# Investigating a thyroid lump

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*This section uses case scenarios to educate doctors on the best approach to the diagnosis and management of patients with different endocrine problems. The appropriate selection of tests and correct interpretation of test results are discussed.*

Thyroid nodules are very common in the adult population, being detected by thyroid ultrasonography in up to 50% of women and about 10% of men. The prevalence increases with age in both sexes. Factors implicated in the pathogenesis of thyroid nodular disease include iodine deficiency, growth disorders and genetic factors such as mutations affecting the thyroid stimulating hormone (TSH) receptor. The vast majority of thyroid nodules are benign.

The detection rate of thyroid cancer has doubled over the past few years. This may reflect greater use of real-time thyroid ultrasonography, early diagnosis of suspicious nodules and probably overdiagnosis of small in-situ carcinomas, but some recent studies suggest that there has been a true increase in the prevalence of significant thyroid cancers.[1] It is important for GPs to have a clear approach to the investigation of thyroid nodules. Selection of investigations and interpretation of results are illustrated by the following four cases.

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**Case 1.** **A 27-year-old man presents with a neck swelling associated with voice hoarseness, neck discomfort and fatigue. He has no family history of thyroid autoimmune or nodular disease or other autoimmunity**

***How would you investigate this patient?***

Thyroid nodular disease is often asymptomatic but possible symptoms include awareness of a lump, difficulty sleeping because of pressure on the trachea, difficulty swallowing or breathing, hoarse voice, neck pain and occasionally obstruction of the trachea. Most patients who undergo surgery for multinodular disease do so because of symptoms rather than suspected thyroid cancer.

Thyroid ultrasonography is indicated for all patients who have: a palpable thyroid nodule; symptoms such as thyroid pain, hoarse voice or airway obstruction; or known multinodular disease. Patients should also have a thyroid function test. Nodules larger than 1 cm on ultrasound examinaton should be investigated with a fine needle aspiration (FNA) biopsy. Smaller nodules should also be biopsied if they have features suggesting malignancy (Box 1 and Box 2).

The patient was referred for thyroid ultrasonography, which showed a single 3.5 x 2.5 x 2.0 cm nodule in an otherwise normal thyroid gland (Figure 1). Thyroid function testing showed he had normal levels of TSH, free thyroxine (T4) and free triiodothyronine (T3). He was negative for thyroid antibodies. An ultrasound-guided FNA biopsy revealed that the nodule was a Hürthle cell neoplasm.

***How should the patient be managed?***

Hürthle cell neoplasms comprise at least 75% oncocytic or Hürthle cells. These cells can be found in thyroid adenomas, carcinomas and other thyroid conditions, including Hashimoto thyroiditis. However, the last is unlikely in this patient because of his normal thyroid function, negative thyroid antibody result, and lack of family history of thyroid or autoimmune disease. It is impossible to differentiate between Hürthle cell cancer and a benign Hürthle cell tumour from cytological findings. This distinction is made at surgery depending on whether there is evidence of capsular or vascular invasion.[2] About 20% of Hürthle cell tumours are malignant.

The patient underwent thyroid lobectomy. No abnormal lymph nodes were found at surgery and final histological examination showed a benign Hürthle cell tumour. The patient was regarded as cured of the disease and needed no follow up except thyroid function tests a few weeks after surgery because hypothyroidism may occasionally develop.

***What is recommended management for nodules considered benign at biopsy?***

If a thyroid nodule is considered benign based on FNA biopsy findings then it would be appropriate to repeat an ultrasound examination in six to 18 months as per the American Thyroid Association (ATA) guidelines.[3] If the nodule is stable in size then the interval between further reviews can be extended. If there has been a significant size increase (e.g. more than 20 to 30%) or other suspicious changes (see Box 1) then the nodule should be re-biopsied. A pathologist may recommend repeat FNA biopsy within three to six months.

An atypical finding in two or more biopsy specimens is an indication for surgical

**1. Ultrasound findings that raise suspicion of thyroid cancer**

- The nodule is taller than it is wide
- Hypoechoic
- Microcalcification (highly specific for papillary thyroid cancer)
- An eroded broken irregular edge suggesting invasion
- Increased blood supply suggesting feeding vessels
- Single nodule in a man, particularly an older man
- Rapid growth of the nodule over a 6-month period
- Eggshell calcification with gaps (may indicate invasion into the thyroid tissue)

**2. Approach to investigating a thyroid nodule[3]**

- **Size:** Nodules > 1 cm should be investigated. Nodules < 1 cm should also be investigated if there is a high suspicion of malignancy on history, examination and ultrasound investigation
- **History:** Risk factors include head, neck or total body irradiation, family history of thyroid cancer or thyroid cancer syndrome in a first-degree relative (e.g. multiple endocrine neoplasia 2), rapid nodule growth and hoarse voice
- **Examination:** Vocal cord paralysis, cervical lymphadenopathy laterally and nodule fixation are suspicious features
- **Investigate with TSH assay:** If TSH level is below normal then consider a thyroid radionuclide uptake scan to identify whether the nodule is hyperfunctioning (low malignancy risk and no need to biopsy) or nonfunctioning (requiring consideration of fine needle aspiration biopsy depending on size and suspicious sonographic features).
- **Thyroid ultrasound examination:** To further assess risk
- **Fine needle aspiration biopsy:** Bethesda category of biopsy specimen guides further management

Abbreviation: TSH = thyroid stimulating hormone.

management. There is controversy as to whether surgery is required for Bethesda category III cytology results, but most clinicians would recommend surgery for all cytological categories from IV down (see Box 3 for definitions of Bethesda diagnostic categories).

**Case 2. A 28-year-old woman with a recent history of goitre and low levels of thyroid peroxidase antibodies (59 IU/L) but normal thyroid function (TSH, 1.35 mIU/L; free T4, 14.5 pmol/L; free T3, 4.1 pmol/L) is referred to a thyroid specialist for further management. The thyroid is very large and firm on palpation, particularly in the central region (isthmus).**

***How should this patient be investigated?***

The presence of an enlarged firm thyroid and thyroid peroxidase antibodies in this patient suggests a diagnosis of Hashimoto thyroiditis. The prevalence of thyroid cancer may be increased in patients with Hashimoto thyroiditis, possibly reflecting increased cell turnover due to the autoimmune reaction.[4,5] Studies of cancer prevalence in patients with Graves disease have had conflicting results.[6] A case could be made that thyroid ultrasound examination should be routine in the assessment of all patients with thyroid disease.

In this patient, real-time thyroid ultrasonography showed the classic changes of medium to late stage Hashimoto thyroiditis, with cystic changes throughout the gland, overall thyroid enlargement and reduced vascularity (use of real-time ultrasonography is outlined in Box 4). An ultrasound examination performed at an external centre reported that the central area was suggestive of 'focal thyroiditis'.

Because of clinical concern about the possibility of thyroid cancer in the central firmer area of the gland and suspicious ultrasound features (markedly hypoechoic area with an irregular edge, no halo and scattered bright microcalcifications; see Figure 2), an ultrasound guided FNA biopsy was performed of the central area. The cytological appearance was described as consistent with Hashimoto thyroiditis with no malignant or suspicious cells (Bethesda category II).

***How should the patient be managed?***

As the patient had proven Hashimoto thyroiditis, with widespread thyroid tissue loss and inflammatory changes, she was treated with low-dose thyroxine. A thyroid technetium uptake scan was not indicated, as the TSH level was normal.

At follow up three months later, the central area of the thyroid gland was increasingly hard on palpation. FNA biopsy was repeated on the side of the central area that felt hardest and looked most abnormal on ultrasound examination; the cytological appearance suggested the diffuse sclerosing variant of papillary thyroid cancer (Bethesda category V).[7] The failure of the first FNA biopsy to detect any pathology besides Hashimoto thyroiditis presumably reflected the site of the biopsy, which was in an area of typical thyroiditis rather than in the cancer.

Following the second FNA biopsy result, a total thyroidectomy was performed. The ATA suggests preoperative assessment of cervical lymph nodes with ultrasound and possible FNA biopsy.[3] In this patient, cervical ultrasound did not reveal any abnormal lymph nodes.

At surgery, there was a large 33 mm tumour mass abutting the thyroid capsule over a 6 mm distance, some invasion of the lymphovascular space close to the surgical margin, small foci of tumour scattered throughout the thyroid and focal extrathyroidal extension, but the tumour did not involve the skeletal muscle. Ten clinically enlarged lymph nodes were removed. Histological examination of the thyroid and all lymph nodes confirmed the diagnosis of a diffuse sclerosing papillary cancer. All 10 lymph nodes showed metastatic papillary carcinoma. There were also changes of Hashimoto thyroiditis, including large interstitial lymphoid aggregates containing prominent germinal centres, throughout the gland.

The surgical management of thyroid cancer varies across different centres and according to tumour characteristics; generally the ipsilateral central (level VI) lymph nodes are cleared and lateral lymph nodes are removed when they are found to be clinically enlarged.

Aggressive variants of papillary cancer such as nodular sclerosing papillary cancer have a worse prognosis and are more likely to metastasise and less likely to respond to radioactive iodine ablation, but overall survival remains good. The patient was therefore treated with iodine-131 at a dose of 4 GBq.

***What is the management after thyroid removal to treat thyroid cancer?***

The patient began taking thyroxine immediately after thyroidectomy and was then treated with radioactive iodine after thyrotrophin-alfa preparation to ablate any remnant thyroid cells.

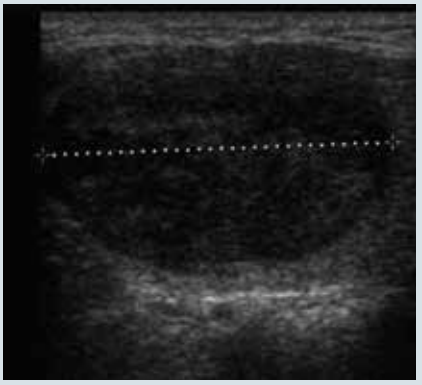

**Figure 1. Single solid hypoechoic nodule in its longitudinal dimension (Case 1). Benign nodules grow along the growth planes of the thyroid whereas malignant nodules expand in all directions, including against the tissue planes.**

**Figure 2. Large suspicious nodular area with an irregular isoechoic edge (arrow) in the central thyroid isthmus in a patient with Hashimoto thyroiditis (Case 2).**

In the past, radioablation of remnant thyroid cancer cells was undertaken after thyroid removal when the TSH level rose above 30 to 35 mIU/L. This required all patients to become hypothyroid, with associated morbidity, economic loss and complications such as depression. Recombinant human TSH (thyrotrophin-alfa) was developed to avoid this requirement. It is PBS listed for use in combination with radioactive iodine in the ablation of remnant thyroid cells in adults post-thyroidectomy without known metastatic disease. Most patients are now treated with thyroxine immediately after thyroidectomy and then with radioactive iodine after thyrotrophin-alfa preparation.

***How should the patient be monitored?***

When the thyroid has been removed by total thyroidectomy and/or radioablation, and no normal or abnormal thyroid cells persist in the body, the serum thyroglobulin level falls to undetectable levels (less than 0.9 µg/L). Serum thyroglobulin level can thus be used to detect residual or recurrent thyroid cancer. ATA guidelines recommend monitoring of serum thyroglobulin every six to 12 months as well as cervical ultrasound examination. A high-sensitivity thyroglobulin assay is available with a functional sensitivity of 0.9 µg/L. It is important to confirm that the patient is negative for thyroglobulin antibodies, as these can cause a false negative thyroglobulin result.

Thyroglobulin levels fall over a period of several months after thyroid removal but can remain elevated for up to six months. A low-dose surveillance diagnostic scan to detect disease recurrence is therefore not performed until nine to 12 months after iodine-131 treatment, at which time thyroglobulin levels are expected to be undetectable. Persistent or increasing levels of thyroglobulin, even if in the low range (e.g. 2 to 4 µg/L), suggest residual or recurrent thyroid cancer locally in the thyroid bed, in the neck or elsewhere. This is an indication to repeat a whole body scan to check for nonphysiological radioiodine uptake, which would confirm the presence of thyroid tissue. If the scan is positive, it is appropriate to consider a second iodine-131 treatment.

In this patient, serum thyroglobulin remained undetectable (less than 0.9 µg/L), and a neck ultrasound examination at six months post-operatively appeared normal. A whole body diagnostic surveillance scan one year after radioiodine treatment also appeared normal, and the patient remained well and disease-free.

There is anecdotal evidence that diffuse sclerosing papillary cancer tends to run in families, and the patient's parents and one of her two brothers were investigated. Interestingly, her father had a large suspicious nodule, which appeared on FNA biopsy to be a benign colloid nodule; this was confirmed at hemithyroidectomy.

***Case 3.*** **A 40-year-old man with hepatitis C treated with interferon beta is referred to an endocrine clinic with a diagnosis of 'thyrotoxicosis' caused by the interferon (type 1 interferons can cause autoimmune diseases because of their immunomodulator effect). The patient has no family history of thyroid disease or autoimmunity, and the hepatitis C virus had been eliminated.**

**He has typical symptoms of hyperthyroidism; thyroid function tests show increased free T4 and free T3 levels and a suppressed TSH level. Tests are negative for thyroid antibodies and TSH receptor antibodies. The patient has no eye signs of Graves disease or other extrathyroid manifestations.**

### 3. Bethesda system for reporting thyroid cytopathology results: recommended diagnostic categories

**I. Nondiagnostic or unsatisfactory**
Cyst fluid only, virtually acellular specimen, other (e.g. obscuring blood, clotting artefact)

**II. Benign**
Includes adenomatoid nodule, colloid nodule, lymphocytic (Hashimoto) thyroiditis in the proper clinical context, or granulomatous (subacute) thyroiditis

**III. Atypia of undetermined significance or follicular lesion of undetermined significance**

**IV. Follicular neoplasm or suspicious for a follicular neoplasm**
Specify if Hürthle cell (oncocytic) type

**V. Suspicious for malignancy**
Suspicious for papillary carcinoma, medullary carcinoma, metastatic carcinoma, lymphoma or other

**VI. Malignant**
Papillary thyroid carcinoma, poorly differentiated carcinoma, medullary thyroid carcinoma, anaplastic carcinoma, squamous cell carcinoma, carcinoma with mixed features (specify), metastatic carcinoma, non-Hodgkin lymphoma or other

### 4. Real-time ultrasonography

Access to in-house 'real-time' ultrasound, on a portable machine, is routine for thyroid specialists in the USA and many parts of Europe but is uncommon in Australia. We consider that there are advantages to thyroid specialists having access to an ultrasound machine to perform their own imaging for thyroid assessment and to guide FNA biopsy, as long as they have expertise in neck ultrasound. Alternatively, patients can be referred to radiologists experienced in the management of thyroid patients. Other uses for real-time ultrasonography include staging of Hashimoto thyroiditis to help determine when thyroxine treatment is needed.


**Figure 3. A single hypoechoic nodule with a sharp edge and halo in a patient who developed hyperthyroidism during treatment with interferon beta (Case 3). The nodule was shown to be 'hot' on a technetium uptake scan.**

*How was this patient investigated and managed?*

Real-time ultrasonography did not show a diffuse goitre; however, a single large nodule with a sharp edge and halo was seen (Figure 3). The thyroid was otherwise normal. A thyroid technetium uptake scan showed that the nodule was 'hot', with suppressed uptake throughout the rest of the gland. FNA biopsy of the nodule was not indicated as the rate of nodular malignancy in these circumstances is negligible.

The patient was treated as an outpatient with low-dose radioactive iodine, which specifically targets the hot nodule; the rest of the gland is expected to return to normal function as the TSH level returns to the normal range. Subsequently, results of thyroid function tests remained normal. In our experience, it can take months to years for a 'hot' nodule to reduce in size.

***Case 4.*** **A 50-year-old woman with Graves disease presents for ongoing management following a relapse of hyperthyroidism. On examination, she has signs of thyroid eye disease and a moderately enlarged thyroid gland wth nodules detected on palpation. Real-time thyroid ultrasonography shows nodules of around 1.5 cm with suspicious features (hypoechoic texture, an irregular edge with no clear halo and surrounding feeding blood vessels) in each lobe (Figure 4). Tests for TSH receptor antibodies are positive. FNA biopsy of two nodules shows atypical features but no definite evidence of malignancy (Bethesda category III).**

**Figure 4. Hypoechoic nodule in the right lobe of the thyroid in a patient with Graves disease (Case 4). The nodule appeared suspicious on imaging and fine needle aspiration biopsy, but was benign on examination after surgery.**

*How was this patient managed?*

The patient was treated with carbimazole to control the hyperthyroidism and became euthyroid. Because of the suspicious features of the nodules, total thyroidectomy was considered a good option for further management of the Graves disease.

At surgery, a moderately enlarged, hypervascular nodular gland was removed, no abnormal lymph nodes were found, and the four parathyroid glands were identified and preserved. The patient was subsequently treated with thyroxine. Histological examination of the thyroid gland showed features of treated Graves disease as well as lymphoid nodules, some with germinal centres, generalised hyperplasia and three very small (1 to 2 mm) papillary cancers scattered through the gland.

It was considered that total thyroidectomy was curative as the small tumours were totally excised and there was no evidence for invasion in the gland or through the capsule. The suspicious nodules that had prompted surgery were presumed to be hyperplastic and nodular areas of inflammation in the gland.

*How should this patient be further managed?*

Radioactive iodine ablation was not offered to this patient as there is no evidence that it would improve her outcome. Six months after surgery, ultrasound examination of the neck revealed no abnormal lymph nodes, and the serum thyroglobulin level was less than 0.9 µg/L.

However, the patient remained very concerned about the possibility of cancer spread and whether she might have additional microcarcinomas in the remnant thyroid gland. She needed reassurance by regular ultrasound examination and measurement of serum thyroglobulin levels. If thyroglobulin levels increase to detectable levels or abnormal lymph nodes are found then radioactive iodine 'ablation' can be performed, although the chance is remote. There is a high rate of incidental papillary thyroid microcarcinomas, but in general they behave very indolently.

**5. Practice points**

- Thyroid nodules are common
- Investigation requires clinical assessment, thyroid function tests and ultrasonography
- Use of fine needle aspiration biopsy is guided by clinical and ultrasound-based suspicion of malignancy
- If the patient is hyperthyroid (low serum TSH level) then a thyroid radionuclide uptake scan is indicated
- Thyroid cytopathology drives further surgical or nonsurgical management
- Radioactive iodine ablation is undertaken when the patient is in a hypothyroid state or after thyrotrophin-alfa administration
- Serum thyroglobulin level is used to monitor disease recurrence
- Thyroid cancer prevalence may be increased in autoimmune thyroid disease

Abbreviation: TSH = thyroid stimulating hormone.

## Conclusion

Thyroid nodules are common and consequently it is important for GPs to have a clear approach to their investigation and management. Practice points are summarised in Box 5. Risk assessment is required with history taking, physical examination, initial thyroid function testing and imaging. Fine needle aspiration biopsy is often necessary, and further treatment will be guided by a thyroid specialist. GPs have an ongoing role in follow up of both benign and malignant thyroid nodules, as a change in clinical symptoms and signs or serum markers should prompt further review. **ET**

### References

A list of references is included in the website version (www.medicinetoday.com.au) of this article.

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