Assessment and management of thyroid nodules in general practice

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Introduction

Thyroid nodules are a common clinical finding. Based on palpation the prevalence of thyroid nodules in the community is estimated to range from 3–7%, however with high resolution ultrasonography, thyroid nodules have been detected in up to 50% of people over 40 years of age.[1] Thyroid nodules are more common in women than in men. In iodine-replete areas, 6.4% of women and 1.5% of men have palpable thyroid nodules,[2] however in areas of iodine deficiency the prevalence of thyroid nodules may increase. Given the relatively high frequency of thyroid nodules, the general practitioner is often faced with the difficulty of how to manage these disorders. Numerous guidelines and reviews are available but most of them are too detailed to be useful in the primary care setting. This paper provides an overview, which incorporates the current international guidelines for the management of thyroid nodules and is relevant to general practice in New Zealand.

Differential diagnosis of thyroid swelling

The thyroid can be either diffusely enlarged or swollen because of nodular change. For the purpose of this paper we will focus on nodular disease. The main clinical concern is to (1) distinguish benign thyroid nodules from malignant neoplasm, and (2) assess whether the nodules are causing compressive symptoms. Thyroid nodules may be solitary or multiple – the presence of multiple nodules does not exclude malignancy. Solitary nodules are more common than multi-nodular goitres clinically and it used to be said that solitary nodules were more likely to harbour malignant disease.[3] More recently it has been found that the risk of cancer is the same in those with true solitary nodules confirmed at operation as those with multinodular goitres.[4]

Fortunately, the majority of thyroid nodules are benign. There are approximately 130–150 new registrations of thyroid cancer each year in New Zealand and 20 deaths; two-thirds of these in women.[5] The differential diagnoses of thyroid nodules include colloid nodules, simple or haemorrhagic cysts and thyroiditis (80% of cases); benign follicular neoplasms (10–15%); and thyroid carcinoma diagnosed in specialist practice (5%).[6]

Clinical assessment

A detailed history and examination is essential in guiding subsequent investigations. Most patients with thyroid enlargement have no symp-

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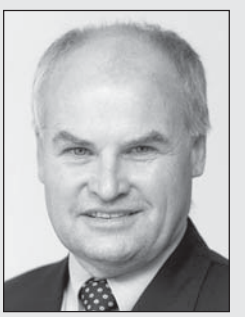

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toms other than a mass in the neck noticed by relatives or coincidentally discovered during medical evaluation. Some people will present with a history of thyroid dysfunction (either hypo- or hyperthyroidism), or a thyroid swelling that is enlarging with time. Nodular thyroid disease can cause compression of vital structures in the neck or chest and the symptoms can include dyspnoea, stridor, dysphagia, dysphonia or hoarseness. A history of pain or tenderness around the neck is usually suggestive of thyroiditis. Sudden pain in the neck is commonly due to a haemorrhage within a cystic nodule. However, sudden pain in a rapidly enlarging nodule should prompt consideration of anaplastic carcinoma or primary lymphoma of the thyroid.

The medication history should be reviewed with particular attention to those drugs which can cause goitre such as lithium, iodine, amiodarone, antithyroid drugs, and iodine containing contrast agents; or food such as kelp.[7]

Important risk factors for thyroid carcinoma include a history (particularly childhood) of previous head and neck irradiation, a family history of thyroid cancer or multiple endocrine neoplasia (MEN) type 2, rapid enlargement of a thyroid mass, or a nodule >4cm in diameter. The presence of compressive symptoms in the absence of an enlarged goitre suggests an underlying malignant lesion. Although thyroid nodules are more common in women than men (a ratio of 4:1),[8] being male is associated with a worse prognosis, as is being young (<20 years of age) or older (>70 years of age).[6]

Particular aspects of the thyroid examination suggestive of underlying malignancy include a firm or hard nodule, fixation of the nodule to adjacent structures, paralysis of vocal cords with recurrent laryngeal nerve involvement (check for hoarseness), and regional or cervical lymphadenopathy. Differentiated thyroid cancer can metastasise to bone, lung or the central nervous system, and signs of involvement of these regions should be borne in mind.

Laboratory investigation

No laboratory test other than histological examination can specifically distinguish benign from malignant thyroid nodules. Measurement of the serum thyroid stimulating hormone level (TSH) is the single most useful test in the initial assessment of thyroid nodules.

If the TSH is below the reference range, free thyroxine (FT4) and triiodothyronine (FT3) levels should be obtained. Approximately 10% of patients with a solitary nodule have suppressed TSH, which suggests a benign hyperfunctioning nodule[6] and requires referral solely for the treatment of their hyperthyroidism. If TSH is elevated, FT4, FT3, as well as antithyroid antibodies (including anti-Thyroid Peroxidase [anti-TPO] and anti-Thyroglobulin [anti-TG] antibodies) should be obtained to confirm Hashimoto's autoimmune hypothyroidism.

On rare occasions co-existing malignancy such as lymphoma may occur in autoimmune thyroid disease and a specialist opinion as well as fine needle aspiration (FNA) may be indicated. A serum calcitonin level is recommended only in patients with a family history of medullary thyroid carcinoma (MTC) or MEN type 2 (which include familial MTC, primary hyperparathyroidism and/or phaeochromocytoma).[9] Routine testing of serum thyroglobulin (Tg) level in the initial evaluation of thyroid nodules is not recommended as the Tg level is increased both in patients with benign or malignant thyroid nodules. Measuring serum Tg is useful in assessing the presence of recurrent disease in the long-term follow-up of patients treated for differentiated thyroid cancer.

Radiological imaging

Diagnostic imaging can be useful in determining the size of the nodule(s), consistency, functionality and presence of any structural compression. The choice of imaging modality depends on the questions to be answered.

If the TSH is suppressed, a pertechnetate (TCO_4^-) thyroid scan should be performed; a hyperfunctioning nodule is nearly always benign. If TSH is normal or elevated, thyroid ultrasonography (U/S) should be obtained. Numerous U/S criteria had been developed in order to differentiate malignant from benign nodules, but no single feature on U/S can independently predict a malignant lesion. American Thyroid Association (ATA) and American Association of Clinical Endocrinology (AACE) guidelines recommend U/S be performed in one or more suspected thyroid nodules unless TSH is suppressed.[8,9] Ultrasound can provide useful information on the size of nodules, which can be informative in following their size over time. In addition U/S can be useful in guiding FNA. Other radiological imaging such as computed tomography (CT) and magnetic resonance imaging (MRI) are rarely indicated unless substernal goitre is suspected or when tracheal compression is being assessed. Contrast enhanced CT is relatively contraindicated in multi-nodular goitre because of the risk of subsequent iodine-induced thyrotoxicosis.

Fine Needle Aspiration (FNA)

FNA of the thyroid is now established as a safe and important part of assessing thyroid nodules.[10] Both the ATA and AACE guidelines strongly recommend FNA as the procedure of choice in the evaluation of thyroid nodules. In the hands of a skilled cytopathologist, FNA of the thyroid is useful diagnostically in at least 80% of the cases. When performed properly, it should have a false-negative rate of less than 5% and a false-positive rate of approximately 1%.[11] The dilemma facing the New Zealand GP is knowing which pathologists

Table 1. Categories of FNA findings

Cytodiagnosis of lesion	Management	Comment
Benign (negative) – colloid nodules – benign cysts – lymphocytic thyroiditis – granulomatous thyroiditis	No further diagnostic studies or treatment is required	Most common diagnoses (65%).[12]
Malignant – papillary carcinoma – follicular carcinoma – *medullary thyroid carcinoma (MTC)	Referral for total thyroidectomy * If FNA reveals MTC, referral to endocrinologist to exclude other disorders such as phaeochromocytoma before thyroidectomy is performed.	Approx. 5% of diagnoses
Suspicious or indeterminate results – follicular neoplasm – Hürthle cell neoplasm – lymphoma	Referral for lobectomy or total thyroidectomy if a concordant autonomously functioning nodule is not seen on radionuclide scan	Approx. 10% of diagnoses Follicular adenomas cannot be reliably differentiated from follicular carcinoma by FNA
Non-diagnostic results	Repeat FNA Surgical removal can be considered when one fails to obtain further useful diagnostic material Surgery should be more strongly considered if the cytologically non-diagnostic nodule is solid on U/S imaging.	20% of diagnoses have too few epithelial cells for analysis Close observation if not for surgical intervention

have the appropriate skills to interpret FNA results, and it is important for GPs to seek such knowledge from the regional thyroid specialists prior to referral for FNA. It is also critical that the cytopathologist be aware of which nodule to sample either by direct communication with the clinician involved or using an-U/S guided approach. The procedure itself is straightforward; complications are rare and primarily involve local discomfort. Use of anticoagulants or anti-platelet agents does not preclude biopsy.

Traditionally, FNA findings are divided into four categories: benign, malignant, indeterminate or suspicious for neoplasm, and non-diagnostic as described in Table 1.

Management

Management of thyroid nodules can be guided by the FNA results. Malignant, suspicious or indeterminate, or non-diagnostic results findings on FNA should be referred either for a surgical or endocrine opinion. In benign lesions, no further diagnostic studies or treatment is required (see Table 1).

The use of thyroxine therapy in the management of FNA-negative nodular thyroid disease is not recommended in iodine-replete areas.[8,13] Exceptions include patients who have an elevated TSH which itself is a goitrogen. Treatment with thyroxine may also be considered in patients from iodine-deficient geographical areas and in young patients with small thyroid nodules. Use of thyroxine in all other cases should be avoided.

When close observation is decided upon in lesions other than malignant (positive) FNAs, ongoing clinical review is necessary as there is a low, but significant, false negative rate of up to 5% with FNA.[14] Serial ultrasonography, with or without repeat FNA, at six to 18 month intervals is recommended, depending on the rate on nodular growth, the previous cytology results (benign versus non-diagnostic), and the patient's expectations and concerns.

In pregnant women the thyroid nodule is treated similarly to those in non-pregnant women. However, radionuclide scanning is contraindicated during pregnancy and cannot be performed. Nodules can be aspirated safely during pregnancy. If malignant cytology is confirmed on FNA, surgery is recommended. Currently, however, there is no consensus whether surgery should be performed during pregnancy or deferred until after delivery.[8,9] If surgery needs to be performed during pregnancy, it is relatively safe during the sec-

ond trimester. Since thyroid cancer is usually indolent in its growth, an alternative strategy is to defer FNA until the postpartum period and to use thyroxine therapy to inhibit nodular growth during pregnancy.

Conclusion

Thyroid nodules are commonly encountered in general practice. Assessment is dependent on a detailed history and physical examination. Serum TSH should be measured in all patients with thyroid nodules. Thyroid ultrasound is performed in all patients unless TSH is suppressed. FNA should then be obtained and a therapeutic strategy guided by FNA results. Referral to an endocrinologist or endocrine surgeon is indicated when (a) the FNA confirms a malignant result, (b) non-diagnostic cytology requires further assessment, or (c) where there is abnormal thyroid function, particularly with a suppressed TSH.

Competing interests

None declared.

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