How to treat

Do you need to read this article?

Try this quiz

1. **Most thyroid cancers only present as a thyroid nodule.**
   True/False
2. **All patients who present with a thyroid nodule should have thyroid function tests and an ultrasound scan of the thyroid.**
   True/False
3. **Ultrasound guidance is not usually required for fine-needle aspiration of easily palpable thyroid nodules.**
   True/False
4. **All patients with FNA cytology reported as Bethesda III and above should be treated surgically.**
   True/False

Answers on page 76

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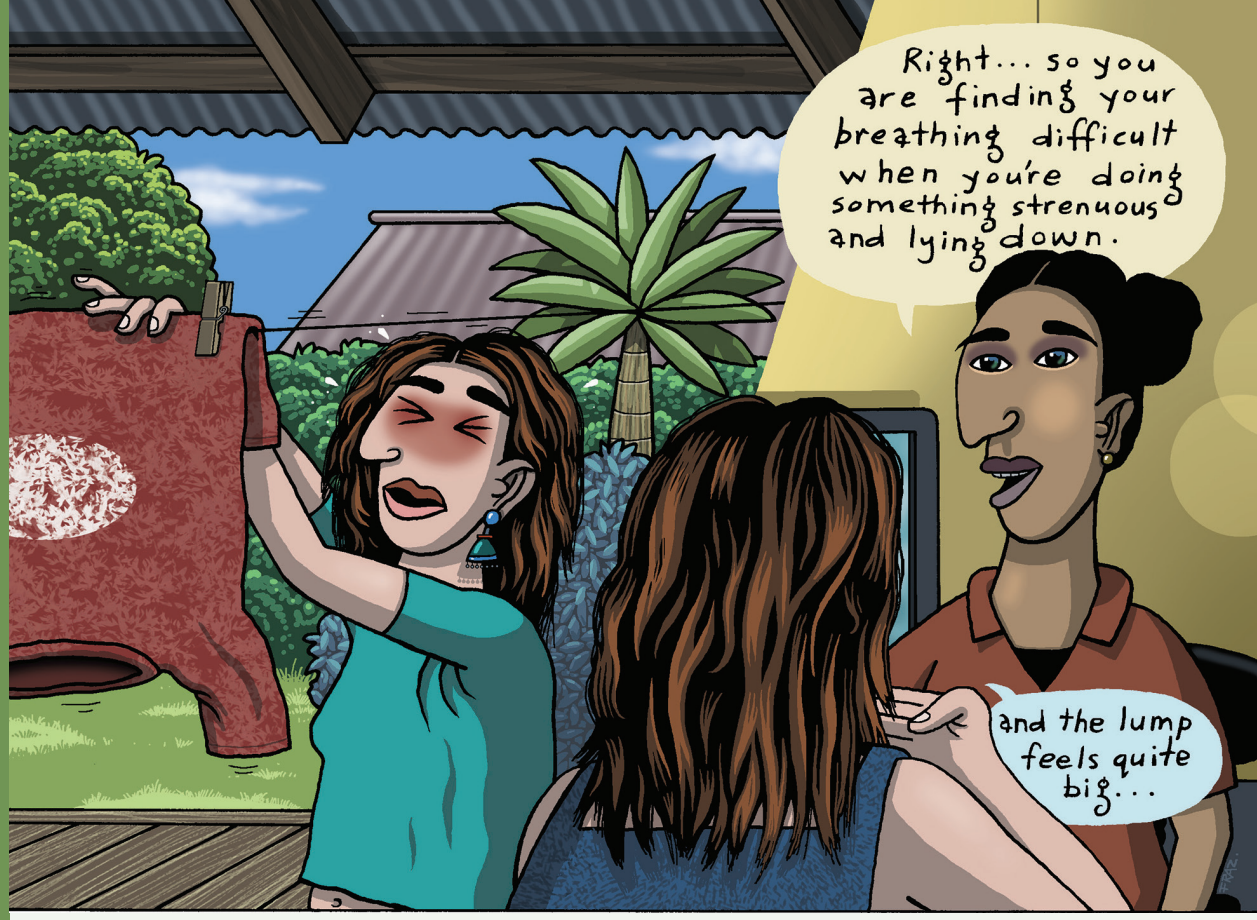

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Thyroid nodules

Otolaryngologist, head and neck surgeon **Francis T. Hall** discusses the evaluation of thyroid nodules, which primarily aims to determine the likelihood of malignancy. He then reviews the treatment of thyroid nodules and thyroid cancer, including recent advances in management

Thyroid nodules are very common. They are more common in women, with some estimates of palpable thyroid nodules occurring in 6 per cent of the female population and 1.5 per cent of the male population.

Thyroid nodules are evaluated to determine:

- the likelihood of malignancy
- the likelihood that the nodule is the cause of symptoms.

While thyroid nodules are extremely common, thyroid cancer is a lot less common. Most patients with thyroid nodules do not have cancer. Ultrasound detects thyroid nodules in 19 to 67 per cent of the population, with 5 per cent being malignant.

Thyroid nodules in children are less common and more likely to be cancerous when compared with thyroid nodules in adults. About 20 per cent of solid thyroid nodules in children are cancerous, compared with only 5 per cent of thyroid nodules in adults.

Thyroid cancer

Thyroid cancer accounts for 1 per cent of all cancers in New Zealand, the incidence is 13 cases per 100,000 persons per year, and about one in 100 people develop thyroid cancer over the course of their lifetime. It is three times more common in women.

There are four main types of thyroid cancer:

- Papillary thyroid carcinoma is the most common type of thyroid cancer and has a tendency to spread to lymph nodes. With good treatment, it has an excellent prognosis. However, several variants of papillary thyroid carcinoma (tall cell, columnar cell, hob nail, diffuse sclerosing, solid, and telomerase reverse transcriptase promoter variants) have a worse prognosis.
- Follicular thyroid carcinoma is the second most common type of thyroid cancer. Even though it may spread to the lungs, it also has an excellent prognosis.
- Medullary thyroid carcinoma is less common. It sometimes runs in families and has an intermediate prognosis. Serum calcitonin is a very useful marker to diagnose medullary thyroid carcinoma and to assess response to treatment.
- Anaplastic thyroid carcinoma is a very aggressive thyroid carcinoma with very poor prognosis.

Other less common types of thyroid cancer include primary lymphoma of the thyroid, squamous cell carcinoma of the thyroid and others.

Red-flag symptoms

Most thyroid cancers only present as a thyroid nodule. Only the more advanced or aggressive thyroid cancers have red-flag symptoms.

Thyroid nodules associated with any of the following require urgent referral:

- rapid growth of the thyroid nodule/mass

The Thyroid Imaging, Reporting and Data System

Composition (select 1)	Echogenicity (select 1)	Shape (select 1)	Margin (select 1)	Echogenic foci (select all that apply)
• **Cystic or almost completely cystic:** 0 points • **Spongiform:** 0 points • **Mixed cystic and solid:** 1 point • **Solid or almost completely solid:** 2 points	• **Anechoic:** 0 points • **Hyperechoic or isoechoic:** 1 point • **Hypoechoic:** 2 points • **Very hypoechoic:** 3 points	• **Wider than tall:** 0 points • **Taller than wide:** 3 points	• **Smooth**: 0 points • **Ill-defined:** 0 points • **Lobulated or irregular**: 2 points • **Extra-thyroidal extension:** 3 points	• **None or large comet-tail artifacts:** 0 points • **Macrocalcifications:** 1 point • **Peripheral (rim) calcifications:** 2 points • **Punctate echogenic foci**: 3 points

Add points from all categories to determine TI-RADS level

TR1	TR2	TR3	TR4	TR5
0 points **Benign** No FNA No follow-up	**2 points** **Not suspicious** No FNA No follow-up	**3 points** **Mildly suspicious** FNA if ≥2.5cm Follow if ≥1.5cm	**4–6 points** **Moderately suspicious** FNA if ≥1.5cm Follow if ≥1cm	**≥7 points** **Highly suspicious** FNA if ≥1cm Follow if ≥0.5cm

Adapted from *Tessler et al, 2017*

Thyroid nodules

Symptoms

Generally, the larger the thyroid nodule, the more likely it is to cause compressive symptoms, such as a feeling of pressure, tightness or a lump in the neck. Thyroid nodules frequently do not cause any symptoms, particularly those less than 2cm in size.

The position of a nodule within the thyroid may also contribute to symptoms. Some experts believe nodules in the posterior part of the thyroid are more likely to cause a globus-type feeling of something in the throat than a similar sized nodule in the anterior part of the thyroid.

If a nodule gets very large, it may cause compression of the trachea, resulting in shortness of breath on exertion and when lying down. Large thyroid nodules may also cause superior vena cava syndrome, with restriction of venous drainage from the head and neck. This is most noticeable when the arms are raised in such activities as hanging out the washing. Patients may go red in the face when doing such activities (positive Pemberton sign).

> “The position of a nodule within the thyroid may also contribute to symptoms”

Investigations

The main goal in evaluating a patient with a thyroid nodule is to determine whether their nodule is cancerous. To do so, ultrasound and fine-needle aspiration (FNA) cytology of suspicious thyroid nodules are the mainstays of investigation.

Thyroid function tests

Occasionally, thyroid nodules become autonomous (also referred to as “toxic” or “hot”) and produce too much thyroid hormone, resulting in hyperthyroidism (anxiety, difficulty concentrating, fatigue, tremor, heat intolerance, etc). A toxic multinodular goitre contains one or more nodules that are no longer under control of thyroid-stimulating hormone (TSH). A suppressed TSH and normal free thyroxine (fT4) level (compensated hyperthyroidism) is often the first indication that a multinodular goitre or thyroid nodule is becoming autonomous.

Thyroid function tests should be requested for all patients with a suspected nodule in the thyroid gland. Most patients will be euthyroid. If a patient is hyperthyroid, referral to an endocrinologist and/or starting them on carbimazole is usually appropriate. A radionuclide thyroid scan can be helpful in elucidating the function of the nodule(s).

Patients with normal thyroid function tests are sometimes surprised when the diagnosis of papillary thyroid carcinoma is made as they may believe a normal thyroid function test means they will not have thyroid cancer. This is not true. Neither is it true that patients with hyperthyroidism do not have thyroid cancer, although thyroid cancer is very uncommon in patients with thyroid nodules and hyperthyroidism.

Ultrasound scans

An ultrasound scan is required for all suspected thyroid nodules. It is used to categorise thyroid nodules according to the Thyroid Imaging, Reporting and Data System (TI-RADS) developed by the American College of Radiology.[1,2] The risk of malignancy increases with a higher TI-RADS classification, as follows:

- TR1 – 0.3 per cent
- TR2 – 1.5 per cent
- TR3 – 4.8 per cent
- TR4 – 9.1 per cent
- TR5 – 35 per cent.

TI-RADS categorises nodules according to their composition (eg, solid, cystic), echogenicity (eg, hypoechoic, isoechoic), shape, margin and echogenic foci (calcification). Points are given for each of these characteristics to determine the TR level. For example, calcification is divided into three categories: coarse calcification (1 point), rim calcification (2 points) and microcalcification (punctate echogenic foci; 3 points). Punctate echogenic foci are commonly seen in thyroid malignancy and need to be distinguished from comet-tail artefacts that are associated with benign colloid nodules.

Recommendations for FNA and ultrasound surveillance are made depending on the size of the thyroid nodule and its TI-RADS classification. For example, FNA is recommended for a 1.5cm TR4 nodule, while ultrasound surveillance is recommended for a 2cm TR3 nodule. A 4cm TR2 nodule requires no follow-up. It is important to remember these recommendations are for asymptomatic euthyroid patients.

The figure above gives a good overview of TI-RADS and recommendations for subsequent management.

Ultrasound-guided FNA

It is recommended that FNA of thyroid nodules is performed under ultrasound guidance. Multiple studies have shown a lower non-diagnostic rate with ultrasound-guided FNA compared with freehand FNA, even for thyroid nodules that are easily palpable.

FNA cytology results are classified according to the Bethesda System for Reporting Thyroid Cytopathology,[3] as shown in Table 1.

Molecular analysis

The American Thyroid Association (ATA) guidelines recommend three options for the management of patients with Bethesda III thyroid nodules:[4]

- diagnostic hemithyroidectomy (also called diagnostic thyroid lobectomy)
- close observation (with ultrasound)
- molecular analysis.

Approximately 10 per cent of thyroid FNAs are reported as Bethesda III (atypia of undetermined significance) and a further 10 per cent are

Table 1. **The Bethesda System for Reporting Thyroid Cytopathology**

Diagnostic category	Description	Risk of malignancy (%)
I	Non-diagnostic or unsatisfactory	12
II	Benign	2
III	Atypia of undetermined significance	16
IV	Follicular neoplasm	23
V	Suspicious for malignancy	65
VI	Malignant	94

Table 2. **Effectiveness of molecular testing techniques for diagnosis of malignancy when thyroid nodules have indeterminate cytology**[5–8]

	Sensitivity (%)	Specificity (%)	Negative predictive value (%)	Positive predictive value (%)
Afirma	97	88	99	65
Idylla ThyroidPrint	92	82	96	66
ThyroidPrint	91	88	95	78
ThyroSeq	94	82	97	66

reported as Bethesda IV (follicular neoplasm), but only about 16–23 per cent of these patients actually have thyroid cancer.[2] However, it is common practice to offer surgery to patients with Bethesda III and IV cytology, in the form of a diagnostic hemithyroidectomy. Although this approach detects and treats thyroid cancer in 16–23 per cent of people in this category, 77–84 per cent of people have an operation with no or little therapeutic benefit.

To help further determine which patients are more likely to have cancer, molecular analysis of FNA specimens can be performed by testing the DNA and RNA of the cells obtained. These tests look specifically for mutations in genes associated with thyroid cancer.

The prevalence of some of the common genetic mutations are listed below.

Prevalence of genetic mutations in papillary thyroid carcinoma:
- *BRAF* – 45 per cent
- *RAS* – 15 per cent
- *RET/PTC* – 15 per cent.

Prevalence of genetic mutations in follicular carcinoma:
- *RAS* – 40 per cent
- *PAX8/PPARg* – 40 per cent.

In the US, Afirma and ThyroSeq are two of the common molecular tests that look at genetic mutations in thyroid cancers. Afirma looks at 593 genes associated with thyroid cancer. Using Afirma, two-thirds of patients with Bethesda III and IV nodules are reclassified as benign.

ThyroSeq looks at 112 genes associated with thyroid cancer. Similarly, ThyroSeq is able to stratify patients with Bethesda III and IV nodules into low, intermediate and high risk of having thyroid cancer. Low-risk patients can be observed. Hemithyroidectomy is recommended for intermediate-risk patients, and total thyroidectomy is recommended for high-risk patients with aggressive types of thyroid cancer.

593 genes associated with thyroid cancer

In New Zealand, ThyroSeq molecular analysis is available, but only if the FNA specimens are sent to Sullivan Nicolaides Pathology in Brisbane, which in turn sends them to Sonic Healthcare in New York, US. The turnaround time is about four to seven weeks, and the cost to the patient is approximately $2300, which is not covered by health insurance.

In the near future, Idylla ThyroidPrint molecular analysis of FNA specimens of thyroid nodules will be available in New Zealand, with results available in 24 hours. Idylla ThyroidPrint looks at 10 epithelial and stromal cell target genes associated with thyroid cancer. It stratifies risk into low (observe) and high (operate).

Table 2 shows the diagnostic performance of different molecular tests.[5–8] It is important to realise that as the prevalence of a disease increases in a population, the positive predictive value increases and the negative predictive value decreases.

In summary, molecular analysis of FNA specimens is a useful adjunct in the evaluation of thyroid nodules for malignancy, which needs to be considered alongside the history, examination findings, thyroid function tests, ultrasound findings and FNA cytology. It is particularly useful when deciding the most appropriate management strategy for patients with indeterminate cytology (Bethesda III and IV) and may reduce the number of diagnostic hemithyroidectomies performed.

Key points

- Urgently refer patients with thyroid nodules if there is rapid growth of the nodule, hoarse voice or lymphadenopathy.
- Patients with palpable thyroid nodules require thyroid function tests (TSH and fT4 levels) and a thyroid and neck ultrasound to determine the TI-RADS level.
- Patients with TR3 nodules ≥2.5cm, TR4 nodules ≥1.5cm and TR5 nodules ≥1.0cm require ultrasound-guided fine-needle aspiration to determine the Bethesda category.
- Bethesda III nodules are frequently treated surgically, Bethesda IV nodules are usually treated surgically, and Bethesda V and VI nodules are always treated surgically (with rare exceptions).
- Patients with Bethesda III or IV nodules are suitable candidates for molecular testing; if they are then deemed low risk, they may be followed with serial ultrasounds.
- Benign symptomatic thyroid nodules may be treated with either thyroidectomy or radiofrequency ablation.
- Patients with thyroid cysts are treated with aspiration; if the cyst recurs, they are good candidates for ethanol ablation.

Special populations

Pregnancy – thyroid nodules and goitres may grow significantly during pregnancy, and in some cases, cause airway obstruction by compressing the trachea. Thyroid nodules in pregnancy are evaluated the same way as in non-pregnant people – with thyroid function tests, an ultrasound and an ultrasound-guided FNA for selected nodules. Obviously, radionuclide thyroid scans are not performed during pregnancy.

Thyroid nodules in the setting of a multinodular goitre – an ultrasound scan in a patient with a goitre involving both thyroid lobes may be reported as showing multiple nodules. Some of these nodules may meet criteria for FNA due to their size and TI-RADS classification. If the patient is symptomatic, there is little to be gained by performing an ultrasound-guided FNA if they are to undergo surgery anyway (discussed below).

Treatment

Thyroxine

Most patients with thyroid nodules are euthyroid (normal TSH and fT4). The treatment of thyroid nodules with thyroid hormone (thyroxine; ie, TSH suppressive therapy) is not recommended in euthyroid patients. Both the ATA and the European Thyroid Association guidelines for thyroid nodule management recommend that

Advances in management

- Molecular analysis of thyroid nodules has reduced the number of patients needing surgery.
- Ethanol ablation for cystic thyroid nodules and radiofrequency ablation for selected solid thyroid nodules are now acceptable alternatives to surgery.
- The treatment of thyroid cancer is more selective than it was 20 years ago.

patients with benign thyroid nodules should not be treated with thyroxine.[4,9] The ATA guidelines state, "Though modest responses to therapy can be detected, the potential harm outweighs benefit for most patients."[4]

Hyperthyroidism

Patients with thyroid nodules and hyperthyroidism (low TSH and high fT4) are initially treated medically, usually with carbimazole.

Operating on hyperthyroid patients is contraindicated due to the risk of a thyrotoxic storm (tachycardia, hypertension, heart failure, arrythmias, high temperature, severe agitation, etc) and the mortality associated with this. Once the hyperthyroidism is under control, they may be considered for surgery.

An autonomously functioning thyroid nodule may be treated with radioactive iodine, hemithyroidectomy or radiofrequency ablation (RFA). A toxic multinodular goitre is best treated with total thyroidectomy.

Thyroidectomy

Patients with significant compressive symptoms usually benefit from surgery, no matter what the TI-RADS and Bethesda classifications of the thyroid nodule are.

Asymptomatic patients with thyroid nodules are treated along the following guidelines:

- **Bethesda I** – consider ultrasound-guided core needle biopsy and treat according to result.
- **Bethesda II** – no treatment.
- **Bethesda III** – consider molecular testing and surgery (especially if high TI-RADS level). Some patients may elect to be followed with serial ultrasound examinations.
- **Bethesda IV** – usually offered surgery.
- **Bethesda V** – surgery.
- **Bethesda VI** – surgery.

Thyroidectomy may involve removing either half (hemithyroidectomy/thyroid lobectomy) or all (total thyroidectomy) of the thyroid. If half the thyroid is removed, it is very uncommon to need thyroid hormone replacement therapy.

Hypocalcaemia due to damage to the parathyroid glands or their blood supply, causing hypoparathyroidism, may occur after total thyroidectomy. Hypocalcaemia is not seen after hemithyroidectomy.

Risks of thyroid surgery include injury to the recurrent laryngeal nerve, resulting in voice change if unilateral and a tracheostomy if bilateral. Injury to the external branch of the superior laryngeal nerve will result in change in pitch of the voice. Postoperative bleeding will result in a return to theatre. Nearly always, the incision heals well, although occasionally a hypertrophic scar may develop.

Radiofrequency ablation

Most doctors are familiar with thyroidectomy, but many are not aware of the option of RFA, which is an effective, approved treatment for some patients with thyroid nodules.

RFA is a non-surgical, scarless procedure performed under local anaesthesia as an outpatient procedure. A 19-gauge radiofrequency probe is inserted into the targeted nodule under ultrasound guidance. Using a "moving shot" technique, all areas of the nodule are targeted. Hydrodissection may be performed at the same time to create a fluid barrier between the nodule and any important structures.

The radiofrequency causes ions within the tissue to oscillate, which results in heating of the targeted tissue to 60°C. This heat is sufficient to cause necrosis of the targeted tissue. Over the subsequent few months, the thyroid nodule shrinks dramatically in size.

All patients require the following investigations before RFA: thyroid function tests, ultrasound scan of the thyroid, and FNA of the thyroid nodule.

Not all thyroid nodules are suitable for RFA. Benign thyroid nodules that are causing symptoms, such as a feeling of pressure in the lower neck or of a lump in the throat, are suitable for this procedure, preferably if they are less than 6cm in size. Some patients with benign thyroid nodules may choose RFA for cosmetic reasons. Thyroid nodules that are making too much thyroid hormone (autonomously functioning thyroid nodules) are very suitable for RFA. Very small thyroid cancers measuring less than 1cm in size (called microcarcinomas) are also suitable for RFA.[10,11]

> "Patients with significant compressive symptoms usually benefit from surgery, no matter what the TI-RADS and Bethesda classifications of the thyroid nodule are"

An advantage of RFA is that only the thyroid nodule is treated. There is no damage to adjacent thyroid tissue and thyroid tissue is not removed. Therefore, there is no need to take thyroid hormone tablets after the procedure.

Another advantage is the fast recovery time. Patients with an office-based job can return to work the following day. Patients who do heavy manual work can return to work two days after the procedure. Following RFA, there may be some discomfort, which is easily managed with paracetamol and ibuprofen.

Ethanol ablation

Ethanol ablation is the treatment of choice for thyroid cysts, which are usually benign nodules that have filled with fluid. The European Thyroid Association guidelines recommend ethanol ablation as the first-line treatment for pure cysts or dominantly cystic thyroid lesions.[9] The ATA guidelines state "recurrent cystic thyroid nodules with benign cytology should be considered for surgical removal or percutaneous ethanol injection based on compressive symptoms and cosmetic concerns".[4]

Most (80 per cent) of thyroid cysts recur after aspiration, while over 90 per cent of thyroid cysts do not recur after drainage and ethanol ablation.

Ethanol ablation is performed under local anaesthetic and ultrasound guidance. Patients with an office job can return to work the same day. Patients who do heavy manual work can return to work the following day.[12]

Treatment of thyroid cancer

Differentiated thyroid carcinoma is the term given to encompass both papillary thyroid carcinoma and follicular thyroid carcinoma. The ATA has guidelines on the treatment of DTC,[4] which are generally followed in New Zealand. These guidelines tend to be updated every five to 10 years, with an update expected this year.

The 2009 ATA guidelines divided patients with DTC into a three-tiered risk system: low, intermediate and high risk. In the 2015 guidelines, this three-tiered risk system was further described as a continuum of risk.[4,13]

Patients with DTC are discussed at a thyroid multidisciplinary meeting and treatment recommendations are made. Twenty years ago, nearly all patients with DTC were treated with total thyroidectomy, radioactive iodine and a suppressive dose of thyroxine. Nowadays, treatment of DTC is more selective and guided by the level of risk.

Many patients are now treated with hemithyroidectomy and without either radioactive iodine of a suppressive dose of thyroxine. Of course, patients treated with a hemithyroidectomy avoid the need to take thyroxine and the potential complication of hypocalcaemia. Patients with DTC and involvement of cervical nodes require a neck dissection in addition to total thyroidectomy.

Patients with DTC treated with total thyroidectomy need thyroid hormone replacement therapy. The dose of thyroxine is monitored with serial TSH and fT4 measurements. The target level of TSH is determined by the risk stratification of the patient and is usually determined by the patient's endocrinologist. The target TSH level for the lowest-risk patients is 0.5–2.0mU/L (low end of normal range), and for the highest risk patients, it is <0.1mU/L.

Patients with DTC are followed clinically and with ultrasound. Patients with DTC treated with total thyroidectomy are also followed with tests for serum thyroglobulin and thyroglobulin antibodies. The thyroglobulin level is interpreted in conjunction with the TSH level (stimulated or unstimulated thyroglobulin level). With good treatment, patients with DTC usually have an excellent prognosis.

The ATA has separate guidelines for the treatment of medullary thyroid carcinoma. Patients with medullary thyroid carcinoma are generally treated with total thyroidectomy and central neck dissection with or without lateral neck dissection. In addition to clinical and radiological follow-up, serial calcitonin measurement is an important part of follow-up. Usually, medullary carcinoma has a less favourable prognosis than DTC.

Finally, the ATA has separate guidelines for the treatment of anaplastic thyroid carcinoma. This has the least favourable prognosis of the four main types of thyroid carcinoma, with very few people achieving long-term survival. ■

The references for this article are available with the online version on nzdoctor.co.nz

Quiz answers

1. True **2.** True **3.** False **4.** False