Assessment of nodular thyroid disorders

In this series, we present authoritative advice on the investigation of a common clinical problem, specially commissioned for family doctors by the Board of Continuing Medical Education of the Royal Australasian College of Physicians.

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Thyroid nodules are common. They have been reported in up to 60% of women aged over 50 years. Nonpalpable thyroid nodules are often identified incidentally when neck ultrasound is performed for other reasons. This review outlines the approach to nodular thyroid disorders where there is no obvious abnormality of thyroid function. The management of overt thyrotoxicosis due to nodular goitre is not considered here.

In contrast to the high prevalence of thyroid nodules, thyroid cancer is uncommon. In Australia, thyroid cancer is associated with an age-standardised mortality of only 0.2 to 0.3/100,000 person-years, a mortality that is 10-fold less than that for bladder or kidney malignancies and about 50-fold less than that for breast or lung cancers. On this basis, the nonselective surgical removal of thyroid nodules because they might be cancerous is inappropriate. It is notable that the high prevalence of occult thyroid cancer at autopsy is not reflected in mortality statistics; small occult thyroid carcinomas do not seem to shorten life. Nevertheless, patients still present with potentially fatal advanced thyroid cancer, and an earlier diagnosis would probably have been beneficial.

Assessing the risk of malignancy

The selection of patients with thyroid nodules who require surgery because of potential malignancy is based on clinical, laboratory, ultrasound, nuclear imaging and cytological criteria. Correlation of these investigations gives far more information than any technique alone. Not all thyroid nodules require all investigations. Several issues to consider in the assessment of patients with nodular thyroid disorders are noted in the box on page 51.

Clinical criteria

Thyroid malignancy is more likely in a patient who has a history of progressive enlargement of a nodule that is firm or hard in consistency.

IN SUMMARY

- **Thyroid nodules, single or multiple, palpable or impalpable, are common; thyroid cancer is uncommon and usually not fatal, with a mortality less than 2% of that of breast or lung cancer.**
- **Investigation of thyroid nodules begins clinically and is followed by a laboratory assessment of thyroid status.**
- **Imaging provides valuable information, but expert cytology from fine needle aspiration biopsy is the key investigation to define which thyroid nodules require surgical removal.**
- **The combination of fine needle aspiration biopsy with ultrasound yields better sensitivity and specificity than biopsy guided by palpation alone. Not all nodules require biopsy.**
- **Most patients with thyroid nodules require no active treatment.**
- **Optimal management of both nodular thyroid disease and thyroid carcinoma requires a multidisciplinary approach, including effective patient education.**

Lymphadenopathy or the rare signs of local invasion of trachea, oesophagus or recurrent laryngeal nerves are highly predictive of malignancy. Malignancy is more likely to develop in:

- males
- patients presenting with a thyroid problem at a young age
- those who had head and neck irradiation in childhood (individuals exposed to the Chernobyl disaster in early childhood are particularly at risk).

Clinical findings that suggest a low risk of malignancy include:

- soft spherical fluctuant nodules, which are suggestive of cysts
- multiple apparent nodules of normal consistency as part of a lobulated goitre (however, the dogma that malignancy is unlikely if there are multiple nodules is misleading, and each nodule needs to be assessed independently)
- sudden thyroid pain that is associated with a nodule, which is usually due to haemorrhage.

Laboratory blood tests

Assessment of thyroid status is indicated in any patient who presents with one or more thyroid nodules. Measurement of the serum thyroid stimulating hormone (TSH) level is the test of choice. Generally, malignant thyroid lesions show normal function, whereas the chance of malignancy is reduced in patients with subnormal or suppressed TSH. If the TSH level is low, nuclear imaging will indicate whether the nodule or nodules are the likely source of subtle thyroid hormone excess – that is, whether the patient has 'subclinical' hyperthyroidism. Active nodules generally do not require biopsy.

In patients with normal or raised TSH levels, measurement of the thyroid peroxidase antibody can be used to identify those with Hashimoto's (lymphocytic) thyroiditis. Hashimoto's thyroiditis is not malignant, and can present as a thyroid nodule. Affected patients typically have high titre thyroid peroxidase antibody. Nodules in Hashimoto's thyroiditis may regress with thyroxine treatment.

The value of routine serum calcitonin measurement to detect medullary thyroid carcinoma remains contentious, but its measurement is important in patients with an unusual goitre or in whom there is a family history of malignant thyroid tumour.

Serum thyroglobulin measurement has little value in establishing the nature of a thyroid nodule, but it is the key follow up assay after thyroid cancer has been treated.

Assessing patients with thyroid nodules: some key points

- The presence of multiple thyroid nodules is no guarantee against a diagnosis of thyroid carcinoma.
- Solid impalpable nodules less than 1 cm in diameter should not be ignored; serial detailed ultrasound can determine whether biopsy is indicated.
- Generally, patients with small occult papillary thyroid carcinomas (<0.5 cm diameter) that are found in thyroid glands removed for another reason require no follow up treatment.
- Although patients with microscopic thyroid carcinoma can present with distant metastases, it is not feasible to completely investigate all patients with thyroid nodules.
- Ultrasound examination is the least invasive technique used to investigate thyroid nodules, but serial comparison can be difficult. Storage of images on compact disc may identify whether solid nodules show progressive change.
- Research is continuing on developing serological, cytological and molecular biology techniques to improve the distinction between benign and malignant thyroid nodules; no current technique has adequate sensitivity and specificity.

Imaging

Ultrasonography

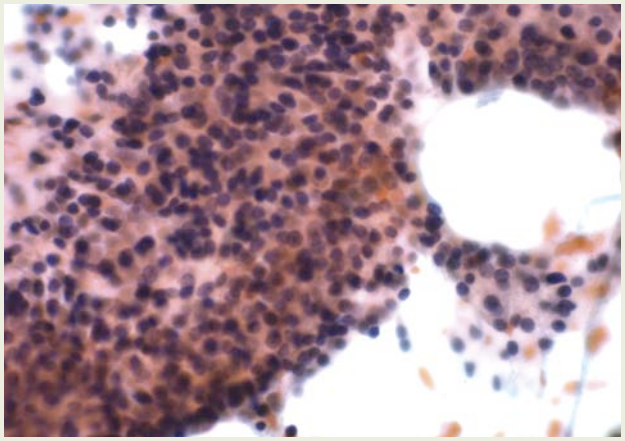
In addition to reporting nodule size and number, an ultrasound report of thyroid nodules should describe the echogenicity and vascularity of the lesion, and whether it is wholly or partly cystic, has distinct margins and shows calcification. Hypoechogenicity, microcalcification, irregular margins, an irregular halo and intranodular vascularity are features that suggest malignancy. Taken together, these findings are a strong indication for biopsy.

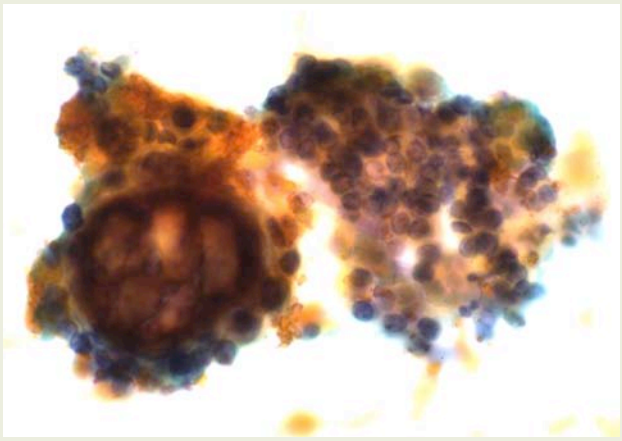
Detailed preoperative ultrasound has an increasing role in the assessment of potential lymph node metastases after the demonstration of malignant cytology. This information can influence the extent of neck dissection necessary at primary surgery.

Nuclear imaging

The finding of a 'cold' or nonfunctioning nodule on isotope imaging is often regarded as a marker

Examples of cytological findings from thyroid nodule biopsies





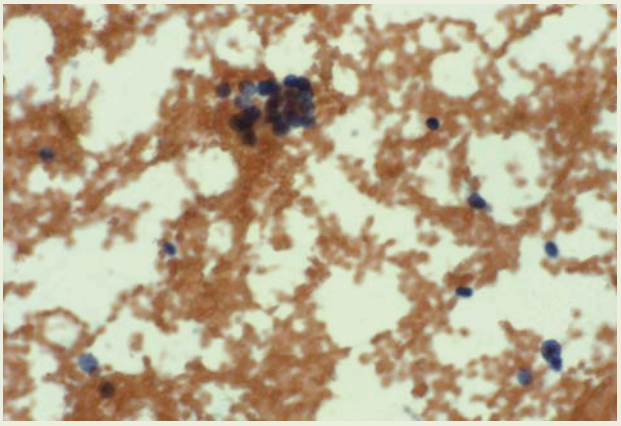


Figure 1 (above left). Hyperplastic nodule (Papanicolaou stain).

Figure 2 (above right). Highly cellular material, nuclear inclusions and grooves, and 'orphan Annie' nuclei indicate papillary carcinoma (Papanicolaou stain).

Figure 3 (left). Follicular carcinoma and benign follicular adenoma can have virtually identical cytology (Papanicolaou stain).

for possible malignancy, but cysts are also cold and usually benign. Classification of mixed solid–cystic nodules is less certain.

A benign multinodular goitre shows uneven function on isotope imaging, with greater isotope uptake in the nodules than in the surrounding tissue. In addition, the goitre may be overfunctioning, or the patient may have subclinical thyrotoxicosis, as confirmed by the finding of suppressed TSH level.

Cytology

A cold solid thyroid nodule should be examined cytologically to rule out malignancy. For clinically suspicious nodules, cytology is becoming the frontline investigation and there is a decreasing reliance on nuclear imaging as the first investigation. European studies suggest that fine needle aspiration biopsy, performed in combination with skilled ultrasound, is the investigation of choice. Use of these two techniques together ensures the biopsy is from the appropriate area, and immediate examination of the aspirate establishes whether there is adequate cellular tissue for testing. Compared with biopsy guided only by palpation, use of fine needle aspiration biopsy with ultrasound reduces the frequency of diagnostically inadequate samples, and adoption of this strategy in Australia has much to recommend it.

A cytological report should include a statement on the amount of cellular material examined, as well as a comment on cellular appearance. A report stating 'no evidence of malignancy' from insufficient cellular material can be misleading. Although a report of potential malignancy may be clear, it is less certain how much cellular material needs to be examined before a benign report is justified. However, the presence of at least six cellular clusters, each containing 10 to 15 cells, is becoming an established criterion.

A cytological sample in which there are regularly arranged cells, uniform nuclei and abundant colloid generally indicates a benign nodule (Figure 1). Such cytological

findings have substantially reduced the number of patients with thyroid nodules requiring surgery.

Papillary carcinoma can be diagnosed with a high degree of accuracy from its specific cytology (Figure 2). If the cytology is conclusive for papillary thyroid carcinoma, which may be multifocal, the treatment of choice is definitive near-total thyroidectomy.

In contrast, follicular carcinoma and benign follicular adenoma can show virtually identical cytology (Figure 3). When a distinction between the two cannot be made, hemithyroidectomy is the standard initial treatment, followed by completion of thyroidectomy if examination of the operative specimen shows follicular carcinoma (e.g. by the presence of capsular or vascular invasion). For patients with benign follicular adenoma, the initial hemithyroidectomy is generally regarded as curative.

After surgery

Depending on the definitive pathology, surgery for papillary or follicular carcinoma may be followed by radioiodine ablation. This is best carried out by withholding thyroxine for three to four weeks after surgery so that radioiodine uptake can be enhanced by a high level of endogenous TSH.

Patients should have been made aware before surgery for presumed thyroid carcinoma that they will most probably need lifelong thyroxine treatment. Thyroxine (Eutroxsig, Oroxine) is given either at replacement dosages or, in patients with high risk pathology, at a dosage sufficient to suppress TSH. The latter approach is generally used in patients after radioiodine ablation, at least until follow up investigations over the subsequent few years indicate successful ablation of all thyroid tissue.

Measurement of serum thyroglobulin, whole body nuclear imaging and, in some instances, positron emission tomography are the key techniques that establish whether all thyroid tissue has been ablated. These investigations are most sensitive when patients have temporary TSH excess; this is achieved by either thyroid hormone withdrawal or by giving recombinant TSH (Thyrogen).

General assessment of patients with nodular thyroid disorders

Apart from assessing the potential for thyroid cancer, the following issues need to be considered in patients with nodular thyroid disorders.

How can thyroid size be reduced medically?

Thyroxine treatment is most likely to reduce gland or nodule size if a patient's serum TSH is elevated or at the high end of normal; it is unlikely to be effective if TSH is already low or suppressed. A six-month trial of thyroxine at a dose sufficient to suppress TSH should be preceded by clinical and ultrasound assessment of thyroid size. If there is no response, thyroxine should be ceased.

Should 'subclinical' thyrotoxicosis be considered?

In patients with persistently suppressed TSH that is associated with nodular thyroid disease (that is, those with subclinical thyrotoxicosis, with normal free thyroxine [T_4] and free tri-iodothyronine [T_3] levels), radioiodine treatment should be considered before there is progression to overt thyrotoxicosis. Sustained subclinical thyrotoxicosis carries an increased risk of atrial fibrillation and has an adverse effect on bone density, especially in the elderly.

Does the thyroid mass pose any threat?

Difficulty in swallowing or respiratory distress, especially related to a change in position at night, can be important symptoms of an obstructive goitre. These features may not be obvious if the gland is predominantly retrosternal. A positive Pemberton sign (arms raised above the head) indicates venous obstruction. Tracheal narrowing on x-ray, rather than tracheal deviation, indicates obstructive potential. A CT scan (without contrast to avoid potential iodine-induced exacerbation of the thyrotoxicosis) will define the full extent of the gland, particularly the retrosternal and retrotracheal components. Near total thyroidectomy can provide dramatic relief. High dose radioiodine may be helpful when surgery is not feasible.

Summary

The effective management of patients with nodular thyroid disease and thyroid carcinoma is multidisciplinary. Optimal results are achieved by effective collaboration among the primary care practitioner, endocrinologist, radiologist, pathologist, surgeon, nuclear medicine physician and clinical chemist. Patient education, to facilitate follow up and monitoring of medication, remains a key feature of successful long term management. Patients should be encouraged to maintain a personal medical record, as follow up often extends beyond their period of contact with any one practitioner. MT

Further reading

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DECLARATION OF INTEREST: None.