2020)

Contests:

Thyroid embryology, anatomy and physiology

Thyroid embryology

The thyroid is principally of *endodermal* origin, and is derived from the floor of the pharynx between the tuberculum impar (the medial swelling of the tongue) and the cupola. An endodermal track migrates down the neck in front of the primitive larynx and divides into right and left branches, which develop into the lateral lobes of the thyroid gland. This track remains connected to the tongue (at a point called the foramen caecum, located at the junction of the anterior and posterior parts of the tongue) by the thyroglossal duct. The duct normally closes at around the fifth week, and the only remnant is a shallow blind pit at the foramen caecum. Remnants of the duct may, however, persist and develop into well-differentiated thyroid tissue (ectopic thyroid) or a cystic lesion (thyroglossal cyst). Occasionally, these may be associated with absence of the thyroid in its orthotopic position, reflecting arrest of migration of the thyroglossal duct. Complete failure of descent may result in a lingual thyroid, at the back of the tongue. Papillary carcinoma of the thyroid may rarely develop in an ectopic thyroid gland. The thyroid is in its normal position just inferior to the cricoid cartilage by the seventh week. Follicles appear and the thyroid begins to secrete hormones by the twelfth week, one of the first organs to do so. The thyroid also has a *neural crest* origin as cells from the neural crest migrate into the ultimobranchial body, which is derived from the ventral part of the fourth/fifth pharyngeal pouch. The ultimobranchial body becomes incorporated into the thyroid and has been thought to develop into the tubercle of Zuckerkandl on the lateral aspects of the thyroid lobes. However, another view is that this may not contribute to any thyroid tissue. The 'neural crest' cells in the ultimobranchial body develop into the parafollicular cells, which secrete calcitonin. Hence, the thyroid gland is derived from both the endoderm of the primitive pharynx (follicular cells) and the ectoderm, i.e. the neural crest (parafollicular cells).

Thyroid anatomy

The thyroid is a highly vascular gland, weighing about 15g, and consists of two lobes, united in the midline by the isthmus, which overlies the second and third tracheal rings. There may also be a pyramidal lobe, superior to the isthmus and often to the left of the median plane. This is present in 50% of individuals and is the remnant of the thyroglossal tract. A fibrous capsule surrounds the thyroid and extends into the gland as septae. This capsule is enveloped by the visceral layer of the pretracheal cervical fascia. Posteriorly, the gland is attached to the cricoid cartilage and the superior tracheal rings by dense connective tissue (Berry's ligament). This attachment of the thyroid to the trachea causes the thyroid to move on swallowing, which helps distinguish thyroid nodules from other neck lumps. The arterial supply is from the superior and inferior thyroid arteries, which lie in the plane between the thyroid capsule and the pretracheal fascia. The superior thyroid artery originates from the external carotid artery and divides into an anterior and posterior branch at the superior pole of the thyroid. The external branch of the superior laryngeal nerve (EBSLN) runs inferolateral to the oblique line of thyroid cartilage and has a close relationship with the superior thyroid artery. It typically runs over the inferior constrictor muscle to reach and supply the cricothyroid (in some cases, the nerve passes deep to inferior constrictor muscle and is therefore not routinely seen at operation). Care must be taken to ligate the superior thyroid artery on the capsule of the thyroid at operation and to be aware of the possibility of damage to the EBSLN when applying diathermy to the small branches of the superior thyroid artery. Damage to the EBSLN results in paralysis of the cricothyroid muscle. This muscle tenses the vocal cords, which is important in production of high pitch, as in singing. The inferior thyroid artery originates from the thyrocervical trunk, which arises from the first part of the subclavian artery. It enters the thyroid on its lateral aspect and has a close relationship with the recurrent laryngeal nerve (RLN). On the left, the RLN runs vertically along the tracheo-oesophageal groove and is usually medial to the inferior thyroid artery. On the right, the RLN runs a more lateromedial course and has a more intimate relationship to the branches of the inferior thyroid artery. Superiorly, the nerve passes through the posterior portion of Berry's ligament (an area where it is prone to damage) before entering the larynx, usually adjacent to the inferior cornu of the thyroid

cartilage. The RLN is the motor supply to the intrinsic muscles of the larynx. An injury to the nerve causes ipsilateral vocal cord palsy. In about 1% of cases there is a non-recurrent right laryngeal nerve, owing to a vascular anomaly in the development of the aorticB€ arches. InB€10%B€of patients there is a thyroidea ima artery, which arises from the brachiocephalic trunk, and passes into the inferior border of the isthmus. The venous drainage of the thyroid is via the superior and middle thyroid veins, which drain into the internal jugular and the inferior thyroid veins, which drain into the brachiocephalic vein. The lymphatic drainage of the thyroid is to the prelaryngeal, pretracheal and paratracheal lymph nodes medially and then to the deep cervical lymph nodes laterally around the carotid sheath.

Thyroid physiology

The thyroid gland consists of two main types of cells – follicular and parafollicular cells. The follicle is the basic functional unit of the thyroid and consists of a single layer of cuboidal (follicular) cells around a store of colloid. The follicular cells synthesize thyroid hormone in four stages, which include:

- ✓ *Iodide trapping*. Iodide is actively transported (by an ATP-dependent process) into the thyroid follicular cell and then to the apical membrane. The average daily requirement of iodine is 150□g. The normal daily Western dietary intake contains approximately 500□g.
- ✓ *Organification*. The iodide is oxidized by the enzyme thyroid peroxidase and then combined with tyrosine to form the inactive iodotyrosines: 3-monoiodotyrosine (MIT) and 3,5-di-iodotyrosine (DIT). The iodotyrosines are incorporated into the soluble protein, thyroglobulin, which is stored as colloid in the follicular lumen of the thyroid.
- ✓ *Coupling*. The iodotyrosines in the thyroglobulin are then coupled to form triiodothyronine or T3 (MIT and DIT) and thyroxine or T4 (two molecules of DIT).
- ✓ *Release*. Colloid is taken up by the thyroid cell by endocytosis to form endosomes.

The thyroglobulin is then hydrolysed to liberate T4, T3, MIT and DIT. The MIT and DIT are deiodinated and the released iodide reused by the thyroid cell. The active hormones, T4 and T3, are secreted into the blood. The vast majority of the released thyroid hormone is in the form of T4 (90%). Most of the T3 (80–90%) is produced by the peripheral conversion of T4. T3 is much more potent than T4. The metabolic activity of thyroid hormone is determined by the amount of free T3 and free T4. Thyroxine is very highly protein bound in plasma (99.95% bound to thyroid-binding globulin, transthyretin and albumin, with about 0.05% free). When bound, T4 is not physiologically active but provides a storage pool of thyroid hormone, which can last 2–3 months (mean half-life of T4 is 6.5 days). Reverse T3 (rT3) is also produced by the deiodination of T4. It is not physiologically active and increased levels of rT3 are produced in hyperthyroidism, and periods of excess catabolism (e.g. burns, sepsis).

Peripheral action of thyroid hormone The principal effects of thyroid hormones are to facilitate normal growth and differentiation and to increase the rate of metabolism. Thyroid hormones act predominantly via a nuclear thyroid receptor (TR), which upregulates gene transcription and thereby increases protein synthesis. T4 is relatively inactive in the periphery, owing to a low affinity for TR in comparison with T3.

Thyroid hormone regulation

Thyroid-stimulating hormone (TSH) is the major regulator of thyroid activity, with increased levels causing hypertrophy of the thyroid. TSH is secreted by the anterior pituitary, and is a glycoprotein with an □□and β□subunit (the subunit being common to follicle-stimulating hormone, luteinizing hormone and human chorionic gonadotrophin). TSH acts by binding to the TSH receptor on the follicular cell membrane, leading to increased thyroid hormone synthesis, predominantly via cAMP as the second messenger. Thyroid-releasing hormone (TRH) is the most important positive stimulus for the production of TSH. TRH is produced in the paraventricular nucleus of the hypothalamus and passes through the median eminence to the anterior

pituitary via the hypophyseal portal system. T3 has a negative feedback on both the anterior pituitary and the hypothalamus.

Parafollicular cells

The parafollicular, or C cells, secrete calcitonin. Calcitonin is a 32 amino acid peptide that lowers calcium largely by the inhibition of osteoclasts. It is of little physiological importance in humans as there is no disturbance of calcium regulation following thyroidectomy, provided that the parathyroids are preserved. It is a sensitive tumour cell marker for medullary thyroid carcinoma (see Differentiated thyroid carcinoma). Calcitonin also has a role in the treatment of Paget disease of the bone.

Hypothyroidism

Epidemiology

Hypothyroidism is one of the most common endocrine disorders, with approximately 5% of the female population developing hypothyroidism at some stage in their lives. The vast majority are caused by primary hypothyroidism, with secondary (anterior pituitary gland disorders) and tertiary (hypothalamic disorders) hypothyroidism being rare. Primary hypothyroidism is usually caused by autoimmune thyroiditis (the commonest among them being Hashimoto's thyroiditis), or by treatment of other thyroid disease [e.g. following surgery or radioactive iodine (RAI) for thyrotoxicosis]. About one-third of patients undergoing a hemithyroidectomy and up to 70% of patients treated by subtotal thyroidectomy are hypothyroid at 10 years, this being influenced by remnant size and the degree of lymphocytic infiltration of the thyroid. The use of RAI in the management of thyrotoxicosis results in 50% of patients developing hypothyroidism in the first year, with 3% per annum subsequent to that. Lifelong follow-up and monitoring of TSH levels are therefore required for these patients. External beam radiotherapy to the neck can result in subclinical or clinical hypothyroidism in up to 50% of patients (usually 2–7 years after treatment). In addition, certain drugs can cause hypothyroidism, including amiodarone and lithium.

Thyroiditis

Several different types of thyroiditis exist. Although there are overlapping features among the different types, they are commonly classified on the basis of histology and/or aetiology. These include:

- ✓ chronic lymphocytic (Hashimoto's thyroiditis)
- ✓ Graves' disease (see Thyrotoxicosis)
- ✓ subacute granulomatous thyroiditis
- ✓ subacute lymphocytic thyroiditis
- ✓ postpartum thyroiditis
- ✓ postsurgical thyroiditis (e.g. following parathyroid surgery)
- ✓ radiation thyroiditis (following RAI and external radiation)
- ✓ suppurative thyroiditis (or thyroid abscess)
- ✓ Reidl's thyroiditis.

The commonest form of thyroiditis and hypothyroidism in the population is a specific autoimmune form of thyroiditis called Hashimoto's thyroiditis. This has a familial predisposition. Females are more commonly affected (male to female ratio 9:1) with the usual age of onset being 40–50, although it can occur at any age. The usual clinical presentation is with painless thyroid enlargement (a firm, rubbery gland); occasionally the patient may present with pain or pressure in the neck. The gland enlarges owing to the lymphocytic infiltrates and areas of focal hyperplasia, caused by TSH stimulation. In the early stages, free T4 and T3 may be normal, with an elevated TSH (subclinical hypothyroidism). The patient may also present with thyrotoxicosis (4%), caused by release of thyroxine, before eventually becoming hypothyroid.

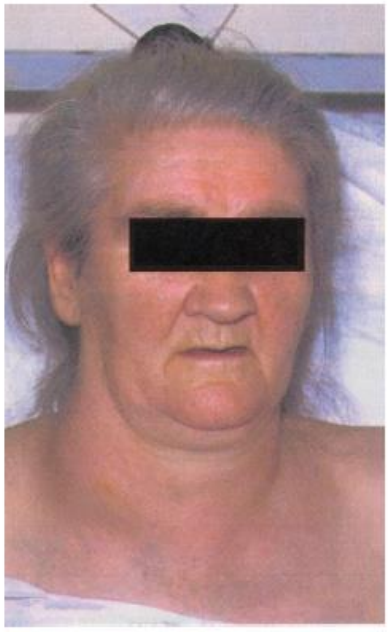
Clinical features

The development of clinical features is variable and often slow and insidious. A significant proportion of patients have mild or non-specific features and the diagnosis is made on biochemistry as part of screening for a variety of medical problems. Common symptoms of hypothyroidism include dry skin, coarse hair, hair loss, brittle nails, weight gain, hoarseness (unrelated to RLN palsy), cold intolerance, paraesthesia, muscle stiffness and aches, drowsiness, lethargy, easy fatigability and constipation. Signs include cool and dry skin,

bradycardia, puffy face and hands and slow deep tendon reflexes. Clinical features are less obvious and often atypical in the elderly. In myxoedema (severe and lifethreatening hypothyroidism), there is progressive deterioration in mental status, localized neurological signs, hypothermia, hypoglycaemia and hyponatraemia. Subclinical hypothyroidism is a biochemical entity defined as raised TSH in the presence of normal levels of T3 and T4. These patients are usually asymptomatic.

Investigations

Investigations are largely biochemical. A thyroid profile usually includes TSH and free T4 (free T3 is sometimes done, especially if T4 levels are normal). Antimicrosomal antibodies (antithyroid peroxidase) are found in 90% of patients with Hashimoto's thyroiditis, but are not specific as they are also found in 70% of patients with Graves' disease. Antithyroglobulin antibodies are found in 60% of patients and are more specific to Hashimoto's thyroiditis. Thyroid ultrasound or isotope scans are usually not required for the diagnosis of hypothyroidism



Patient who developed lymphoma on a background of Hashimoto's thyroiditis.

Treatment

The aim of treatment is to normalize the TSH level by giving supplemental thyroxine. Thyroxine is absorbed in the small intestine and has a half-life of 7 days. Care must be taken when instituting therapy in the elderly or patients with coronary artery disease, when a lower dose should be initially administered (starting at 25□g and increasing by 25□g increments every 2 weeks). After TSH levels are stabilized, therapy is monitored by checking the TSH level on an annual basis. The treatment of subclinical hypothyroidism is debatable and best done in conjunction with a medical endocrinologist. Consensus statements suggest thyroxine treatment in patients with TSH levels persistently above 10.0 mU/L.

Long-term consequences

Patients with autoimmune thyroiditis have an increased predilection for other autoimmune disorders (such as pernicious anaemia). Patients with Hashimoto's thyroiditis also have a higher risk of developing a thyroid lymphoma than the general population. Eighty per cent of all β-cell thyroid lymphomas develop on a background of Hashimoto's thyroiditis.

Hyperthyroidism

Epidemiology

Hyperthyroidism refers to the state of increased synthesis and secretion of thyroid hormones. Thyrotoxicosis is defined as excess levels of circulating thyroid hormones, which includes hyperthyroidism but also other uncommon conditions in which high levels may be due to destructive thyroiditis and excessive release, ectopic secretion (from struma ovarii or choriocarcinoma) or excessive ingestion of thyroid hormones. Thyrotoxicosis is caused in the vast majority of instances by primary thyroid pathology (including Graves' disease, toxic multinodular goitre and solitary toxic adenoma).

Graves' disease

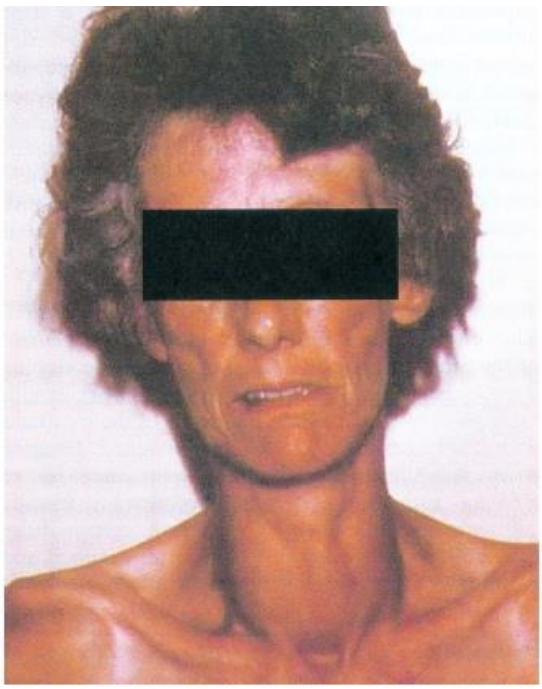
Graves' disease (also called Basedow disease in mainland Europe) is an autoimmune disorder, characterized, in 90% of cases, by the presence of an immunoglobulin G antibody against the TSH receptor. The antibody is termed thyroid-stimulating immunoglobulin or TSH receptor antibody (TRAb) and stimulates the follicular cells, leading to excess production of thyroxine, hyperplasia and hypertrophy of the gland. Graves' disease is commoner in females (female to male ratio 7:1) and is not premalignant. The thyroid in patients with Graves' disease is usually diffusely enlarged, although sometimes multinodularity (or asymmetric enlargement) is noted. Thyroid cancer has occasionally been detected in surgically resected thyroid gland specimens of patients with Graves' disease. The nature of this association is uncertain and a previous presumption of increased aggressiveness of thyroid cancer in such patients has not been established.

Other causes of primary thyrotoxicosis

Plummer disease (described originally in 1913) is the term given to a hyperfunctioning thyroid, which may be either multinodular or a solitary nodule. A *toxic multinodular goitre* usually develops in a large, longstanding multinodular goitre of at least 10 years' duration. A *solitary toxic adenoma* is an autonomous nodule that produces enough thyroid hormone to cause hyperthyroidism. An unusual cause of thyrotoxicosis is the Jod–Basedow phenomenon, which is caused by the excessive release of thyroxine in an iodine-deficient patient on resumption of dietary iodine intake or administration of intravenous contrast. The phenomenon is most commonly observed in patients over 50 years with a longstanding multinodular goitre.

Clinical features

Symptoms include anxiety, tremor, palpitations, hyperactivity, increased appetite, weight loss, fatigue, heat intolerance, diarrhoea, menstrual irregularity and skin changes. Signs include warm and moist skin, irritability, restlessness and other psychiatric manifestations and features of a hyperdynamic circulation (and atrial fibrillation in the elderly). Other uncommon features include myopathy, gynaecomastia, decreased fertility, hyperpigmentation, splenomegaly and lymphadenopathy. Patients with Graves' disease may also have an infiltrative dermopathy often affecting the legs. This has been paradoxically termed 'pretibial myxoedema'. Thyroid eye disease, which is often associated with Graves' disease (see below), manifests in its early stages as prominence of the eyes, irritation and increased watering of the eyes and in later stages as periorbital oedema, chemosis (conjunctival oedema), lid and/or globe lag, ophthalmoplegia and visual loss. Investigations



Proximal upper limb myopathy in a patient with thyrotoxicosis.

TSH levels are suppressed in thyrotoxicosis. In Graves' disease, antimicrosomal (thyroid peroxidase antibody) and antithyroglobulin antibodies are raised in 70% of patients, whereas the TRAb is raised in 90% of patients. Antibodies are usually absent in toxic multinodular goitre and solitary adenomas. Ultrasound or isotope scans are generally unhelpful in the investigation of Graves' disease, except in postpartum thyrotoxicosis, when it may be necessary to differentiate Graves' disease from self-limiting postpartum thyroiditis. In a toxic multinodular goitre, isotope scanning will usually show multiple hot areas, and will help determine the presence and extent of retrosternal extension. In a solitary toxic adenoma, an isotope scan will demonstrate the hot nodule with suppression of the extranodular thyroid tissue. Differentiation between a solitary toxic adenoma and a toxic multinodular goitre can help plan the extent of thyroidectomy. Fine needle aspiration (FNA) is usually used to exclude an associated thyroid neoplasm in the presence of a solitary or dominant thyroid nodule.

Treatment of Graves' disease

Antithyroid drugs

These are the mainstay of initial treatment. Although the hyperthyroid state can usually be well controlled, relapse rates are around 50–60%. Male sex, large goitres, high levels of thyroid hormones, high levels of TRAbs and smoking increase the risk of relapse. The thionamides (carbimazole, propylthiouracil and methimazole) block the organification (iodination) of the tyrosine residues on the thyroglobulin molecule, by

inhibiting the enzyme thyroid peroxidase. Carbimazole is converted to its active constituent methimazole (which is primarily used in the USA). The traditional dosing regimen is 20–40mg of carbimazole (100–150mg of propylthiouracil) to render patients euthyroid and maintaining low-dose treatment for 12–18 months. An alternative treatment regimen ('block and replace' regime) involves using a much higher dose of antithyroid drugs along with thyroxine to maintain euthyroidism. The advantage of this latter regimen is faster control of hyperthyroidism with less frequent use of TSH measurements; the disadvantage being a higher incidence of side effects. Side effects of these drugs include rash, arthralgia and gastrointestinal disturbances; rarer but more serious side effects include agranulocytosis, vasculitis and hepatitis. Treatment with recombinant granulocyte colonystimulating factor has been reported to shorten recovery time in patients with thionamide-induced agranulocytosis.

Radioactive iodine

RAI uses the high-energy β particles of 131I to ablate thyroxineproducing follicular cells. It is the treatment of choice in elderly patients, patients with small glands or those who are unfit for surgery. Contraindications to RAI include pregnancy (RAI freely crosses the placenta and activity in the maternal bladder causes fetal irradiation), breastfeeding (both iodine and pertechnetate are excreted in breast milk) and patients with severe toxicity (as patients may develop thyroid storm if markedly toxic and should be pretreated with beta-blockers). Carbimazole is stopped 48 hours before and restarted 3–5 days after RAI. The usual dose of I_{131} given is 500–750MBq and the maximum effects of treatment occur 3–4 months after the dose of RAI. Hypothyroidism is an almost inevitable consequence of treatment (see Hypothyroidism). RAI may exacerbate clinically evident ophthalmopathy and systemic corticosteroids may be indicated to reduce this risk. Although debatable, some studies suggest a small increase in cardiovascular and cancer-related mortality.

Surgery

Traditionally, the standard surgical treatment in Graves' disease was a subtotal thyroidectomy, the aim of which was to leave behind a small volume of thyroid tissue in each lobe so as to leave the patient euthyroid. However, the drawbacks were a risk of recurrent thyrotoxicosis (around 10%) and the observation that up to 70% of patients will develop hypothyroidism at 10 years. The current trend therefore is to perform a near total or total thyroidectomy and immediate institution of thyroxine postoperatively. This serves to eliminate the disease with negligible recurrence rates. There are concerns that the complications such as RLN damage and hypoparathyroidism may be higher with the more radical operation, but this has not been shown to be the case in experienced hands.

Treatment of toxic adenoma/multinodular goitre

For patients with toxic adenoma and toxic multinodular goitre, surgery and RAI are effective and safe treatment options. Factors favouring surgery include contraindications to RAI, large or compressive goitres, indeterminate or suspicious nodules, nodules with retrosternal extension and coexisting hyperparathyroidism needing surgery. Factors favouring the use of RAI include elderly, unfit patients, patients with small nodules and previous neck surgery. Occasionally, elderly patients unfit or unwilling to undergo either surgery or RAI may be maintained on long-term low-dose antithyroid drugs.

Thyroid nodules

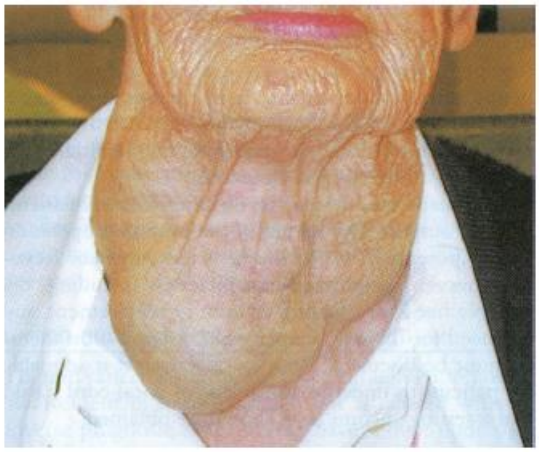
Epidemiology

Nodular thyroid disease is common and the incidence increases with age. The prevalence of palpable nodules in areas of adequate iodine intake is 4–7% but autopsy studies and ultrasonography have shown the true figure to be much greater with around 50% of adults having nodules. In areas of severe iodine deficiency, the prevalence can be as high as 90%. A wide range of benign and malignant pathology can

account for patients presenting with a thyroid nodule(s). Malignant diseases are covered later, but the list of benign pathology includes:

- ✓ colloid or multinodular goitre (may present as solitary/dominant nodule)
- ✓ thyroiditis
- ✓ simple or haemorrhagic cysts
- ✓ follicular adenomas
- ✓ thyroid abscess.

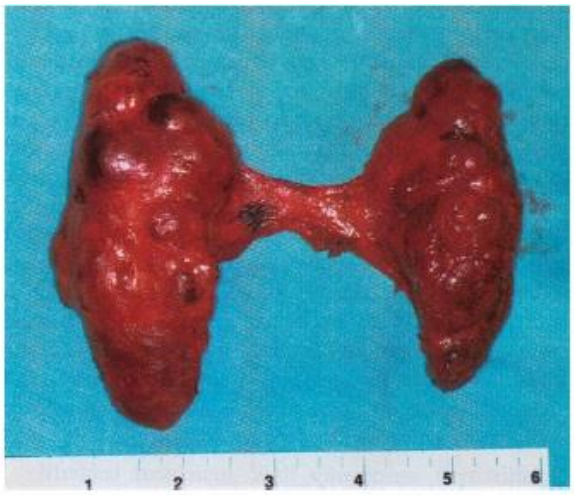
In a multinodular goitre, enlargement of the thyroid tends to start as diffuse hyperplasia of the gland, with subsequent areas of focal hyperplasia (which may be dependent on TSH stimulation) and areas of regression and colloid degeneration; a multinodular goitre may be non-toxic (euthyroid) or toxic (Plummer disease). The aetiology of a multinodular goitre is poorly understood, but is thought to be multifactorial: genetic predisposition to dyshormonogenesis, iodine deficiency, drugs (notably amiodarone and lithium), ingestion of brassica vegetables and autoimmunity. Thyroid cancer, however, is rare, affecting around four in 100000 individuals per year and constituting 1% of all malignancies. The difficulty for the clinician and patients in the management of nodular goitre is to strike the right balance that avoids overtreatment of common benign nodular disease and enables early detection and treatment of thyroid cancer. This is compounded by the need for diagnostic excision in the all too common scenario of indeterminate or inconclusive cytology.



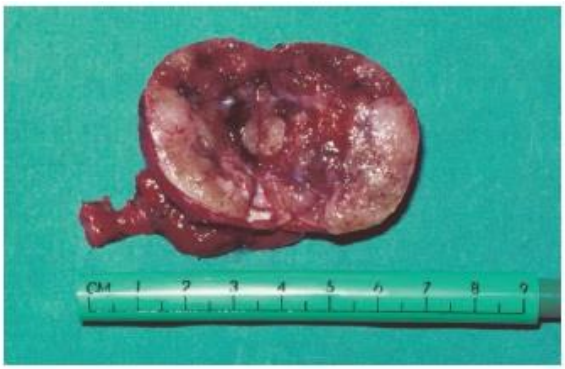
Patient with longstanding multinodular goitre.

Clinical features

The majority of thyroid nodules are asymptomatic and are found fortuitously by the patient or on routine clinical examination. The lumps are largely painless, but the sudden presentation of a painful swelling is almost pathognomonic of haemorrhage into a simple colloid nodule. Patients with thyroiditis sometimes have local discomfort and tenderness. Compressive symptoms such as difficulty in breathing and/or swallowing are usually seen in very large, multinodular goitres. These goitres can cause significant deviation and/or tracheal compression; the latter may be associated with stridor. Compressive or obstructive symptoms are more common when the goitre grows posteriorly



Dominant nodule in the right upper thyroid lobe of a multinodular goitre.



Solitary nodule – benign.

or in a retrosternal direction; around 10% of multinodular goitres will have a retrosternal extension. These goitres may cause compression of large veins at the thoracic inlet leading to dilated veins in the head, neck and upper limbs. Elevation of the arms in conjunction with deep inspiration can often precipitate engorgement of veins in the upper half of the body, flushing and respiratory distress in these patients (Pemberton's sign). Rapidly worsening symptoms especially in association with voice change can be a sign of malignancy, but a malignant tumour can also be extremely slow growing and be present for many years before being discovered. Although the vast majority are benign, features of hyperthyroidism and hypothyroidism should be elicited in all these patients (see previous sections). Nodules in patients with a past history of neck irradiation and a family history of thyroid malignancy clearly have a high likelihood of being malignant. The very young and elderly are at increased risk for malignancy. There is an increased incidence of follicular cancer in iodine-deficient endemic goitrous areas and an increase in papillary cancer in iodine-rich regions. Solitary nodules convey a greater risk of malignancy in males, and a family history of endocrine disease suggests the possibility of medullary thyroid carcinoma. Papillary carcinoma may also be familial and has been described with familial adenosis polyposis (Gardner syndrome) and also ataxia–telangiectasia. Consistency can be misleading as, although a hard fixed nodule is likely to be malignant, a benign colloid nodule can also be hard with dystrophic calcification. Associated cervical lymphadenopathy and features of RLN palsy are highly suggestive of malignancy. However, associated lymph nodes could be reactive (especially in presence of thyroiditis) and nerve palsy could occasionally be secondary to compression by a longstanding, large multinodular goitre.

Risk factors for thyroid malignancy

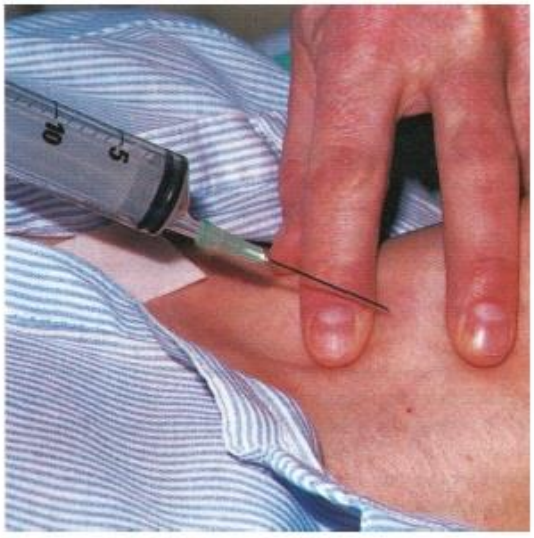
- Age – a new thyroid nodule in patients <20 years or >50 years
- Male sex
- Clinical features – consistency, fixation, size, solitary versus multiple nodules
- A history of head and neck irradiation
- Familial history of thyroid malignancy of multiple endocrine neoplasia (MEN) 2
- Recurrent laryngeal nerve palsy
- Cervical lymphadenopathy

Investigations

Fine needle aspiration cytology

Fine needle aspiration cytology (FNAC) is now a routine and important investigation in patients presenting with a solitary thyroid nodule or a dominant nodule in a multinodular goitre. It may be a curative procedure for simple thyroid cysts, although patients with recurrent cysts and those with residual solid areas should be reaspirated or considered for surgery. FNA is, however, not required in patients with multinodular goitre without a dominant nodule and also in patients with a diffuse goitre who are hyperthyroid (as in Graves' disease). Cytological assessment may be performed using a wet-fixed or air-dried preparation or alternatively utilizing a cell block method in which the thyroid architecture is preserved. The authors perform several passes of the needle for each nodule and find good patient compliance with few complications. The procedure can also be easily repeated. In the UK, the cytology report is usually classified into one of the following categories:

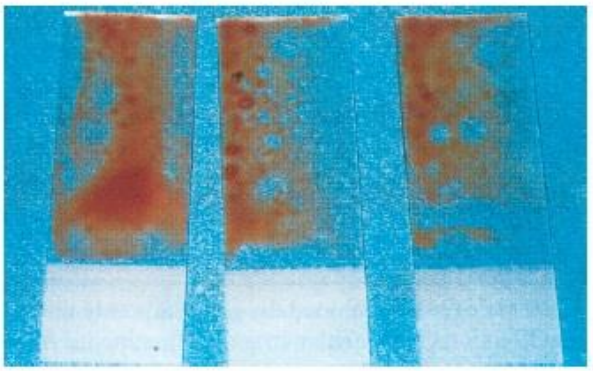
- ✓ Thy1 (inadequate or non-diagnostic)
- ✓ Thy2 (benign or non-neoplastic)
- ✓ Thy3 (indeterminate, possibly neoplastic)
- ✓ Thy4 (suspicious of malignancy)
- ✓ Thy5 (diagnostic of malignancy).



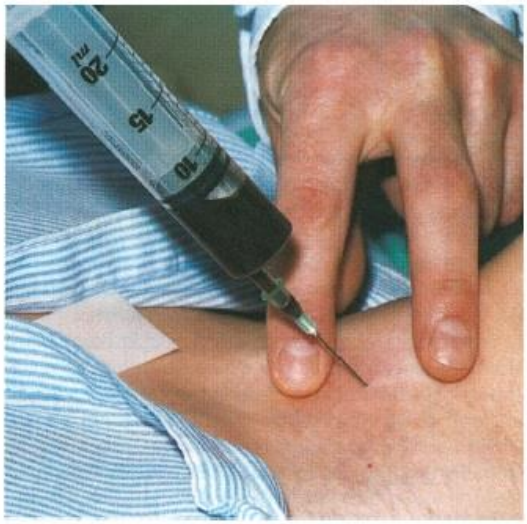
Fine needle aspiration: fixation of a nodule with the index and middle fingers prior to aspiration.

Thy1 and Thy2 categories are sometimes suffixed as Thy1c and Thy2c, respectively, to indicate the possibility of a cystic lesion. Recently, the Thy3 category has been subdivided into Thy3a to indicate a lesion with atypical features of uncertain significance and Thy3f to indicate the likelihood of a follicular neoplasm. Often, a confident diagnosis of colloid nodule (Thy2) or thyroiditis (Thy2), papillary, medullary and anaplastic carcinoma (Thy5), lymphoma (Thy5) and even metastatic deposits (Thy5) can be made. A major limitation of the technique is the evaluation of follicular lesions where histology is required to differentiate benign follicular lesion from carcinoma; the latter diagnosis is dependent upon the presence of capsular and vascular invasion. Core biopsy for these follicular lesions has been suggested by some authors, but increases the risk of haematoma and may still be inadequate for a definite histological diagnosis. The positive and negative predictive values of a clear FNA result are over 98%. However, inadequate specimens should lead to repeat aspiration. Surgery may sometimes be indicated in a patient with repeated inadequate cytology. Benign lesions may be managed conservatively and FNA repeated to confirm the diagnosis. Clinical suspicion, increasing size of nodules, compressive symptoms and associated hyperthyroidism may be indications for surgery in nodules with benign cytology. Patients with indeterminate, suspicious and malignantB€ results should undergo a thyroidectomy. The diagnosis of indeterminate and suspicious lumps may in the future be improved with immunocytochemical techniques.

Fine needle aspiration: the aspirate is spread evenly between two slides.



Fine needle aspiration: the specimen is to be air-dried before sending to the laboratory.



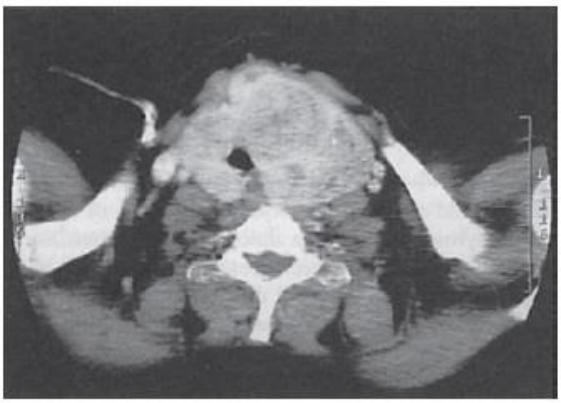
Fine needle aspiration cytology: a diagnostic and sometimes also a therapeutic procedure (as seen here with aspiration of a thyroid cyst).

Blood tests

These should be requested to measure TSH and free T4 levels. The majority of patients with a thyroid nodule are euthyroid but coexisting thyroid dysfunction may point to the underlying pathology. For example, a hyperthyroid patient with a solitary nodule suggests a benign toxic (autonomous) nodule, whereas hypothyroidism may indicate nodular Hashimoto disease possibly with lymphomatous change. The presence of thyroid dysfunction will also influence further management. Patients with hyperthyroidism who need surgery would need to be made euthyroid with antithyroid drugs. In patients with a positive family history of MTC, serum calcitonin should be measured to aid diagnosis. This is also used for monitoring following treatment of MTC.

Imaging

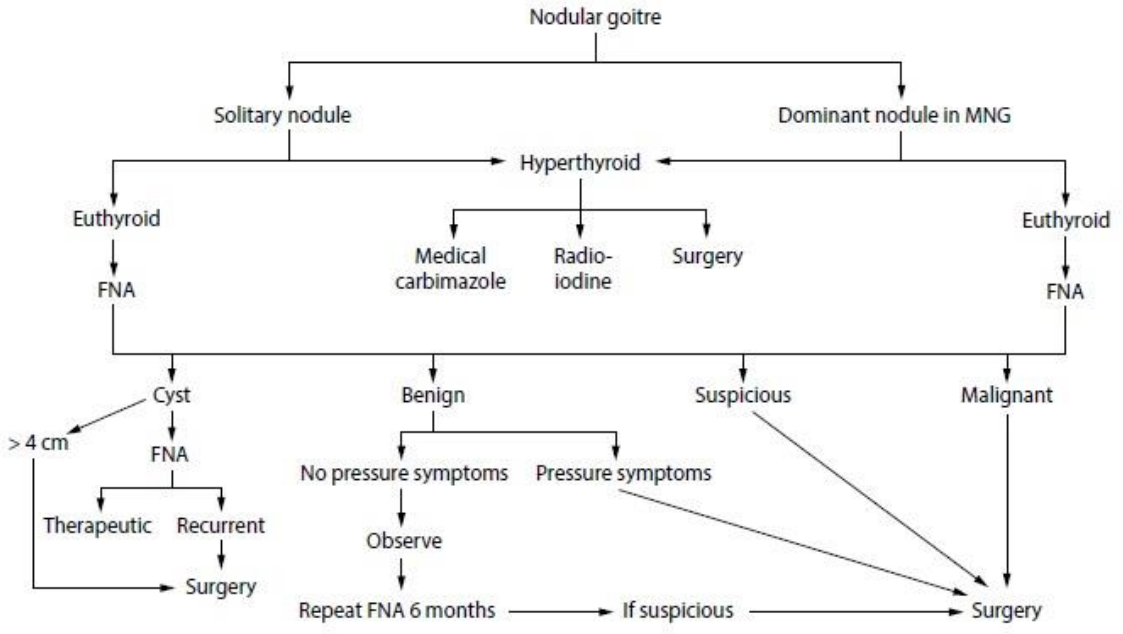
High-resolution ultrasonography is now often performed as part of the diagnostic work-up of a thyroid nodule. It is sensitive in identifying impalpable nodules as small as 0.3mm in diameter. Ultrasound detects multinodularity in around 50% of all nodules thought to be solitary on examination. It differentiates cystic from solid lesions and can identify associated lymphadenopathy, which could be a marker for malignancy. Other ultrasound features of malignancy include nodules with spiculated margins, hypoechogenicity and microcalcifications, but none of the findings are accurate enough to dictate clinical management. Its routine use in all patients presenting with a thyroid nodule or a multinodular goitre is probably unnecessary. An ultrasound is, however, quite useful in specific clinical scenarios. Ultrasound is used to characterize and guide FNA of a barely palpable nodule or an impalpable lump detected incidentally on other imaging [such as CT or positron emission tomography (PET)]. For patients being managed conservatively, ultrasound may also help in monitoring nodule size during follow-up. In the follow-up of patients with thyroid cancer, neck ultrasound helps to identify locoregional recurrence. Chest radiograph, CT and MRI have little role in the differentiation of benign and malignant lumps, but do help to determine the presence and degree of retrosternal extension and extent of tracheal deviation or compression. Isotope scanning is not useful in differentiating between malignant and benign lesions and its role is now limited to patients with coexisting hyperthyroidism to aid in the diagnosis of a solitary toxic adenoma and to determine areas of hyperfunction in a patient with toxic multinodular goitre.



CT scan of the neck demonstrating tracheal deviation and compression.

Treatment

This section will focus on the management of benign nodular disease. The treatment of the various forms of thyroid cancer will be covered in subsequent sections. FNAC may be both a diagnostic and therapeutic tool for the management of simple thyroid cysts. However, surgical excision may still be required in a small number of patients in whom there is recurrent cyst formation or a suspicious residual nodule. A long-term follow-up study of putatively benign thyroid nodules has demonstrated that just over a third of nodules disappear and most nodules reduce in size over a 10–30 year period (Kuma *et al*. 1992). However, 26% of enlarging nodules were found to be malignant. A further report by the same group (Kuma *et al*. 1994) on clinical re-examination, FNAC and ultrasound-guided FNAC to assess nodules over 9–11 years has clearly demonstrated that 99% of benign nodules remain benign, with the majority decreasing in size or disappearing during the follow-up period. The worrying clinical feature remains an increase in nodule size. Clearly there should be a high index of suspicion for lesions that increase in size during follow-up.



Algorithm for the management of a patient with a thyroid nodule. FNA, fine needle aspirate; MNG multinodular goitre.

Surgery

The majority of multinodular goitres are benign and not associated with significant compressive symptoms and can therefore be treated conservatively. However, surgery is indicated for the following reasons:

- ✓ suspected or proven malignancy on FNA
- ✓ compression of the trachea or oesophagus
- ✓ significant recent growth of a dominant nodule (suggestive of malignancy)
- ✓ local neck discomfort
- ✓ cosmetic reasons.

The need for surgery is based on the overall assessment of symptoms, clinical risk factors and cytology. Indeterminate, suspicious or malignant cytology are clear indications for surgery. Recurrent cysts and solid nodules that repeatedly yield an inadequate sample on cytology are also indications for surgery. Other scenarios in which surgery is considered include patients with large nodules causing pressure symptoms (e.g. dyspnoea, dysphagia or choking sensation), nodules increasing in size on follow-up and increased patient anxiety especially in the context of a family history of thyroid cancer. Surgery for nodular thyroid disease usually includes one of the following operations:

- ✓ hemithyroidectomy/lobectomy for unilateral disease
- ✓ isthmectomy for a solitary nodule confined to the isthmus
- ✓ total thyroidectomy for bilateral nodularity and solitary nodules with malignant cytology.

Nodule excisions and subtotal resections of either the lobe or the thyroid gland are no longer performed. In patients with a preoperative diagnosis of thyroid cancer, a prophylactic central node dissection is performed by many authors at the time of the total thyroidectomy. If suspicious/confirmed lateral lymph node metastases are present, aB€lateral node dissection is also done (see below). During a hemithyroidectomy/lobectomy for unilateral disease with indeterminate/suspicious cytology, the surgeon palpates the contralateral lobe through the strap muscles. If the other lobe is grossly normal and there is no associated lymphadenopathy, a total thyroid lobectomy removing isthmus and pyramidal lobe (if present) is performed preserving the parathyroid glands, the EBSLN and the RLN. This is a safe procedure with low morbidity when performed in experienced hands. Frozen section may occasionally be useful in confirming malignancy leading to total thyroidectomy and avoiding a second operation. If there is any doubt (particularly with follicular lesions) then the neck is closed and formal paraffin histology is awaited.

Non-surgical options of treatment of benign non-toxic goiter

Several non-surgical options have been explored in an attempt to avoid surgery in patients with benign non-toxic goitre. RAI is a particularly useful alternative to surgery in patients who are unfit for surgery, unwilling to consider surgery and in those with recurrent disease. RAI may reduce goitre volume by around 50% and improve compressive symptoms. The drawbacks include transient hyperthyroidism, occasional increase in goitre size, late onset hypothyroidism and the theoretical increased risk of malignancy. The lack of a consistent effect may be related to low or patchy uptake in many patients – an argument for higher dose recommended by some authors. More recently, recombinant TSH has been used to increase uptake at lower doses and may prove more effective than RAI alone. Thyroxine and iodine supplementation have been tried but are not routinely recommended in view of inadequate response rates, side effects (hyperthyroidism, cardiovascular and skeletal problems) and potential for regrowth following cessation of treatment. Percutaneous injection of ethanol has also been tried, but its use is largely experimental.

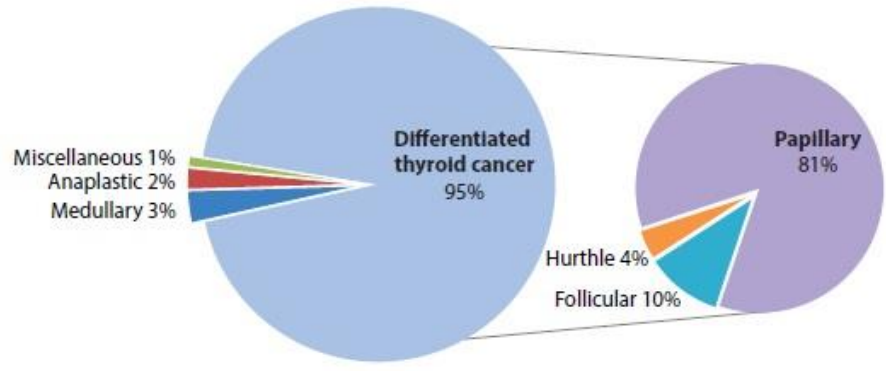
Thyroid cancer

Thyroid cancer is uncommon; the age-standardized incidence rate in the UK is around three per 100в•›000 per year. The incidence in the USA is twice that in Europe; the reasons for this are not clear but could be related to the increased use of imaging resulting in the detection of early stage, good prognosis cancers. Most thyroid cancers fall under the category of differentiated thyroid cancer (DTC), among which papillary thyroid cancer (PTC) makes up the vast majority.

Differentiated thyroid cancer

Epidemiology

These cancers arise from follicular epithelial cells of the thyroid gland. The incidence of DTC in general and PTC in particular has more than doubled in the last 30 years. Interestingly, however, the



Thyroid cancer types and subtypes.

incidence of follicular thyroid cancer (FTC) has not increased; this is at least partly due to a recent increase in the number of follicular cancers being classified as follicular variant PTC.

Papillary thyroid cancer

PTC accounts for around 80% of all malignant thyroid tumours. The histological diagnosis rests on characteristic nuclear features. Typical PTC shows a complex papillary architecture. It is also classically described as 'psammoma bodies', which are spherical areas of concentrically laminated calcifications in stroma or lymphatic spaces. Many variants of PTC exist and these include encapsulated, microcarcinoma (<1cm), follicular, oncocytic, clear cell, diffuse sclerosing, tall cell, columnar cell, solid and cribriform variants. PTC typically spreads by the lymphatic route and occult lymph node metastases are thought to be present in around half of patients without any evidence of lymphadenopathy. The prognosis of these cancers in general is very good with >90% 10-year survival. Some subtypes such as the diffuse sclerosing, tall cell and columnar cell variants carry a worse prognosis.

Follicular thyroid cancer

This accounts for around 10% of all thyroid tumours. These tumours also arise from follicular cells, but lack the nuclear features of PTC. Iodine deficiency is thought to play an important role in its development. The cellular appearances are indistinguishable from follicular adenomas and therefore, as explained earlier, cytology is inadequate to differentiate between follicular adenomas and carcinomas. The types of FTC include minimally invasive follicular carcinomas, widely invasive follicular carcinomas, oncocytic follicular carcinomas and clear cell carcinomas. These cancers are often multifocal and spread predominantly by the haematogenous route to organs such as lung and bone. Lymph node metastases are uncommon. Prognosis is slightly worse than PTC; survival is around 85% at 10 years.

Hurthle cell cancer

Hurthle cell cancer (HCC) is a distinct variant of FTC, although Hurthle cells can be found in a variety of other neoplastic and non-neoplastic conditions. Hurthle cells typically have abundant altered mitochondria that fill up the cytoplasm resulting in the characteristic eosinophilic granular cytoplasm. In HCC, the lesion is composed predominantly (>75%) of Hurthle cells. These have a poorer prognosis than other FTCs and are slightly resistant to radioiodine. In variance with other FTCs, lymph node metastases occur in around 20% of patients with HCC.

Poorly differentiated cancers

These lie in the spectrum between differentiated and undifferentiated (anaplastic) cancers and arise from the follicular epithelium. These are often infiltrative and have necrotic areas and obvious vascular invasion. Insular, trabecular and solid patterns are recognized.

Mixed tumours

These are also recognized, in which varying proportions of the above tumour types are seen.

Prognosis

The prognosis of DTC is in general excellent with overall cure rates of around 90%. In general terms, 80–90% of patients will fall within the 'best' prognostic group, in whom diseasespecific death occurs in no more than 2% of patients. In the worst prognosis groups, the 20-year mortality rate is around 75– 95%. Some subtypes

(tall cell, diffuse sclerosing and columnar varieties of PTC, HCC) and some factors (such as male sex, age >45 years at diagnosis, incomplete resection, extrathyroidal spread, presence of distant metastases) are associated with a worse prognosis and have higher recurrence rates. Several classification systems have been proposed to stratify risk and include the following:

- ✓ AMES: Age, Metastases, Extent of primary tumour, Size of presentation.
- ✓ AGES: Age, Grade, Extent of primary tumour, Size of tumour.
- ✓ MACIS: Metastases, Age, Completeness of resection, Invasion of extrathyroidal tissues, Size of tumour.
- ✓ TNM staging (5th edition):

– *Tumour*

– Tx: Primary tumour not identified or assessed

– T0: No evidence of primary tumour

– T1a: Tumour ≤1cm, limited to thyroid

– T1b: Tumour >1cm and ≤2cm

– T2: Tumour >2cm and ≤4cm, limited to thyroid

– T3: Tumour >4cm, limited to the thyroid or with minimal extrathyroidal extension to strap muscles of perithyroidal soft tissue

– T4a: Tumour invading subcutaneous soft tissues, larynx, oesophagus or RLN

– T4b: Tumour invading prevertebral fascia, carotid sheath or mediastinal vessels

– *Node*

– Nx: Regional lymph nodes not assessed

– N0: No regional lymph node metastasis

– N1a: Level VI node metastases

– N1b: Metastases to unilateral, bilateral or contralateral cervical nodes (levels I, II, III, IV or V), retropharyngeal nodes or superior mediastinal nodes (level VII).

– *Metastasis*

– Mx: Metastasis not assessed

– M0: No distal metastases

– M1: Distal metastases present.

Clinical features and investigations

These have largely been discussed in the section on thyroid nodules. The diagnosis of DTC may be made on clinical grounds, by thyroid cytology or following a thyroidectomy. Most cases are diagnosed following a lobectomy or total thyroidectomy for nodules that are apparently benign, indeterminate or suspicious on cytology. In patients with cytology diagnostic of cancer, an ultrasound (with or without CT/MRI in some

centres) may help to detect abnormal regional lymph nodes. This will enable an appropriate level lymphadenectomy to be done at the time of thyroidectomy. In patients with clinically palpable lymphadenopathy or locally advanced disease (abnormal regional lymph nodes or a locally infiltrative tumour), CT or MRI of the neck is essential to ascertain the extent of extrathyroidal spread and lymphadenopathy.

Treatment

Thyroidectomy is the primary treatment for most patients with DTC. Most surgeons recommend total or near total thyroidectomy for all patients with DTC but unilateral lobectomy and isthmectomy may be adequate for some *low-risk* patients with DTC such as:

- ✓ patients with papillary microcarcinoma (<1cm)
- ✓ minimally invasive follicular cancer without vascular invasion in young patients
- ✓ the encapsulated follicular variant of PTC.

In the significant proportion of patients in whom the diagnosis is only made following an isthmectomy or hemithyroidectomy and a completion thyroidectomy is required, this should be performed within 7 days or after 3 months have elapsed from primary surgery to minimize risks of morbidity associated with postoperative scarring.

Lymph node dissection

The need for and extent of lymphadenectomy depends on the type of cancer (PTC and HCC are associated with lymph node spread) and the presence of palpable lymphadenopathy. Lymph nodal spread is usually first to the central compartment (levels VI and VII) and then to levels III, IV and V in the lateral compartment. However, occasionally skip metastases occur. Patients with obvious lymph node metastases need a central compartment node dissection and lateral compartment node dissection on the involved side. Levels I and II are usually spared but if involved should be dissected as well. The role of prophylactic central compartment dissection in patients with PTC and HCC without obvious nodal disease is more controversial. Proponents of routine prophylactic central neck dissection point to the high incidence of occult lymph node metastases in PTC and demonstrate low rates of side effects such as RLN damage and hypoparathyroidism in experienced hands. Opponents of prophylactic neck dissection argue that occult nodal metastases are unlikely to affect long-term outcomes and can be dealt with if and when identified on follow-up. The authors adopt a selective policy and perform a prophylactic central node dissection in patients with high-risk features such as male sex, age >45 years, tumour >4cm in diameter, extracapsular spread and extrathyroidal invasion.

Radioactive iodine

An ablative dose of RAI (I_{131}) is used as standard adjuvant treatment following total or near total thyroidectomy for DTC. The treatment is based on the premise that thyroid cancer cells in DTC are iodine avid and would be ablated by RAI. RAI is not recommended for patients undergoing only a hemithyroidectomy for low-risk disease. The ablation of any residual thyroid tissue also facilitates the use of thyroglobulin as a tumour marker to screen for residual and recurrent disease. Thyroid hormones are usually withdrawn in preparation for RAI treatment to allow TSH levels to rise and increase iodine uptake by thyroid tissue. Patients receiving RAI within 3–4 weeks after thyroidectomy do not need treatment with thyroid hormones. However, for patients in whom RAI treatment may be delayed or for patients needing further RAI treatment for residual or recurrent disease, treatment with T3 is started and this is withdrawn for 2 weeks before RAI treatment. Patients are also advised a low-iodine diet for 2 weeks prior to treatment. Although

preablation diagnostic I_{132} is now not routinely used, it may help in assessment of residual thyroid surgery if completeness of resection is not known. Postablation diagnostic scans are often carried out to assess the effectiveness of ablation.

Thyroxine suppression

Normal thyroid cell differentiation and proliferation is TSH dependent. TSH receptors are also present in DTC cells. Thyroxine suppression treatment is based on the principle that high doses of thyroxine would suppress TSH levels and thereby proliferation of thyroid cancer cells. Patients receive lifelong thyroxine, at doses necessary to suppress TSH to undetectable levels. T3 may be used if follow-up radioactive iodine scans or ablation are required, as it has a shorter half-life than thyroxine, and only requires to be stopped 2 weeks prior to RAI use. Long-term effects of suppressive doses of thyroxine include cardiovascular morbidity and osteoporosis.

External beam radiotherapy

External beam radiotherapy to the neck is used only in patients with extensive extrathyroidal disease and in patients whose tumours are not radioiodine avid.

Follow-up of patients with differentiated thyroid cancer

Recurrent thyroid cancer may occur soon after initial therapy or years later. Patients with thyroid cancer should be followed up lifelong in a multidisciplinary thyroid cancer clinic. AB€history and examination looking for evidence of recurrent neck lumps and features of thyrotoxicosis and measurements of TSH and thyroglobulin (including thyroglobulin antibody) levels should be done at every visit. Calcium levels should also be measured in patients who have persistent hypothyroidism following surgery. A follow-up diagnostic radioactive iodine scan may be needed in patients with high-risk disease or if the serum thyroglobulin levels are high/rising, which should be minimal or undetectable in patients who have undergone definitive treatment (surgical and radioactive iodine). Diagnostic and ablation scans both require hormone withdrawal, although more recently recombinant TSH has been used as an alternative. Ultrasound scanning of the neck may be necessary in patients with palpable lumps and rising thyroglobulin levels, although it also used routinely for follow-up in some centres. 18-Fludeoxyglucose–PET scanning can help detect recurrent disease in scan-negative patients with rising thyroglobulin levels. Recurrent differentiated thyroid cancer Recurrence may be local or regional (in the neck) or systemic. Treatment will depend on the subtype of DTC, the nature and extent of initial treatment and the site of recurrence. Surgery is the mainstay of treatment of local/regional recurrence. Surgery may be followed by RAI scanning with/without ablation and, in some cases, external beam radiotherapy. Distant metastases will usually occur in the lungs or skeletal system. Although distant metastases cause cancer death in 10–15% of patients with DTC, they are compatible with long-term survival. They may present as a result of local symptoms, neurological complications or rising thyroglobulin levels. Radioactive iodine is the mainstay of treatment for recurrent disease. Palliative surgical procedures may be appropriate if there are orthopaedic/ spinal complications. It should be remembered that metastases may be solitary. Remission will occur in 50% of patients with distant metastases that take up radioiodine (10 years survival 25–40%).

Medullary thyroid cancer

Epidemiology

MTC accounts for up to 5% of all thyroid cancer. This tumour arises from the parafollicular C cells of the thyroid, which have a neural crest origin. Around a quarter of these cases are familial. The disease may occur in one of four clinical settings:

1. sporadic
2. familial – MEN 2A
3. familial – MEN 2B
4. familial non-MEN-associated MTC.

The mortality rate for MTC exceeds that of DTC; overall, the 10 year survival rate is around 75%. Factors that indicate a poor prognosis include age >40 years at presentation, male sex, extrathyroidal spread, nodal involvement, metastases, tumour aneuploidy, negative amyloid staining and familial disease. However, long-term survival of patients with metastatic disease is common in MTC . Clinical features and investigation

Sporadic MTC usually presents as a thyroid nodule and/or lymph node enlargement. Associated symptoms include those secondary to airway/oesophageal compression, pain, diarrhoea and rarely Cushing syndrome owing to gut peptide or adrenocorticotrophic hormone release by the tumour. The diagnosis may be confirmed on thyroid cytology or following lobectomy for a thyroid nodule. In all cases, family history for thyroid cancer/phaeochromocytoma should be determined. The absence of a family history does *not* preclude an apparently sporadic MTC being the index case of genetically determined disease. If the diagnosis of MTC is made on cytology, preoperative investigations should include basal calcitonin and carcinoembryonic antigen (CEA), ultrasound of the neck to identify multiple thyroid lesions (a marker of familial disease) and lymph node enlargement. CT/MRI may identify mediastinal node involvement. Genetic screening (on a venous blood sample) for a *Ret* proto-oncogene mutation is required in all patients to exclude familial disease; but this can wait until after surgery.

Phaeochromocytoma must be excluded prior to operation in all cases by a normal 24 hour urine collection for catecholamines/metanephrines. In families affected by or likely to be affected by genetically determined MTC, screening for *Ret* mutations in individuals at risk should be performed. Prophylactic thyroidectomy is indicatedB€ in family members without clinically apparent disease but who are carriers of the germline *Ret* mutation. The different *Ret* mutations are associated with different degrees of susceptibility and disease aggressiveness and recent recommendations on the age at which prophylactic thyroidectomy should be performed in children positive for this mutation are based on the site of the mutation. Treatment The current standard operation in the absence of lymph node metastases is total thyroidectomy and central compartment neck node dissection. Biopsy and frozen section examination of any enlarged jugulocarotid lymph nodes from either side of the neck should be performed. If these nodes are positive they should be removed and a lateral neck dissection should be done. IfB€lymph node metastases are detected preoperatively in the lateral compartment, a selective node dissection of this compartment should be done at the same sitting. If there is evidence of involvement of anterior/superior mediastinal node involvement at presentation, these nodes should be cleared (sternotomy would be required). In all cases the parathyroid gland should be identified and preserved. In MEN 2 patients only enlarged parathyroid glands should be excised. After surgery *replacement* doses of thyroxine are given. There is no indication for TSH suppression or radioactive iodine in the treatment of MTC.

Follow-up of patients with medullary thyroid cancer

Long-term follow-up of these patients is required. At review, basal calcitonin, CEA and TSH levels should be measured in addition to a history and physical examination. Detectable or raised calcitonin and/or CEA levels

indicate residual or recurrent disease and warrant a search for locoregional and metastatic disease. This requires the use of high-resolution CT of the neck/chest/liver, and/or one or more of the isotope scans with pentavalant dimercaptosuccinic acid, 123I-metaiodobenzyl guanidine or radiolabelled octreotide. Further treatment decisions (including surgical resection or observation) are made in a multidisciplinary forum and are influenced by the presence of symptoms, levels of tumour markers, findings on imaging, age and associated morbidity. Patients with MEN 2 require biochemical testing to exclude a phaeochromocytoma and primary hyperparathyroidism at least on an annual basis. Treatment of recurrent/metastatic disease

Surgery is the treatment of choice for local/regional recurrence. MTC is generally considered resistant to chemotherapy. The response to radiotherapy is generally poor but may be useful in patients with inoperable disease and symptomatic bone metastases. Diarrhoea may be severe and intractable in recurrent disease and should be controlled by the use of antidiarrhoeal agents including codeine phosphate and loperamide.

Undifferentiated thyroid carcinoma

Epidemiology

Undifferentiated or anaplastic thyroid carcinoma, in contrast to well-differentiated thyroid carcinoma, is a highly aggressive tumour, with around 70% of patients having metastases at the time of presentation. This is more common in areas with iodine deficiency and endemic goitre. Undifferentiated thyroid carcinoma may be classified as small cell, large cell or spindle cell, which may resemble sarcomas. Small cell carcinomas must be distinguished pathologically from lymphoma, which has a far more favourable prognosis.

Clinical features and Investigations

Diagnosis can usually be confirmed by a core biopsy under local anaesthetic, as FNA for cytology may not be diagnostic. Patients generally present with a large, hard, ill-defined cervical mass fixed to adjacent structures. There is often a history of a longstanding goitre. The sex incidence is similar and most patients present between 60 and 70 years of age. Occasionally, undifferentiated thyroid carcinoma may develop as a transformation of a previously treated well-differentiated thyroid carcinoma, which may have been in remission for a considerable time.

Treatment

Treatment of these patients is with a multimodal approach using surgery, radiotherapy and chemotherapy. Surgery is feasible and often necessary to relieve symptoms. Even in the absence of extrathyroidal spread, it is only considered a palliative procedure. Often only debulking is possible and a tracheostomy is required. Tracheal/oesophageal stenting should sometimes be considered if surgery is not successful or possible. External beam radiotherapy is usually given to these patients in an attempt to slow tumour progression. Response to chemotherapy is generally poor but regimes containing doxorubicin can give partial remission in around 20% of patients. Undifferentiated thyroid carcinoma is not responsive to 131I therapy. In some centres, preoperative chemoradiation followed by total thyroidectomy in patients has shown some promise. However, no standard treatment protocol exists currently and efforts are under way to investigate newer chemotherapeutic agents including tyrosine kinase inhibitors in an attempt to improve response. The prognosis remains very poor, with the majority of patients dead within a year of diagnosis.

Thyroid lymphoma

Epidemiology

Thyroid lymphomas are rare, occur more often in women (female to male ratio 3:1) and the incidence increases with age (most patients are aged >60 years). Thyroid lymphoma is often associated with a history of autoimmune thyroid disease (80% of patients). Clinical features and investigations

The diagnosis is often suspected clinically by the history of longstanding goitre/hypothyroidism and a rapidly enlarging neck mass with a minority complaining of compressive symptoms. FNA is often inconclusive but usually shows plenty of lymphocytes. A core biopsy is needed to confirm the diagnosis and allow immunohistochemical subtyping of the lymphoma. Most thyroid lymphomas are mucosa-associated lymphoid tissue lymphomas and diffuse large β-cell lymphomas. CT scanning often shows homogeneous thyroid enlargement without invasion of adjacent structures. CT of the chest, abdomen and pelvis is also done as part of staging of the lymphoma. Other investigations for lymphoma include full blood count, β2-microglobulin and bone marrow biopsy.

Treatment

Some patients will present with acute airway obstruction. Intravenous steroids can achieve rapid resolution of symptoms but, wherever possible, it should be given after a tissue diagnosis has been obtained. External beam radiotherapy may also be of value in relieving acute symptoms. There is no evidence that surgery offers any benefit to patients with lymphoma. Following diagnosis and treatment of upper airway symptoms the patient should be referred to an oncologist. Staging with CT scanning, liver function tests and full blood count is performed. Treatment for this disease includes chemotherapy (the 'CHOP' (consists of cyclophosphamide, doxorubicin, vincristine and prednisolone) regimen) and/or radiotherapy.

Thyroidectomy

It was not until the early twentieth century that thyroidectomy became a safe and acceptable operation with the advent of general anaesthesia, antisepsis and haemostatic techniques. Theodore Kocher of Berne, Switzerland, was the chief protagonist of these methods and, for his lifetime devotion to the development of safe thyroid surgery, was awarded the Nobel Prize in 1909, by which time the previous high mortality had fallen to <1%. Further advances by William Halsted, Charles Mayo, George Crile and Frank Lahey led to techniques that remain the basis of safe thyroid surgery and continue to be practised today by trained endocrine surgeons.

Preoperative preparation

As with all surgical procedures, a full and written informed consent should be obtained after explaining the need for the operation, the implications of having the procedure, the risks of complications (see below), alternative treatment options and any other relevant details the patient might wish to discuss. AB€higher risk of complications should be emphasized when reexploration or cancer surgery is performed. Preoperative preparation should include laryngoscopy to exclude pre-existing unilateral nerve palsy, especially if the patient has undergone previous thyroid surgery. A serum calcium level is also routinely obtained as baseline to compare postoperative calcium levels with.

Surgical principles and approaches

Removal of one or both thyroid lobes, isthmus and additional thyroid tissue, such as the pyramidal lobe, as well as identification and preservation of the laryngeal nerves and parathyroid glands are the key objectives of thyroid surgery. A detailed knowledge of surgical anatomy, meticulous dissection and care to avoid bleeding are crucial to the achievement of these objectives. A number of different instruments and aids are

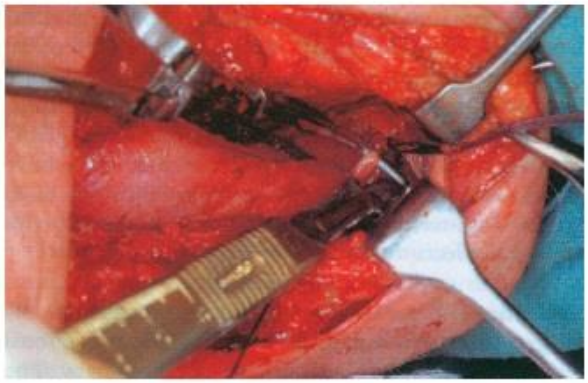
now in use for dissection including the traditional ‘tie and cut’, bipolar diathermy, clips, ultrasonic dissection and thermal coagulation. However, these cannot replace careful dissection by experienced hands. The standard approach to a thyroidectomy is through a collar incision in the neck. Endoscopic approaches have been described for small thyroid nodules (<3cm in diameter), the primary aim of which is to avoid a neck scar. These procedures, however, involve the introduction of a camera and endoscopic instruments through incisions in the chest and axillae; have no proven superiority in terms of clinical outcomes; have a prolonged learning curve; and are not practised by the authors. Further description will only relate to the open approach. ItB€ is acknowledged that there will be significant variations in operating technique as practised by surgeons across the world; the following technique is the one that is used by the authors.

Operative steps

General anaesthesia with endotracheal intubation is deployed and the patient is placed supine on an operating table 15^0head-up and the neck in near full extension with a sandbag (or inflatable bag) in the interscapular position. Access A collar incision is used two finger-breadths above the sternal notch extending to both sternomastoid muscles. The incision is extended through subcutaneous fat and platysma down to the deep fascia and, by a process of blunt and sharp dissection, this plane (anterior to the anterior jugular vessels) is extended superiorly to the level of the thyroid notch and inferiorly to the sternal notch, with the skin flaps then held apart using a selfretaining retractor. The strap muscles on either side are separated by dividing the deep fascia in the midline and retracted laterally. This should be as long as possible to enable full access to the operative field. Transverse division of the strap muscles is not routinely required but may be occasionally used for safe access to a large or vascular goitre. The deeper sternothyroid muscle is usual slightly adherent to the capsule and is separated from it with careful blunt and sharp dissection. The middle thyroid veins, when present, are divided to increase access to the thyroid lobe, which is then delivered using traction from the index finger on a small swab over the lobe with the strap muscles retracted laterally. The lateral aspect of the thyroid lobe is now exposed from the superior pedicle superiorly to the lower pole inferiorly. The plane between the thyroid, larynx and oesophagus medially and the carotid artery laterally is opened by dividing the loose areolar tissue in this region; this increases the mobility of the thyroid lobe.

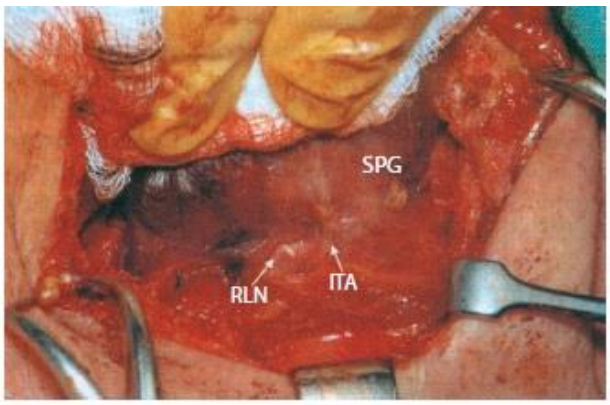
Superior pedicle

The upper pole is then retracted inferolaterally to open the space between the superior thyroid vessels and the cricothyroid muscle. The branches of the superior thyroid pedicle are divided at their entry into the thyroid on the surface of the capsule well away from the EBSLN, which usually runs along the surface of (or within) the cricothyroid but may also pass between the branches of the vessels where it is in danger of injury if mass ligation of the superior thyroid pedicle is carried out. The superior pole of the lobe may now be delivered partially into the midline. Further ligation of the small vessels entering the thyroid capsule may be required at this stage and care should be taken to avoid injury to the superior parathyroid gland.



Division of the left superior thyroid artery.

The recurrent laryngeal nerve



Exposure of the neurovascular intersection of the inferior thyroid artery (ITA) and recurrent laryngeal nerve (RLN). The superior parathyroid gland (SPG) can be found within a 2 cm radius cranial to the intersection, usually posterior to the RLN and thyroid gland. Note the looping of the RLN within Berry's ligament close to its insertion beneath the cricothyroid.

Medial retraction on the lobe will now bring into view the deeper aspect of the middle third of the thyroid lobe and theB€adjacent junction between the inferior thyroid artery and the RLN. The RLN can be identified in three locations – upper (at the point of entry into the larynx at around the cricothyroid junction), middle (at the junction with the inferior thyroid artery) and lower (between the medial wall of the carotid artery and the lateral wall of the thymus). The nerve is seen following dissection of the overlying fascial layers and recognized as a white cord with an overlying vasa nervosum. The nerve lies in the tracheo-oesophageal groove (especially on the left) and runs upwards, passing anterior, posterior or through the branches of the inferior thyroid artery. However, its course is variable, especially on the right side. The right RLN lies in a more oblique direction. In around 1% of cases the right nerve may be non-recurrent and pass medially close to the inferior thyroid artery before turning to ascend to enter the larynx. These nerves also occasionally divide into branches before entering the larynx where the inferior cornu of the thyroid cartilage is a fairly constant landmark for its point of entry. The nerve is perhaps most in danger at its point of entry into the larynx as it passes through the suspensory ligament of Berry, where it often adopts a curving loop, and the nerve must be carefully identified in this region before dividing the suspensory fascia by staying close to the thyroid capsule at all times.

The parathyroid glands

The superior parathyroid gland is most commonly found superior to the inferior thyroid artery and posterior to the RLN, and the inferior gland often lies inferior to the inferior thyroid artery and anterior to the RLN. Attempts should be made to identify both the superior and inferior glands during lobectomy, but it may sometimes be appropriate to avoid an extensive dissection simply to identify the parathyroid glands as the dissection increases the risk of devascularizing the glands. In addition to the glands, care should be taken to preserve individual branches of the thyroid arteries supplying them. It is for this reason that the inferior thyroid artery is not ligated at its trunk, so as to preserve the small branches supplying the parathyroid glands. If the parathyroid glands are rendered ischaemic at thyroidectomy the individual gland may be excised and is minced into 1mm cubes and autotransplanted into a pocket in the sternomastoid muscle.

Resection of the lobe

Dissection is continued by dividing the individual branches/ tributaries of the main thyroid arteries and veins close to the thyroid capsule. Further dissection aims to divide the dense fascia binding the thyroid lobe to the trachea and larynx with particular attention to clipping and ligation near Berry's ligament, where troublesome bleeding may obscure the entry point of the RLN to the larynx. The mobilization is now complete and dissection is continued to include the isthmus and pyramidal lobe where present. The cut surface of the contralateral thyroid lobe is usually sutured with fine absorbable sutures to the tracheal fascia to obtain haemostasis. Wound closure

The sandbag is now removed (or the inflatable bag can be deflated) from under the patient's spine and the neck space is examined for bleeding (occasionally a Valsalva manoeuvre may be performed by the anaesthetist). Haemostasis is secured and the wound is closed in layers (strap muscles, platysma and subcuticular layers) with 3/0 Vicryl or Monocryl. Drains are not required routinely, but may be useful in cases of significant oozing from the thyroid bed to prevent seromas after resection of very large goitres and if a neck dissection has also been done.

Total and subtotal thyroidectomy

In patients undergoing total thyroidectomy for cancer, bilateral multinodular disease or Graves' disease, the opposite lobe will be mobilized in a similar manner to that described above. Central compartment (with/without lateral compartment) node dissection may also be done at the same time (see below for details). Subtotal thyroidectomy, in general, is avoided, although it may be useful in Graves' disease if compliance with thyroxine replacement postoperatively is unlikely. In this procedure, a small remnant (usually 4–5g of tissue) is left on each side of the trachea and sutured to the trachea with 3/0 Vicryl absorbable sutures to secure haemostasis. Some surgeons instead perform a unilateral total lobectomy leaving a single larger remnant on the contralateral side, which is an acceptable alternative strategy. Retrosternal goitre Ligation and division of the superior vessels is essential before any attempt is made to deliver the retrosternal component. This is achieved by introducing a finger down into the mediastinum behind the sternum and using gentle traction, which may be aided by the use of a bent dessert spoon when dealing with a very large multinodular gland. Care should be taken to avoid injury to the RLN, which may occasionally lie on the surface of the retrosternal component. A mediastinal split is seldom necessary.

Variations in technique

There are many variations to the above-described steps, which are useful in different situations. It may be appropriate to mobilize the lower pole first in some instances, especially if there is significant upper pole enlargement and extension towards the base of the skull. Early division of the isthmus is also a useful technique to aid in the mobilization of the lobe, especially in large goitres.

Complications of thyroid surgery

Thyroidectomy is a commonly performed and safe surgical procedure with a low morbidity and negligible mortality when performed by appropriately trained surgeons. General complications are those of anyone undergoing a general anaesthetic such as cardiac events, chest infection and venous thromboembolism, but these are uncommon following thyroid surgery with a current mortality rate in several large series approaching zero. The morbidity of thyroidectomy from its specific complications, however, continues to be a matter of concern. Clearly, meticulous attention to operative technique is required and this is now an area for the trained endocrine surgeon rather than a general surgeon. Litigation for thyroidectomy complications amount to approximately 5% of general surgical claims, most of which involve RLN injury. To avoid damage to the RLN a detailed knowledge of its variable anatomy and identification during surgery is essential. Bilateral palsy is exceedingly rare but may lead to temporary or permanent tracheostomy. This is most likely to be a problem in redo surgery when one RLN has already been permanently damaged. The frequency of RLN injury following thyroid surgery should be <1%, although audits of this outcome should reflect case mix and operative experience. The EBSLN is also at risk during thyroidectomy and permanent voice damage following its injury may occur and may be difficult to

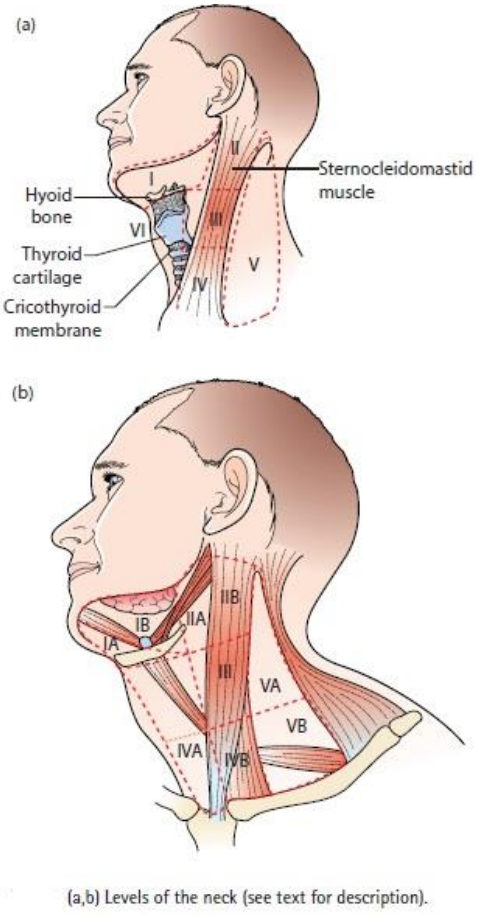
Specific complications of thyroidectomy

- Respiratory distress: immediate postoperative period
  - RLN palsy
  - Acute laryngeal oedema
  - Wound haematoma
- Voice change (hoarseness, weakness, loss of high pitch): transient or long term
  - Injury to the EBSLN
  - RLN palsy
- Hypoparathyroidism: transient or long term
  - Bleeding
  - Infection
  - Hypothyroidism
  - Hypertrophic scarring or keloid

detect on indirect laryngoscopy. Such injury may be minimized if the nerve is identified and preserved during superior thyroid artery ligation. Parathyroid damage producing hypocalcaemia is the second largest category of thyroid-related medicolegal claims and, although usually temporary, a long-term hypoparathyroid state has been shown to occur in up to 5% of cases. Most cases occur because of interruption of the arterial supply or obstruction of venous drainage, although inadvertent excision may also occur. Hypothyroidism after total thyroidectomy is avoided by thyroxine replacement therapy, but can also occur with time after a subtotal resection. Recurrent hyperthyroidism after a subtotal resection presents more of a problem, as reoperation is associated with a significant increase in complications. Radioiodine ablation is probably a safer alternative to redo surgery. Postoperative reactionary haemorrhage is potentially catastrophic but can be avoided with meticulous haemostasis. However, the most serious and life-threatening complication is postoperative airway obstruction due to acute laryngeal oedema, which may or may not be associated with haematoma. The oedema is thought to be related to impaired lymphatic drainage of the larynx causing this internal oedema. A well-positioned collar incision along a skin crease (if possible) gives adequate exposure and an excellent cosmetic result. However, wound complications occasionally occur and include a suture granuloma (which can be minimized by the use of absorbable suture material or clips), infection (cellulitis, abscess formation), hypertrophic scarring and keloid formation (especially in patients with an underlying predisposition).

Neck dissection

Radical neck dissection was first described by Jawdynski, a Polish surgeon in 1888. It was, however, popularized in the early twentieth century by Crile, a US surgeon, with whose name the operation remains synonymous today. The radical nature of the operation and the associated morbidity led to modifications of the technique in which vital structures such as the sternocleidomastoid, internal jugular vein and the spinal accessory nerve were preserved. These modifications led to the procedure being called 'modified radical' or 'functional' neck dissections and were developed by surgeons including Suarez, Bocca, Gavilan and Ballantyne. Further modifications involving excision of one or more lymph node groups in select compartments (levels) of the neck were termed 'selective' neck dissection. Neck dissection terminology was standardized in 1991 by the American Academy's Committee for Head and Neck Surgery and Oncology. Lymph node groups were classified into levels, and six levels of the neck were initially described (level VII was added at a later stage).



(a,b) Levels of the neck (see text for description).

- ✓ *Level I* is bounded by the midline medially, the body of the mandible superiorly, the posterior belly of the digastric laterally and the hyoid bone inferiorly. This level is further subdivided into level IA (the submental triangle) and level IB (the submandibular triangle) separated by the anterior belly of the digastric muscle.
- ✓ *Level II* is a triangular area bounded by the posterior belly of the digastric/stylohyoid muscle anteriorly, the posterior border of the sternomastoid posteriorly and an imaginary line along the inferior border of the hyoid bone inferiorly. The spinal accessory nerve divides this into a level IIA (anteroinferior to the nerve) and level IIB (posterosuperior to the nerve).
- ✓ *Level III* is the area below level II to the level of the cricothyroid notch (clinical landmark) or omohyoid (surgical landmark). The posterior border is again formed by the posterior edge of the sternocleidomastoid and the medial/anterior boundary is the lateral border of the sternohyoid muscle.

- ✓ *Level IV* is the area below level III, with the other boundaries being the posterior border of the sternocleidomastoid posteriorly, the clavicle inferiorly and the lateral border of the sternohyoid muscle anteromedially.
- ✓ *Level V* is a triangular-shaped area bordered anteriorly by the posterior border of the sternocleidomastoid, the clavicle inferiorly and the anterior border of trapezius posteriorly. This is further subdivided into an upper VA around the spinal accessory nerve and a lower VB (or supraclavicular nodes) around the transverse cervical vessels; these being divided by the inferior belly of the omohyoid muscle.
- ✓ *Level VI* is also called the anterior compartment; this extends from the hyoid bone superiorly to the suprasternal notch inferiorly and the medial border of the carotid sheath laterally.
- ✓ *Level VII* is strictly mediastinal and refers to the area behind the manubrium and extends from the suprasternal notch superiorly to the brachiocephalic vein inferiorly.

General principles of neck dissection in thyroid cancer

Thyroid cancers are in general slow growing and lymph node metastases in thyroid cancer have not been shown to influence survival. Although berry picking of involved lymph nodes is to be condemned, the other extreme of radical and supraradical neck dissection is largely unnecessary and harmful in patients with thyroid cancer. Selective node dissection is the most commonly employed procedure. The need for and the extent of lymph node dissection in thyroid cancer has already been discussed. Thyroid surgeons often refer to levels VI and VII as the central compartment and levels II–V as the lateral compartment. The commonest levels involved and operated upon in thyroid cancer are levels VI and VII (central compartment). Prophylactic central compartment neck dissection is routine in MTC and often selective in PTC. Lateral compartment lymph node dissection in thyroid cancer is usually done as a therapeutic procedure (i.e. when lymph nodes are palpable or shown to be pathological) and involves a selective clearance of levels IIA, III, IV and VB. Involvement of levels I, IIB and VA is very rare. As mentioned previously in relation to thyroidectomy, a clear explanation of the need for and planned extent of lymphadenectomy should be given preoperatively. Complications specific to lymphadenectomy such as seroma formation, wound infection, bleeding from major vessels and damage to surrounding vital structures should be discussed.

The vital structures in the various neck compartments (apart from the carotid sheath vessels, trachea and oesophagus) and consequences of their injury

	Vital structures	Consequence
Central compartment dissection	Parathyroid glands	Hypoparathyroidism
	Recurrent laryngeal nerves	Voice change, aspiration, tracheostomy (very rare)
	External branch of the superior laryngeal nerve	Inability to raise pitch of voice
Lateral compartment dissection	Salivary glands (level I) – very rare	Salivary fistula
	Marginal mandibular branch of the facial nerve (level I) – very rare	Drooping of the angle of the mouth on the ipsilateral side
	Spinal accessory nerve (levels II and V)	Drooping of the shoulder, and neck and shoulder dysfunction
	Hypoglossal nerve (level II)	Atrophy of the tongue and deviation towards the side of the palsy
	Vagus nerve	Vocal cord palsy (see as for the recurrent laryngeal nerve)
	Sympathetic chain	Horner syndrome (ptosis, miosis, anhidrosis, enophthalmos and loss of ciliospinal reflex)
	Cervical plexus injury	Numbness and paraesthesiae (often settles spontaneously)
	Thoracic duct (level V)	Chyle leak/fistula
	Phrenic nerve (level III/IV)	Ipsilateral diaphragmatic palsy
	Brachial plexus (level V)	Sensory and motor deficit affecting the shoulder and upper limbs

Literature:

1. Essential Surgical Practice. Higher Surgical Training in General Surgery. Fifth Edition. Edited by Alfred Cuschieri and George B Hanna
2. Abraham P, Acharya S. Current and emerging treatment options for Graves' hyperthyroidism. *Ther Clin Risk Manag* 2010;**6**:29–40.
3. Cooper DS, Doherty GM, Haugen BR, *et al*. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 2009;**19**: 1167–1214.
4. Fast S, Nielsen VE, Bonnema SJ, Hegedьs L. Time to reconsider nonsurgical therapy of benign non-toxic multinodular goitre: focus on recombinant human TSH augmented radioiodine therapy. *Eur J Endocrinol* 2009;**160**:517–528.
5. Kuma K, Matsuzuka F, Kobayashi A, *et al*. Outcome of long standing solitary thyroid nodules. *World J Surg* 1992;**16**:583–587.
6. Kuma K, Matsuzuka F, Yokozawa T. Fate of untreated benign thyroid nodules: results of long term follow up. *World J Surg* 1994;**18**:495–498.
7. Nagaiah G, Hossain A, Mooney CJ, *et al*. Anaplastic thyroid cancer: a review of epidemiology, pathogenesis, and treatment. *J Oncol* 2011;**2011**:542358.
8. Werga P, Wallin G, Skoog L, *et al*. Expanding role of fine-needle aspiration cytology in thyroid diagnosis and management. *World J Surg* 2000;**24**:907–912.
9. Halsted WS: The operative story of goitre. Johns Hopkins Hosp Rep 19:71, 1920.
10. Thompson NW: The history of hyperparathyroidism. Acta Chir Scand 156:5–21, 1990.
11. Kocher T: Uber Kropfextirpation und ihre Folgen. Arch Klin Chirurgie 29:254, 1883.
12. Kaplan EL, Kadowaki MH, Schark C: Routine exposure of the recurrent laryngeal nerve is important during thyroidectomy. In Simmons RL, Udekwu AO (eds): Debates in Clinical Surgery, vol 1. Chicago, Year Book, 1990, pp 191–206.
13. Henry JF, Audriffe J, Denizot A, et al: The non-recurrent inferior laryngeal nerve: Review of 33 cases including 2 on the left side. Surgery 104:977–984, 1988.
14. Thompson NW, Demers M: Exposure is not necessary to avoid the recurrent laryngeal nerve during thyroid operations. In Simmons RL, Udekwu AO (eds): Debates in Clinical Surgery, vol 1. Chicago, Year Book, 1990, pp 207–219.
15. Moosman DA, DeWeese JS: The external laryngeal nerve as related to thyroidectomy. Surg Gynecol Obstet 127:1011, 1968.
16. Cernea CR, Ferraz AR, Nishio S, et al: Surgical anatomy of the external branch of the superior layrngeal nerve. Head Neck 14:380–383, 1992.
17. Lennquist S, Cahlin C, Smeds S: The superior laryngeal nerve in thyroid surgery. Surgery 102:999, 1987.
18. Friedman M, LoSavio P, Ibrahim H: Superior laryngeal nerve identification and preservation during surgery. Arch Otolaryngol Head Neck Surg 128(3):296-303, 2002.
19. Kaplan EL, Sugimoto J, Yang H, Fredland A: Postoperative hypoparathyroidism: Diagnosis and management. In Kaplan EL (ed): Surgery of the Thyroid and Parathyroid Glands. New York, Churchill Livingstone, 1983, pp 262–274.
20. Gilmour JR: The embryology of the parathyroid glands, the thymus and certain associated rudiments. J Pathol 45:507, 1937.
21. Taylor S: Surgery of the thyroid gland. In DeGroot LJ, Stanbury JB: The Thyroid and its Diseases, 4th ed. New York, John Wiley & Sons, 1975, pp 776–779.

22. Grodski S, Cornford L, Sywak M, Sidhu S, Delbridge L: Routine level VI lymph node dissection for papillary thyroid cancer: Surgical technique. ANZ J Surg 77(4):203-208, 2007.
23. Ezzat S, Sarti DA, Cain DR, Braunstein GD: Thyroid incidentalomas. Prevalence by palpation and ultrasonography. Arch Intern Med 154:1838–1840, 1994.
24. DeGroot LJ: Clinical features and management of radiation-associated thyroid carcinoma. In Kaplan EL (ed): Surgery of the Thyroid and Parathyroid Glands. Edinburgh, Churchill Livingstone, 1983, p 940.
25. Kaplan EL: An operative approach to the irradiated thyroid gland with possible carcinoma: Criteria technique and results. In DeGroot LJ, Frohman LA, Kaplan EL, Refetoff S (eds): Radiation Associated Carcinoma of the Thyroid. New York, Grune & Stratton, 1977, p 371.
26. Kaplan EL, Mhoon D, Kaplan S, Angelos P: Radiation-induced thyroid cancer: The Chicago experience. Surgery 146(6):979-985, 2009.
27. Sinnott B, Ron E, Schneider AB: Exposing the thyroid to radiation: A review of its current extent, risks and implications. Endocr Rev 210(5):756-773, 2010.
28. Naunheim KS, Kaplan EL, Straus FH II, et al: High dose external radiation to the neck and subsequent thyroid carcinoma. In Kaplan EL (ed): Surgery of the Thyroid and Parathyroid Glands. New York, Churchill Livingstone, 1983, pp 51–62.
29. Shafford EA, Kingston JE, Healy JC, et al: Thyroid nodular disease after radiotherapy to the neck for childhood Hodgkin's disease. Br J Cancer 80:808–814, 1999
30. Ron E: Thyroid cancer incidence among people living in areas contaminated by radiation from the Chernobyl accident. Health Physics 93(5):502-511, 2007

All the illustrated materials are taken from «Essential Surgical Practice. Higher Surgical Training in General Surgery. Fifth Edition. Edited by Alfred Cuschieri and George B Hanna»

Tests

1. What is not typical for multiple endocrine neoplasia type 1 (MINI syndrome)?
A. Formed by tumors or hyperplasia of the parathyroid glands, insular apparatus of the pancreas, pituitary gland
B. Formed by tumors or hyperplasia of the adrenal glands, pancreas, pituitary gland
C. the most constant manifestation of MENI is hyperparathyroidism (90-100%)
D. pituitary Adenoma is detected in almost all patients
E. Is a genetic autosomal dominant abnormality
2. To make a diagnosis of malignant goiter, the following studies are used:
A. thyroid scintigraphy
B. detection of antibodies in plasma by titration
C. measurement of basal exchange
D. Establishing the iodine binding index
E. Puncture and aspiration biopsy
3. Which of the following statements concerning treatment of pheochromocytoma is incorrect?
A. the only treatment method is extirpation of the tumor
B. the need for conservative treatment during preoperative, intraoperative, postoperative period for blood pressure correction
C. enucleation of the tumor, partial resection of the adrenals or total adrenalectomy
D. intraoperative interventions on the adrenal gland can provoke a hypertensive crisis
E. Adrenalectomy is performed by thoracic access only
4. Indications for surgical treatment of goiter are as follows:
A. Ineffective conservative treatment
B. Initial parenchymal goiter
C. Hyperthyroid goiter
D. Nodular goiter
E. suspected malignancy of the goiter
5. What statements regarding benign thyroid tumors are correct?
A. Are represented as adenomas, asymptomatic, slow developing
B. Arise acutely, develop rapidly
C. early and often metastasize
D. 70% are detected as a "cold" node on scintigraphy
E. 70% are detected as a "hot" node on scintigraphy
6. In the treatment of goiter, the following operations can be applied (depending on the situation):
A. Subtotal thyroidectomy
B. Total lobectomy
C. Total thyroidectomy
D. Subtotal lobectomy
E. Radical neck dissection
7. Treatment of thyrotoxicosis has the following goals:
A. correction of arrhythmias and tachycardia
B. Reducing hyperthyroidism
C. Prevention of thyrotoxic crises
D. Inhibition of cortical-diencephalophysiological centers
E. Treatment of hyperparathyroidism

8. Manifestations of a thyrotoxic crisis include:
A. Hyperthermia, tachycardia, arterial hypertension
B. Thermophobia, increased sweating, paresthesia
C. Agitation, confusion, vomiting
D. Exophthalmia, insomnia, muscle atrophy
E. All of the above
9. Men II b syndrome does not include:
A. Medullary thyroid carcinoma
B. Pheochromocytoma
C. intestinal Ganglioneuroma
D. Insulinoma
E. Mucosal neuroma
10. Complications of thyroidectomy include all except:
A. Recurrent nerve paresis
B. Mixedems
C. Tetanic crisis
D. Thyrotoxic crisis
E. Exophthalmic syndrome

1	2	3	4	5	6	7	8	9	10
B	AE	E	ACDE	AD	ABCD	ABCD	AC	D	E

Situational tasks:

1. The patient K., 37 years old, asked for medical help with complaints of unpleasant sensations in the neck area. Then on the anterior surface of the neck on the left to palpate the tumor-like formation. Doesn't make any other complaints. From the family history, it was established that there were oncological diseases on the maternal side. On examination, a 3x4 cm dense node is palpated in the left lobe of the thyroid gland. The lymph nodes in the neck are not detected. Ultrasound study obtained data for nodular goiter. A fine needle aspiration biopsy was performed – a proliferating goiter.
   1) Determine the patient's treatment tactics.
   2) If you decide to operate on a patient, list what indications for surgery for nodular goiter?
   3) Schedule a preoperative examination.
   4) Specify the scope of the operation and what research should be performed during the operation?
   5) If the final histological examination diagnosed cancer (papillary, follicular) of the thyroid gland, what should be the treatment strategy?

1. The Patient is rcommended an operation.

2. The operation is indicated if the node size is more than 3 cm – if it increases in size by more than 5 mm in 6 months (provided that the ultrasound study is performed on a single device), - if there are risk factors for thyroid cancer (men with single nodes, the presence of cancer in close relatives, hoarseness of voice, radiation to the head and neck in the anamnesis)

3. General Clinical examination: clinical analysis of blood and urine.
- Duration of bleeding, clotting time, prothrombin index.
- Biochemical tests (blood glucose, bilirubin, urea, creatinine, total protein, alanine aminotransferase, aspartate aminotransferase). X-ray of the chest and chest organs. Examination by an otorhinolaryngologist, laryngoscopy, e, consultation with a therapist

4. Subtotal resection of the left thyroid lobe with urgent histological examination of the nodular formation.

5. The patient should be sent to the Oncology clinic. The operation is shown-removal of the remaining tissue of the left lobe with the isthmus, removal of pretracheal and peritracheal tissue with lymph nodes, revision of the right lobe and neck tissue on the right.

2. Patient K., 64 years old, complained of a causeless cough and a feeling of pressure in the right neck area. When examined in the area of the right lobe of the thyroid gland, a node of tight-elastic consistency is determined up to 3 cm in diameter. Neck lymph nodes are not enlarged
   1. Your preliminary diagnosis.
   2. Assign a plan for the patient's examination.
   3. What information can chest radiography provide for thyroid disease?
   4. For what purpose is currently used radioisotope research in diseases of the thyroid gland?
   5. Name the accepted stages of morphological examination of the gland.

1) Nodular goiter
2) General Clinical examination: clinical analysis of blood and urine.

- Duration of bleeding, clotting time, prothrombin index.
- Biochemical tests (blood glucose, bilirubin, urea, creatinine, total protein, alanine aminotransferase, aspartate aminotransferase). X-ray of the chest and chest organs. Examination by an otorhinolaryngologist, laryngoscopy, e, consultation with a therapist

3) Chest radiography allows you to suspect a retrosternal goiter or metastases of thyroid cancer by the presence of additional shadows in the mediastinum.
4) Radioisotope study at the site of isotope accumulation

3. A 36-year-old patient went to the doctor due to the fact that there were unpleasant sensations in the neck area on the right and here she felt a tumor-like formation. Doesn't make any other complaints. When viewed from the right in the projection of the right lobe of the thyroid gland, a round-shaped tight-elastic tumor formation is palpated in a diameter of up to 5 mm.the neck lymph Nodes are not enlarged. Suspected cyst of the thyroid gland.

   1. What special tests should be performed to make a final diagnosis and the expected results?
   2. What diseases should be diagnosed differentially?
   3. What are the mechanisms of thyroid cysts formation?
   4. Tactics of treatment of cysts of the breast.

1) The thyroid gland has a weakly echogenic formation of a rounded shape with clear, even contours and a smooth inner surface. In the cyst cavity, sometimes a large and fine suspension can be traced.
2) Nodular goiter, thyroid cancer, thyroid adenoma.
3) Cysts are formed more often due to cystic or hemorrhagic degeneration of the adenoma or adenomatous nodes.
4) Puncture and sclerosis of the cyst. If the contents continue to accumulate, cystectomy is performed.