Approach to goitre in family medicine practice

Opening Vignette

Angela, a 21-year-old university student, presented to your practice with symptoms such as fatigue, anxiety and heat intolerance. Upon further questioning, she revealed that she had experienced 6 months of unintentional weight loss, insomnia, oligomenorrhoea, loose stools and occasional palpitations. She reported that her aunt had a 'thyroid issue' but was unable to clarify the exact aetiology. On examination, we understood that Angela was tachycardic with a heart rate of 110 beats per minute, afebrile and normotensive. She had a thyroid stare and mild chemosis, but no proptosis or ophthalmoplegia. She had a smooth non-tender goitre and thyroid bruit with no palpable nodules. You ordered thyroid function testing and an erythrocyte sedimentation rate test.

WHAT IS A GOITRE?

A goitre is an abnormal enlargement of the thyroid gland. It can present either as a solitary nodule or diffuse enlargement and may be associated with symptoms of hypothyroidism or hyperthyroidism.

HOW RELEVANT IS THIS TO MY PRACTICE?

Goitre is a common condition in primary care practice. It can present as a complaint of a neck lump with or without associated mass effect, such as dysphagia, stridor or dysphonia. Patients may have clinical manifestations of hyperthyroidism or hypothyroidism. Based on a study of 15,008 adults residing in ten iodine-replete cities across China, the prevalence of goitres detected on ultrasonography was 15.7%.[1] With the advent of computed tomography and magnetic resonance imaging, family physicians may also encounter patients with incidental thyroid nodules, found in up to 16% of these scans.[2] Thyroid malignancies can occur in 7%–15% of nodules[3] and depend on individual risk factors such as age, gender, radiation exposure and family history.

During the initial assessment of a patient with a goitre, general practitioners must consider the myriad of causes and appropriate management at the primary care level. A frequent dilemma is the urgency of referral and whether to refer the patient to an endocrinologist or a surgeon.

We provide a summary of the common causes of goitre encountered in family practice and provide a management algorithm to aid in the right siting and care of this group of patients.

WHAT CAN I DO IN MY PRACTICE?

Clinical approach

In a patient who presents with an anterior neck mass, it is prudent to consider other differential diagnoses apart from a goitre [Table 1]. These can be categorised into three main causes.

Congenital abnormalities are usually non-tender and slow growing. They remain asymptomatic unless an infection occurs, which can result in a tender mass with fever or discharging sinuses.

Inflammatory causes from cervical lymphadenopathy can be attributed to either infective or non-infective causes.[4] Submental cervical lymphadenitis tends to be associated with infections of the lip, floor of the mouth and skin of the cheeks. The referral for imaging and evaluation should be considered in patients with persistent lymphadenopathy despite 6 weeks of monitoring or suspected bacterial lymphadenopathy with worsening symptoms despite initial antibiotic treatment.

Neoplastic lesions can be either benign or malignant. Benign masses, which are generally slow growing, include lipomas, epidermal cysts or neuromas. Malignant masses may be due to primary cancers (such as lymphomas or sarcomas) or lymph node metastases from cancers of the head and neck, upper respiratory tract, oesophagus or a distant site.

History

The following four main questions in history-taking are helpful in distinguishing the causes of the goitre.

What are the characteristics of the goitre and its possible triggers?

- Duration: Has it been present since childhood?
- Involvement: Is it diffusely enlarged or a solitary nodule?
- The rate of growth: Is it slow growing or rapidly enlarging? (rapid enlargement may be suggestive of malignancies such as anaplastic thyroid carcinoma or lymphoma)
- Associated symptoms: (a) Focal pain or fever would be suggestive of thyroiditis. Patients may present with sudden onset of pain with rapid enlargement if spontaneous haemorrhage into a thyroid nodule occurs. Anaplastic thyroid carcinoma may also present as a rapidly enlarging and painful neck mass and (b) ophthalmic symptoms in Graves' disease include diplopia, blurring of vision, orbital pain or gritty sensation with increased tearing
- Recent upper respiratory tract infections in up to 2–8 weeks may precipitate subacute thyroiditis
- Iodine-deficient diets lead to the formation of colloid nodular goitres

Table 1. Differential diagnoses of an anterior neck mass.

Category	Differential diagnosis	Features
Thyroid	Goitre	Anterior midline mass Moves upwards with swallowing but not on tongue protrusion May be associated with signs of hyperthyroidism or hypothyroidism May be associated with extrathyroidal signs (eye, skin or nail changes in Graves' disease)
Congenital	Thyroglossal duct cyst	Anterior midline mass Moves upwards with swallowing and tongue protrusion
	Congenital dermoid cyst	Does not move with swallowing or tongue protrusion Attached to skin
	Plunging ranula (retention cysts)	Slow growing mass that extends into the neck Non-tender
Inflammatory	Cervical lymphadenopathy Infective Reactive viral Bacterial Parasitic Non-infective Sarcoidosis	Infective causes Usually resolves in 2-6 weeks Associated with localising sources of infection Non-infective causes May have cough, dyspnoea and/or constitutional symptoms May have hilar lymphadenopathy seen on imaging
Neoplastic	Benign Lipoma Epidermal cyst Neuroma	Lipoma Solitary subcutaneous nodule Soft, painless and mobile Positive 'slippage sign' Slow growing Epidermal cyst Non-fluctuant mass Presence of central punctum Neuroma Mobile and perpendicular to course of nerve May have positive Tinel's sign
	Malignant Primary cancer (lymphoma and sarcoma) Lymph node metastases from cancers of the head and neck, upper respiratory tract, oesophagus or distant site	Matted and hard solid mass Associated with regional lymphadenopathy Does not move with swallowing May have B symptoms in lymphomas (weight loss and night sweats)

- A personal history of autoimmune diseases (such as myasthenia gravis, Addison's disease, pernicious anaemia, type 1 diabetes mellitus, rheumatoid arthritis, systemic lupus erythematosus or vitiligo) is associated with autoimmune thyroid diseases such as Graves' disease and Hashimoto's thyroiditis.

Are there any compressive symptoms?

Compressive symptoms due to impingement or displacement of the trachea, oesophagus or great vessels can occur in large goitres or those with retrosternal extension. This is due to the confined space of the thoracic inlet.

Tracheal compressions may manifest as dyspnoea, stridor, wheezing or cough. Depending on the severity of compression, symptoms may occur at rest, on exertion or with positional changes. Patients with goitres with intrathoracic extension may experience dyspnoea during manoeuvres that push the thyroid into the thoracic inlet, such as bending forward or lying supine.

Hoarseness of voice may be seen in patients with invasion or compression of the recurrent laryngeal nerve, causing transient or permanent vocal cord paralysis. Occasionally, goitres may compress the cervical sympathetic chain, resulting in Horner's syndrome with a triad of ptosis, miosis and decreased sweating on the ipsilateral side of the face. Patients may have dyspnoea due to phrenic nerve paralysis. Rarely, superior vena cava syndrome manifesting as facial swelling and jugular vein thrombosis may develop.

Are there clinical manifestations of hyperthyroidism or hypothyroidism?

The functional nature of a goitre affects the differentials which should be considered. Symptoms of hyperthyroidism include palpitations, diarrhoea, weight loss despite increased appetite, heat intolerance, oligomenorrhoea or anxiety. Classical signs such as tremor or hyperactivity may be absent in the elderly with 'apathetic thyrotoxicosis', whose predominant symptom may be that of lethargy and weakness. The differential diagnoses to consider in goitres with hyperthyroidism can be found in Table 2. Conversely, patients with hypothyroidism may have lethargy, cold intolerance, weight gain, depression,

Table 2. Differential diagnosis of goitre and hyperthyroidism.

Category	Differential diagnosis	Distinguishing features
Diffuse swelling	Graves' disease	Commonly affects females aged 30-60 years May have concomitant autoimmune diseases May have associated eye signs characteristic of Graves' ophthalmopathy May have Graves' acropachy or pretibial myxoedema Positive serum autoantibodies to thyrotropin receptor Diffuse uptake on radionuclide thyroid uptake scan
	Toxic multinodular goitre	Palpable nodular goitre or presence of multiple nodules seen on thyroid ultrasonography One or more focal areas of increased uptake on radionuclide thyroid uptake scan
	Initial stage of subacute thyroiditis	Tender diffuse goitre Precipitated by upper respiratory tract infection Initial hyperthyroidism followed by hypothyroidism No uptake on radionuclide thyroid uptake scan
Solitary nodule	Toxic adenoma	Palpable thyroid nodule Corresponding area of increased uptake on radionuclide thyroid uptake scan with suppression of the rest of the gland

constipation, severe bradycardia, hypothermia or altered sensorium with confusion or obtundation in myxoedema coma.

Are there any associated symptoms suggestive of malignancy (including risk factors)?

Risk factors of a thyroid malignancy include male gender, age less than 20 years or more than 65 years, history of head and neck radiation, family history of thyroid cancer and multiple endocrine neoplasia type 2 (MEN2).[5] Features suggestive of malignancy include:

- Rapid growth of the goitre over time, which may suggest anaplastic thyroid carcinoma or lymphoma
- Hard, single nodule and/or nodules fixed to surrounding structures
- Hoarseness due to recurrent laryngeal nerve invasion
- Non-resolving cervical lymphadenopathy
- Symptoms or signs of distant metastases
- Symptoms suggestive of thyroid lymphoma, such as fever, weight loss and night sweats.

Physical examination

The physical examination can be grouped under three main categories, examination of the goitre and the surrounding structures, and identifying clinical signs of thyroid dysfunction and extrathyroidal signs specific to Graves' disease.

Examination of the goitre and surrounding neck structures

- Inspection: Look for scars indicating previous thyroid surgery or injury. Is there a diffuse enlargement or localised solitary swelling of the goitre? Ask the patient to swallow water and look for the movement of the goitre. A goitre and thyroglossal cyst both move with swallowing. Owing to its attachment to the foramen caecum at the base of the tongue, a thyroglossal cyst would also move up with tongue protrusion, whereas a goitre would not.
- Palpate from behind the patient, with the neck bent slightly to relax the sternocleidomastoid muscles: Determine the goitre's extent, size, consistency and tenderness (clinically palpable thyroid nodules are generally more than 1 cm in size). Check for regional cervical lymphadenopathy. Palpate for any tracheal deviation, and percuss for any retrosternal extension.
- Others: Auscultate for bruit over the thyroid, which may be heard in Graves' disease. Pemberton's sign may be elicited for patients with suspected retrosternal extension of goitres. It is positive when the patient develops signs of facial plethora, respiratory depression, stridor and distension of neck veins after bilateral upper limb elevation for a minimum of a minute. This implies thoracic inlet obstruction.

Clinical signs of thyroid dysfunction

Apart from eliciting symptoms from the history, physical examination can also reveal other signs in patients with thyroid hormonal dysfunction. Patients with hyperthyroidism have tremors and diaphoresis. There may also be proximal muscle weakness and hyperreflexia. Patients with hypothyroidism have dry skin with coarse hair, non-pitting oedema and delayed deep tendon reflexes, especially the ankle reflex.

Extrathyroidal signs specific to Graves' disease (eye signs, dermopathy and nail changes)

Eye signs indicative of Graves' disease would include exophthalmos, proptosis (forward displacement of the eyeball), chemosis (conjunctival oedema), lid lag and limited extraocular movement. Clinically significant thyroid eye disease is shown in Figure 1. Pretibial myxoedema is localised non-pitting thickening and induration of the skin over the lower legs or dorsum of feet in patients with Graves' disease. Some may also display thyroid nail disease with clubbing of the fingertips, soft tissue swelling or onycholysis.

WHAT ARE THE MAIN CAUSES?

The nature of the thyroid enlargement is a key determinant of the goitre's possible aetiology. Therefore, the initial clinical

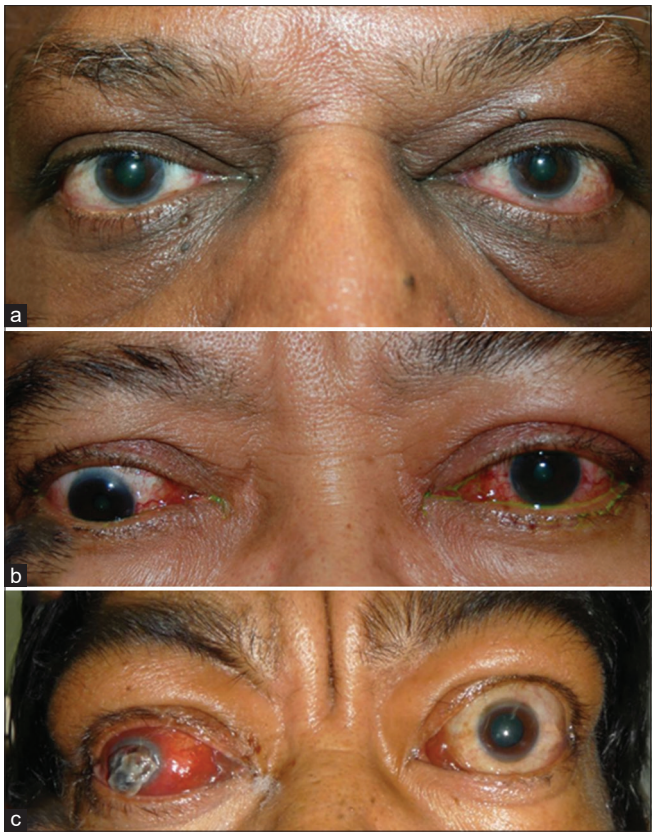

Figure 1: Photographs show examples of clinically significant active thyroid eye disease (TED): (a) mild active TED with conjunctival injection and eyelid oedema, (b) moderate active TED with conjunctival injection, eyelid retraction, chemosis and right eye hypotropia and (c) severe active TED with corneal ulceration. [Reproduced with permission from Lim *et al*. Thyroid eye disease: a Southeast Asian experience. Br J Ophthalmology 2015; 99:512-8.]

examination should focus on differentiating a diffusely enlarged goitre from a solitary thyroid nodule.

Diffusely enlarged goitre

Multinodular goitre

Multinodular goitre is a nodular enlargement of the thyroid gland in the absence of autoimmune thyroid disease, cancer or underlying inflammation. It is the most common thyroid disorder, and is more common in women, with a female-to-male ratio of 13:1.[6] As iodine deficiency contributes to the formation of multinodular goitre, the incidence of this condition is higher in iodine-deplete areas. The diagnosis is based on physical examination and ultrasonography. Compressive symptoms may occur in some patients. Thyroid function can be normal or consist of hyperfunctioning nodules, termed 'toxic' multinodular goitre. Thyroid autoantibodies are usually absent or low. Imaging for suspicious nodules and the extent of the goitre can be performed, with corresponding fine-needle aspiration cytology (FNAC), as indicated. Management of the multinodular goitre depends on its size, symptoms and the patient's preferences. Thyroidectomy is indicated for patients with concomitant thyroid malignancy, compressive symptoms and large nodules of more than 4 cm. This is due to higher risks of malignancy and increased false-negative rates in these large goitres during FNAC. Radioactive iodine (RAI) ablation therapy is an alternative if the above indications are absent and the patient is hyperthyroid. A small, asymptomatic and benign multinodular goitre can be expectantly managed with regular monitoring using ultrasonography and serum thyroid function tests.

Autoimmune causes (Graves' disease and Hashimoto's thyroiditis)

Autoimmune thyroid diseases are caused by the body's immune response to specific thyroid antigens.

Graves' disease is an autoimmune disease caused by thyrotropin receptor antibodies (TRAb). It is the most common cause of hyperthyroidism. Smoking can result in a twofold increase in the risk of its development. The incidence is eight times greater in women than in men, and it commonly affects women between 30 and 60 years of age.[7] Graves' disease is classically associated with a diffuse goitre, hyperthyroidism with or without Graves' ophthalmopathy. Rarely, patients may have pretibial myxoedema or acropachy. Hyperthyroidism is due to autoantibody-induced activation of thyroid-stimulating hormone (TSH) receptors, which increases thyroid hormone secretion. A positive TRAb found on blood tests would further support the diagnosis of Graves' disease. Thyrotoxicosis, if left untreated, may result in a thyroid storm, congestive cardiac failure and dangerous arrhythmias such as atrial fibrillation and cardiovascular collapse.

Hashimoto's thyroiditis, also known as chronic autoimmune thyroiditis, occurs because of autoimmune-mediated obliteration of the normal thyroid gland due to lymphocytic infiltration, fibrosis and loss of follicular epithelium. The peak incidence of Hashimoto's thyroiditis occurs in women aged 30–50 years, who often present with painless and diffuse enlargement of the thyroid gland. Some are euthyroid initially but may progress to hypothyroidism.[8] Diagnosis was further supported with positive anti-thyroid peroxidase antibodies (TPOAb) or anti-thyroglobulin antibodies (TgAb).

Subacute thyroiditis

Subacute thyroiditis, also known as de Quervain's thyroiditis, presents with a tender diffuse goitre and may be associated with fatigue, fever or pharyngitis. It is often preceded by an upper respiratory viral infection. Thyroid dysfunction may occur in stages for some patients. Initial thyrotoxicosis lasting 3–6 weeks, owing to the destruction of thyroid follicles, can occur in around 50% of patients.[9] Subsequent progression to hypothyroidism (which may last for up to 6 months) is observed in 30% of patients. Patients eventually revert to the euthyroid stage with a resolution of the goitre approximately a year after onset. Initial investigations reveal leucocytosis, elevation of serum erythrocyte sedimentation rate (ESR) and no uptake on a radionuclide thyroid uptake scan. Treatment

in symptomatic individuals is usually with non-steroidal inflammatory agents and beta blockers. Anti-thyroid drugs are not required owing to the risk of subsequent hypothyroidism.

Solitary thyroid nodule

A thyroid nodule is a localised lesion that appears distinct from the surrounding thyroid gland during palpation or on ultrasonography. It may present as a solitary thyroid nodule in a normal thyroid gland or as a dominant thyroid nodule in a diffuse or multinodular goitre.

Dominant nodule of multinodular goitre (euthyroid/toxic)

More than 50% of patients with a clinically palpable solitary nodule were eventually found to have multiple nodules on ultrasonography.[5] Although most multinodular goitres are euthyroid, some with large hyperfunctioning nodules may develop hyperthyroidism. As patients with multinodular goitres have the same incidence of malignancy transformation as those with solitary thyroid nodules, they should be evaluated using a similar approach.[3] Ultrasonography should be performed to evaluate each nodule within a multinodular goitre instead of focusing only on the dominant nodule, to avoid missing a possible underlying malignancy.

Thyroid cyst

Thyroid cysts are discrete hypoechoic areas observed on ultrasonography, as they are mostly fluid-filled. True simple cysts are benign but tend to be rare and are found in only 1% of nodules.[10] Most thyroid cysts have mixed solid components, with areas of cystic degeneration. Most cysts are degenerating thyroid adenomas. A higher proportion of cystic components in a nodule indicate a lower possibility of malignancy. FNAC can be performed on mixed cystic-solid lesions that are 2 cm or larger, or lesions with suspicious ultrasonography features [Box 1]. Aspiration may also relieve compressive symptoms by large cystic nodules. Purely cystic nodules do not need to be biopsied. Surgical excision is indicated in benign symptomatic cysts that re-accumulate despite recurrent aspirations or if there are suspicious features in a mixed cystic-solid thyroid lesion, in cases where benign cytology cannot be obtained.

Simple/colloid goitre

Colloid goitres, also known as 'simple goitres', are benign lesions. They consist of colloid, which is an acellular glycoprotein where thyroid hormones are stored. Approximately 60%–70% of thyroid nodules are colloid nodules.[11] Ultrasonography often reveals comet-tail artefacts, which are due to reverberation echoes between two surfaces. FNAC may be required if there are further suspicious features. Patients with colloid nodules are followed up every 6 months or yearly with repeat ultrasonography. Surgical excision is performed only if these goitres are complicated by compressive symptoms.

Box 1. Thyroid ultrasonography features suspicious of malignancy.

Solid hypoechoic nodule
Irregular margins (infiltrative and micro-lobulated)
Microcalcifications
Taller than wide shape (where the anteroposterior dimension-to-transverse dimension ratio is 1 or more on ultrasonography)
Rim calcification
Abnormal lymph nodes with microcalcifications, cystic aspects, peripheral vascularity, hyperechogenicity or round shape

Neoplasm (adenoma and malignancy)

Neoplastic thyroid nodules can be divided into benign or malignant. Follicular adenomas are benign lesions. Thyroid nodules with FNAC showing follicular cells with atypia require surgery to exclude capsular and vessel invasion observed in follicular cancer. If histology results confirm follicular adenoma with organised follicular cells, a hemi-thyroidectomy would suffice and no further follow-up is required.

Thyroid malignancies are classified into three main types: differentiated cancers (papillary or follicular cancers, which account for 90%–95% of cancers), medullary cancers (which account for 6% of cancers) and undifferentiated cancers (anaplastic cancers, which account for less than 1% of cancers).[12] Management differs according to the type of malignancy. In differentiated cancers, surgical thyroidectomy is the mainstay of treatment along with neck dissection in patients who have cervical lymph node metastasis (common in papillary thyroid cancer), with consideration of RAI ablation and subsequent TSH suppression in certain candidates who have a high risk of recurrence. Well-differentiated thyroid cancer generally has a good prognosis after completion of treatment. Medullary cancers require further evaluation for concomitant hyperparathyroidism and pheochromocytoma before surgery, as they are associated with MEN2. Anaplastic cancers tend to be locally advanced or have distal metastases at the time of diagnosis, given their fast and aggressive course, with a mortality rate of nearly 100%. Therefore, the role of surgery is limited in this group of patients, and palliation is often required.

WHAT INVESTIGATIONS ARE REQUIRED?

In primary care

After a thorough history-taking and physical examination, performing a serum thyroid function test is a useful first-line investigation to provide more clues to the aetiology and subsequent management. Serum TSH levels allow initial determination of the patient's thyroid function.

- Low TSH and high free thyroxine (fT4) levels are consistent with a hyperfunctioning goitre. In such cases, performing a serum TRAb test is helpful to support the diagnosis of Graves' disease, as opposed to toxic multinodular goitres. This is because up to 90% of patients with Graves' disease have positive TRAb, whereas it is usually negative or very low in toxic multinodular goitres and subacute thyroiditis.[7]

- High TSH and low fT4 levels indicate hypothyroidism. High levels of TPOAb or TgAb support the diagnosis of Hashimoto's thyroiditis. The sensitivity of TPOAb is more than 90% for Hashimoto's thyroiditis and is further increased to 97% if both TPOAb and TgAb are measured.[8]
- Serum TSH that is elevated or within the upper limit of normal has been associated with an increased risk of malignancy within a thyroid nodule; hence, further evaluation with ultrasonography is advised.[3]

Other tests that may be useful for hyperthyroid patients include serum ESR, which may be elevated in patients with subacute thyroiditis.[7]

In tertiary care

Imaging

Ultrasonography of the thyroid gland is recommended in all patients presenting with goitres, as part of the initial investigation.[3] Apart from detecting nodules that are not palpable, it can characterise the goitre and look for suspicious features of malignancy [Box 1] that require FNAC. Figure 2 shows an ultrasonography image of a papillary thyroid cancer.

Fine-needle aspiration cytology

FNAC is efficient, safe, cost-effective and the gold standard for cytological diagnosis of suspicious thyroid nodules on ultrasonography to rule out malignancy.[3] It is not required for purely cystic thyroid nodules. The results of FNAC are reported using the six categories of the Bethesda System for Reporting Thyroid Cytopathology, which estimates the corresponding risk of malignancy. Subsequent management will then be based on the category. The six categories are: (a) unsatisfactory, (b) benign, (c) atypia, (d) follicular neoplasm (which may require excision to truly differentiate between a benign follicular adenoma from a follicular carcinoma), (e) suspicious for malignancy and (f) malignant.

WHAT ARE THE PRINCIPLES OF MANAGEMENT IN PRIMARY CARE?

Management of a goitre should be directed at its cause, associated thyroid dysfunction and compressive symptoms.

Graves' disease

On initial review, patients may present with palpitations due to thyrotoxicosis. Oral beta blockers such as propranolol may be useful in controlling tachycardia and relieving symptoms of tremors. A relative beta-1 selective beta blocker such as atenolol may be used with close monitoring in patients with well-controlled asthma. In patients with contraindications such as uncontrolled asthma, an alternative would be calcium channel blockers such as diltiazem.[9]

The treatment of Graves' disease depends on patient factors (such as age, pregnancy or women who are yet to conceive) and goitre factors (such as a huge retrosternal goitre or high suspicion of malignancy). There are three main treatment options: (a) anti-thyroid drugs that block thyroid hormone synthesis, (b) RAI that ablates the thyroid gland and (c) thyroidectomy. The principles of treatment are summarised in Figure 3.

Anti-thyroid drugs (thionamides) are the preferred initial therapy for most patients, including older patients with limited life expectancy. Because of the higher risk of hepatotoxicity with propylthiouracil, thiamazoles such as carbimazole should be the recommended first-line drug, except for women in the first trimester of pregnancy. This is because thiamazoles have been associated with severe birth defects (such as aplasia cutis, choanal and oesophageal atresia) in up to 4% of patients, as compared to the risk of minor birth defects (including pre-auricular sinuses and neck cysts) found in about 2% of patients on propylthiouracil.

Patients also must be counselled on the risks of agranulocytosis while on anti-thyroid drug treatment and be advised to seek medical attention if they develop fever, sore throat or oral ulcers. The incidence of agranulocytosis has been found in 0.1%–0.3% of patients on anti-thyroid drugs.[9] Prior to initiation of anti-thyroid drugs, a baseline full blood count and liver function tests are recommended. There are currently no consensus recommendations for routine monitoring of differential white blood cell counts or liver function tests in patients taking anti-thyroid drugs, unless they develop a fever with pharyngitis or symptoms indicative of hepatotoxicity (such as pruritic rash, jaundice, pale stools, dark urine, joint pains, abdominal pain, anorexia or fatigue). Minor, non-vasculitic skin reactions (such as pruritus and transient rashes) can be treated with antihistamines without cessation of anti-thyroid drugs. In cases with persistent minor side effects, switching between types of anti-thyroid drugs and exploring alternatives of RAI ablation or surgery can be considered.

The initial dose would depend on the clinical severity of the hyperthyroidism, fT4 level and size of the goitre. Patients with larger goitres and higher levels of fT4 would require a higher dose (such as carbimazole 30 mg every morning). A dose ratio of carbimazole to propylthiouracil in divided doses of 1:10 is recommended when switching from one drug to another. The dose is titrated every 4–6 weeks based on clinical symptoms and the initial level of fT4, as the normalisation of TSH usually lags by 3–6 months. The dose can be halved when the fT4 value halves. Hence, these patients would need to be on chronic follow-up with a family physician, with periodic serum thyroid function tests. Therapy should be continued and weaned, if possible, over 18 months. Remission is defined as normal serum TSH, fT4 and triiodothyronine (T3) for one year after discontinuation of anti-thyroid drugs, and can be achieved in up to 50%–60% of patients after treatment for 2 years.[9] Further prolonged

treatment beyond 18 months has not been shown to improve the remission rate. Remission is more likely in young patients with smaller goitres, mild hyperthyroidism, lower T3 levels and those with low TRAb.[7]

For patients in whom medical treatment has failed or is contraindicated and those who are not keen on surgery, RAI therapy is another effective option. Contraindications would include women who are considering conception within 6 months, pregnant or lactating women, and those with active Graves' ophthalmopathy or uncontrolled hyperthyroidism. Patients are expected to develop hypothyroidism after treatment and need lifelong thyroxine replacement. Suitable patients can be referred to nuclear medicine specialists for RAI therapy. This involves administrating RAI via an odourless and colourless oral tablet. Patients must be euthyroid before referral. They would then have to avoid contact with pregnant women and young children for a week and avoid conception for 6 months.

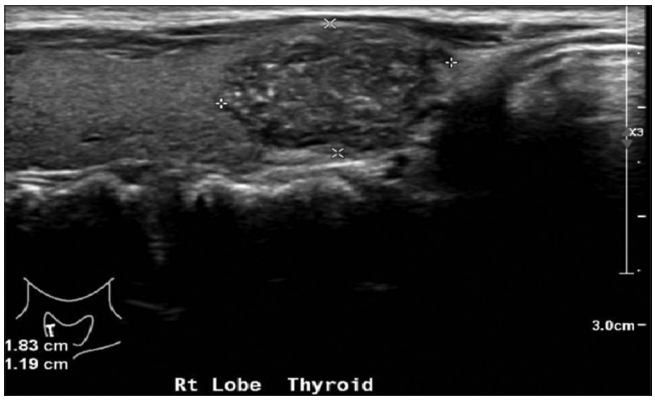

Figure 2: US image shows a 1.8-cm right thyroid nodule that is hypoechoic with irregular margins and microcalcifications. Fine-needle aspiration cytology subsequently revealed papillary thyroid cancer.

Thyroid surgery can be considered in patients whose medical treatment has failed, who have contraindications for RAI therapy, or who have large goitres causing compressive symptoms or goitres with malignant features. The care of patients after thyroidectomy is further discussed later in this article.

Patients with thyroid eye disease would benefit from an early referral to ophthalmologists for further assessment.

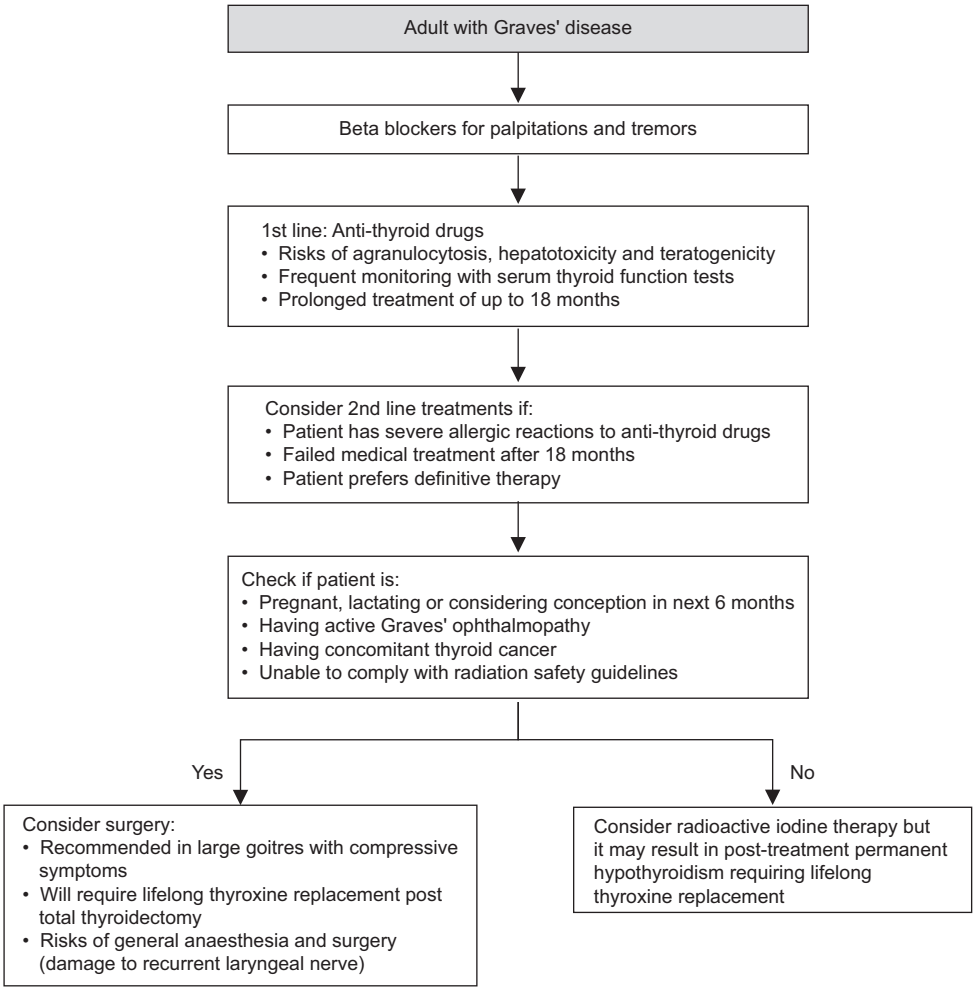

Figure 3: Flowchart shows the management principles of Graves' disease.

Hashimoto's thyroiditis

Thyroid hormone replacement is indicated in patients with hypothyroidism due to Hashimoto's thyroiditis. The dose of oral levothyroxine that is initiated depends on the initial serum TSH level, age, comorbidities and body weight. In a young and healthy patients with elevated serum TSH, the full replacement dose based on a body weight of 1.6 mcg/kg can be initiated.[8] In elderly patients with mildly elevated serum TSH or those with known coronary artery disease, lower doses of levothyroxine (e.g., 12.5–25.0 mcg daily) can be started, with gradual titration and close monitoring of response and tolerance. To prevent the reduction of absorption, oral levothyroxine should be taken 4 hours apart from other medications such as iron or calcium supplements. Dose adjustments are usually made 4–6 weeks after initiation. Overall, the aim is for serum TSH to be near the lower limit of normal. After the target serum TSH level is reached, patients can be reviewed every 6 months or annually. Most patients will be on indefinite treatment with thyroxine. Surgery is rarely indicated, unless there are significant compressive symptoms despite medical treatment.

Post thyroidectomy

General practitioners may also have to care for patients who have had a thyroidectomy, which may be a total thyroidectomy or hemi-thyroidectomy (removal of a lobe of the thyroid gland). The management would differ depending on the initial indication for the surgery (benign or malignant).

Thyroid hormone replacement

Patients who have had a total thyroidectomy for benign goitres (e.g. Graves' disease and multinodular goitres) need long-term thyroxine replacement and periodic clinical review with serum thyroid function test. Those who undergo total thyroidectomy for thyroid malignancy are first treated with RAI therapy to ablate residual thyroid tissues, particularly if they have extensive extrathyroidal spread or metastasis (as discussed later in this article). After RAI therapy, patients receive thyroxine replacement at supraphysiological doses to achieve TSH suppression, which reduces the risk of recurrence. The degree of suppression depends on the risk of recurrence of thyroid cancer and must be balanced with the potential side effects from subclinical hyperthyroidism. These include angina in patients with ischaemic heart disease, increased risk of atrial fibrillation and risk of osteoporosis in both genders, especially the elderly and postmenopausal women.[13]

Radioactive iodine ablation

RAI therapy is used to ablate the remaining thyroid tissue after surgery for better surveillance of cancer recurrence in the future or as adjunctive therapy for local or distant metastatic thyroid cancer. Patients are advised to be on a low iodine diet for 2–3 weeks before treatment to ensure iodine depletion from cells for effective RAI therapy. Levothyroxine is withdrawn before treatment to raise TSH and improve radioiodine uptake. After treatment, patients can expose others to radiation emitting from their bodies or through bodily fluids. They should avoid sharing utensils, sleeping in the same bed with others, sexual contact and close contact with children and pregnant women for some time after treatment. The duration depends on the dose of RAI therapy administered, ranging from 1 day to 3 weeks.[14] Pregnancy should be delayed to 6 months after RAI therapy to ensure that any thyroid dysfunction is adequately treated. For men, the conception should be delayed for about 4 months.

Postoperative hypoparathyroidism

Transient or permanent postoperative hypoparathyroidism may occur if there is disruption of the blood supply to the parathyroid glands during thyroidectomy.[13] This can result in hypocalcaemia (which may manifest as circumoral numbness, tingling in the fingers and toes, Chvostek's sign and carpopedal spasm) and hyperphosphataemia. This may be permanent if it is persistent for more than 6 months after surgery. Patients with permanent hypoparathyroidism are treated with oral calcium replacement with activated vitamin D (calcitriol) to facilitate the absorption of calcium and with adequate magnesium replacement. Calcium targets should be within the lower limit of normal (often in the range of 2.00–2.20 mmol/L) to prevent resultant hypercalciuria from the complete correction of hypocalcaemia in these patients.

WHEN SHOULD I REFER TO A SPECIALIST?

An adult patient presenting with a goitre can be managed according to the flowchart shown in Figure 4. Goitres with concomitant stridor and respiratory distress, signs of thyroid storm or severe hypothyroidism would warrant an immediate referral to the emergency department. Goitres with red flags suggestive of malignancy (rapid enlargement over a few weeks and/or non-resolving cervical lymphadenopathy) and compressive symptoms (such as dysphagia or dysphonia) should be urgently referred within 1–2 weeks to a thyroid surgeon for further assessment.

The following cases should be referred to a thyroid surgeon:

- All solitary nodules and non-toxic multinodular goitres for further imaging, subsequent FNAC and consideration for surgery.
- Patients with Graves' disease in whom medical treatment has failed and have contraindications for RAI therapy, or with large obstructive goitres for consideration of thyroidectomy.

The following cases should be referred to an endocrinologist:

- Pregnant patients with goitres and/or hyperthyroidism or hypothyroidism (these patients should also be co-managed with obstetricians)
- Goitres with hypothyroidism
- Subacute thyroiditis

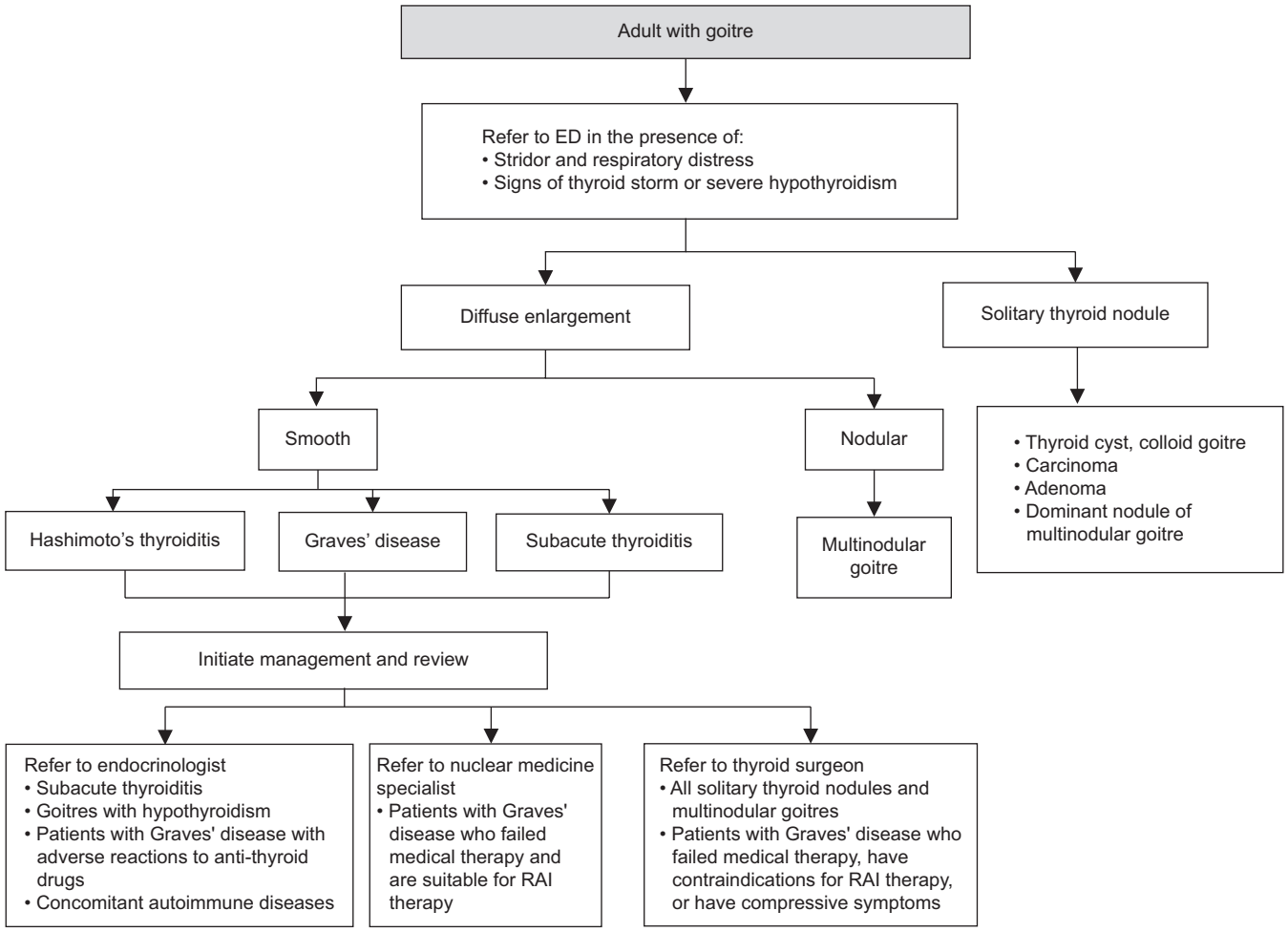

Figure 4: Flowchart shows management and referral of goitres. ED: emergency department, RAI: radioactive iodine

- Toxic multinodular goitres without compressive symptoms
- Patients with Graves' disease who experienced adverse side effects to anti-thyroid drugs or have poor response despite prolonged medical treatment with recurrent relapses
- Autoimmune thyroid disease with concomitant autoimmune conditions (such as type 1 diabetes mellitus).

Patients with Graves' disease in whom medical treatment has failed and do not have compelling contraindications for RAI therapy can be referred to nuclear medicine for RAI therapy.

TAKE HOME MESSAGES

1. Goitre is an abnormal enlargement of the thyroid gland, presenting as a solitary thyroid nodule or diffuse enlargement of the thyroid gland. Patients with goitres can be euthyroid, hypothyroid or hyperthyroid.
2. Red flags include compressive symptoms such as dysphagia, dyspnoea or any voice change. Persistent or suspicious cervical lymphadenopathy is also associated with thyroid malignancy. These patients should be referred to specialists urgently.
3. Initial investigations include a thyroid function test and thyroid ultrasonography. Anti-thyrotropin receptor antibody testing should be ordered for hyperthyroidism and anti-thyroid peroxidase antibody testing for hypothyroidism to differentiate the etiologies of Graves' and Hashimoto's thyroiditis, respectively.
4. The choice of specialist referral depends on the suspected aetiology of the goitre. A goitre with thyroid hormone dysfunction likely of autoimmune aetiology should be referred to an endocrinologist, while a solitary thyroid nodule that is euthyroid is usually referred to a surgeon.
5. FNAC is the gold standard for the cytological diagnosis of suspicious thyroid nodules on ultrasonography to rule out malignancy.
6. Patients with thyroid malignancies who have undergone total thyroidectomy may be receiving supraphysiologic doses of thyroxine for TSH suppression to reduce the risk of recurrence.
7. Treatment options for Graves' disease include anti-thyroid medication (thionamides), RAI and surgery. Carbimazole is an appropriate first-line therapy with regular thyroid

function monitoring.

8. Women with uncontrolled Graves' disease despite anti-thyroid medication who are considering pregnancy should be referred for consideration of thyroid surgery (RAI is contraindicated in those actively planning to conceive).

Closing Vignette

You asked Angela to return to your clinic once the results were available. The tests revealed overt hyperthyroidism, with TSH <0.005 (range: 0.270–4.200) mIU/L and fT4 >100.0 (range: 12.0–22.0) pmol/L. ESR was within normal limits. After confirming that she did not have asthma, you started her on propranolol 10 mg twice daily and carbimazole 30 mg every morning, ordering repeat thyroid function tests with TSH receptor antibody in four weeks' time. You counselled her on the symptoms of thyroid storm before her leaving your room and referred her to a tertiary centre for specialist management with an endocrinologist.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Jocelyn Ling Sui Yeo[1], MBBS, Nicole Therese Wen Min Yong[2], MBBS, Dinesh Carl Junis Mahendran[3], MBBS (Hons), FRACP, Clement Luck Khng Chia[4], MBBS, FRCSEd

[1]Family Medicine Programme, National Healthcare Group Polyclinics, [2]Yong Loo Lin School of Medicine, National University of Singapore, [3]Division of Endocrinology, Department of General Medicine, [4]Endocrine Surgical Service, Department of Surgery, Khoo Teck Puat Hospital, Singapore

Correspondence: Dr. Clement Luck Khng Chia,
Consultant, Endocrine Surgical Service, Department of Surgery,
Khoo Teck Puat Hospital, 90 Yishun Central, 768828, Singapore.
E-mail: Chia.clement.lk@ktph.com.sg

Received: 24 Feb 2021 **Accepted:** 23 Nov 2021 **Published:** 18 Nov 2022

REFERENCES

1. Shan Z, Chen L, Lian X, Liu C, Shi B, Shi L, *et al*. Iodine status and prevalence of thyroid disorders after introduction of mandatory universal salt iodization for 16 years in China: A cross-sectional study in 10 cities. Thyroid 2016;26:1125-30.
2. Youserm DM, Huang T, Loevner LA, Langlotz CP. Clinical and economic impact of incidental thyroid lesions found with CT and MR. AJNR Am J Neuroradiol 1997;18:1423-8.
3. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, *et al*. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association Guidelines Task Force on thyroid nodules and differentiated thyroid cancer. Thyroid 2016;26:1-133.
4. Chang SSY, Xiong M, How CH, Lee DM. An approach to cervical lymphadenopathy in children. Singapore Med J 2020;61:569-77.
5. Mandel SJ, Langer JE, Kaplan MM. Clinical evaluation and management of thyroid nodules. In: Braverman LE, Cooper DS, editors. Werner and Ingbar's The Thyroid: A Fundamental and Clinical Text. 10th ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2012:650-1.
6. Medeiros-Neto G. Multinodular goiter. In: Feingold KR, Anawalt B, Boyce A, *et al.*, editors. Endotext [Internet]. South Dartmouth, MA: MDText.com Inc; 2000.
7. Degroot LJ. Graves' disease and the manifestations of thyrotoxicosis. In: Feingold KR, Anawalt B, Boyce A, *et al.*, editors. Endotext [Internet]. South Dartmouth, MA: MDText.com Inc; 2000.
8. Akamizu T, Amino N. Hashimoto's thyroiditis. In: Feingold KR, Anawalt B, Boyce A, *et al*., editors. Endotext [Internet]. South Dartmouth, MA: MDText.com Inc; 2000.
9. Ross DS, Butch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, *et al*. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid 2016;26:1343-421.
10. Ross DS. Cystic thyroid nodules. In: UpToDate. Available from: https://www.uptodate.com/contents/cystic-thyroid-nodules. [Last accessed on December 29, 2020].
11. Hoang VT, Trinh CT. A review of the pathology, diagnosis and management of colloid goitre. Eur Endocrinol 2020; 16:131-5.
12. Lee K, Anastasopoulou C, Chandran C, Sebastiano C. Thyroid cancer. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; 2021.
13. Kaplan E, Angelos P, Applewhite M, Mercier F, Grogan R H, *et al*. Surgery of the thyroid. In: Feingold KR, Anawalt B, Boyce A, *et al*, editors. Endotext. South Dartmouth, MA: MDText.com Inc; 2000.
14. American Thyroid Association Taskforce on Radioiodine Safety; Sisson JC, Freitas J, McDougall IR, Dauer LT, Hurley JR, *et al*. Radiation safety in the treatment of patients with thyroid diseases by radioiodine 131I: Practice recommendations of the American Thyroid Association. Thyroid 2011;21:335-46.

Access this article online

Quick Response Code:

Website: https://journals.lww.com/SMJ

DOI: 10.4103/SINGAPOREMEDJ.SMJ-2021-091

How to cite this article: Yeo JL, Yong NT, Junis Mahendran DC, Chia CL. Approach to goitre in family medicine practice. SINGAPORE MED J 2022;63:604-14.

SMC CATEGORY 3B CME PROGRAMME

Online Quiz: https://www.sma.org.sg/cme-programme

Deadline for submission: 6 pm, 30 December 2022

Question	True	False
1. Thyroid stare and lid lag are specific signs of Graves' disease.		
2. Signs such as tremor and hyperactivity may be absent in elderly hyperthyroid individuals.		
3. Simple/non-vasculitic rash is a contraindication to continuing carbimazole treatment.		
4. A high erythrocyte sedimentation rate is suggestive of subacute thyroiditis.		
5. Toxic multinodular goitre is the most common cause of hyperthyroidism.		
6. Smoking is a significant risk factor for Graves' disease.		
7. Thionamide therapy is recommended to individuals with subacute thyroiditis.		
8. Thyroid-stimulating hormone levels can remain suppressed for many months even after successful therapy for hyperthyroidism.		
9. 1.6 mcg/kg (full replacement dose) of thyroxine should be started in hypothyroid elderly individuals.		
10. Breastfeeding is a relative contraindication to radioactive iodine ablation.		
11. Suspicious thyroid ultrasonography features include the presence of microcalcifications.		
12. If fine-needle aspiration cytology of a thyroid nodule yields follicular cells, the nodule is always benign and no further treatment is required.		
13. Anaplastic thyroid cancer is usually resectable at presentation.		
14. Patients with medullary thyroid cancer can have concomitant pheochromocytoma and hyperparathyroidism.		
15. Thyroxine replacement is usually withheld prior to radioactive iodine therapy for thyroid cancer.		
16. Thyroxine replacement is given at supraphysiologic doses for patients with thyroid cancer who have undergone total thyroidectomy and radioactive iodine therapy.		
17. Patients who have undergone total thyroidectomy may have circumoral numbness and tingling in the fingers and toes.		
18. Patients with goitre and recent changes in voice should be referred to nuclear medicine physicians for radioactive iodine treatment.		
19. Papillary and follicular thyroid cancers are well differentiated and have a good prognosis.		
20. Papillary thyroid cancers are commonly associated with cervical lymph node metastasis.		