

Nodular thyroid disease

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ABSTRACT Nodular thyroid disease is common. Ultrasound examination of the neck for a variety of reasons has revealed a linear increase in the prevalence of thyroid nodules from negligible at 15 years to 50% by the age of 60. Only 10% of these nodules are palpable by experienced examiners. Conversely, 50% of patients referred to a thyroid clinic with an apparently solitary thyroid nodule will be found to have a multinodular goitre. In the absence of marked asymmetry, rapid growth or an obvious 'cold' area on isotope imaging, multinodular goitre is, for practical purposes, a benign condition that may be associated with hyperthyroidism at presentation or in future years. On the other hand, a solitary palpable nodule may be malignant and the issue for the clinician is to identify the 5% that are malignant (usually papillary or follicular carcinomas) by using a combination of clinical assessment, imaging, thyroid function tests and cytology. Ultrasound-guided fine needle aspiration of impalpable thyroid nodules identified by imaging has demonstrated that malignancy is as common as in palpable solitary nodules. Although the natural history of these thyroid incidentalomas in an ageing population is not known, growth is likely to be slow and, in the UK at least, it is not common practice to adopt an aggressive policy of investigation and treatment.

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CLINICAL ASSESSMENT

The history is, as ever, important. The rapid enlargement of an established nodule or its first appearance over a period of 24–48 hours, accompanied by pain which may radiate to the ear, is diagnostic of a haemorrhage into the nodule. Often, by the time of the consultation two to three weeks later, the nodule is markedly reduced in size or no longer evident and the patient can be reassured that there is no need for further action. A thyroglossal cyst is midline and may move with protrusion of the tongue.

Previous irradiation of the head and neck some years previously, usually for lymphoma, is associated with an increased risk of the development of both benign and malignant nodules. Papillary carcinoma is familial in some 5% of patients. There is also an increased risk of thyroid nodules in patients with familial adenomatous polyposis (Gardner's syndrome) and multiple hamartoma syndrome (Cowden's disease). Medullary carcinoma of the thyroid may be familial as part of a type 2 multiple endocrine neoplasia syndrome.

Pointers to malignancy on examination of the neck include firmness and irregularity of the nodule, fixation to surrounding structures, diameter in excess of 4 cm, cervical lymphadenopathy, and youth or old age. Papillary carcinoma may present with an enlarged cervical lymph node and the primary may be so small as only to be evident on ultrasound. A goitre that is obviously

multinodular without marked asymmetry is a benign disorder. The goitre begins in adolescence or young adulthood as a diffuse thyroid enlargement and, if the uncharacterised stimulus to thyroid growth continues, the result is nodular hyperplasia that will eventually lead to hyperthyroidism in old age.

THYROID FUNCTION TESTS

Serum concentrations of T3, T4 and thyroid-stimulating hormone (TSH) are usually normal in patients with nodular thyroid disease. The finding of a suppressed serum TSH concentration with normal or raised serum concentrations of T4 and/or T3 indicates autonomous function in one or more nodules, which can be demonstrated by imaging with technetium-99m (^{99m}Tc). These patients have benign disease, and further investigation is not necessary prior to treatment by surgery or, more commonly, with radioactive iodine.

IMAGING

Scintigraphy

Imaging with ^{99m}Tc plays a useful role in assessing patients with nodular thyroid disease in whom serum TSH concentrations are suppressed. In the case of a solitary autonomously functioning nodule (toxic adenoma), all the isotope is concentrated within the nodule with little or no uptake in the rest of the gland. Some patients in whom only a single nodule is palpable will show evidence of multiple areas of autonomous

TABLE 1 Likely outcome of fine needle aspiration of a clinically solitary thyroid nodule in a euthyroid patient

Cytological diagnosis	Benign (75%)	Malignant (5%)	Inconclusive (10%)	Repeatedly unsatisfactory (10%)
Recommended treatment	Reassure	Surgery	Surgery	Surgery
Comments	Despite reassurance, some patients wish to undergo surgery, not only for cosmetic reasons but also for ultimate peace of mind.	Almost always papillary carcinoma, occasionally medullary and rarely secondary deposits from renal or breast carcinoma. Although FNA will allow a diagnosis of anaplastic carcinoma and sometimes lymphoma, the presentation of these conditions is usually with a large, rapidly expanding goitre which may be associated with thyroid failure.	It is not possible to distinguish on cytological grounds between the more common follicular adenoma and follicular carcinoma. Histological examination of the nodule is required. A cytology report should indicate that the cells are derived from a follicular neoplasm.	Either due to lack of epithelial cells, e.g. cyst, or poor technique.

function within the gland. Scintigraphy is also valuable in patients with multinodular goitre who have normal serum TSH concentrations. Nodules that show a reduced uptake of isotope justify fine needle aspiration (FNA) to exclude the presence of malignancy. Imaging of euthyroid patients with solitary nodules is not helpful. Nodules that fail to concentrate isotope are more likely to be malignant than those that concentrate isotope with the same intensity as the rest of the gland, but FNA (see below) is a more reliable discriminator.

Ultrasound

Ultrasound is widely used in the investigation of nodular thyroid disease, largely because it enhances the income of thyroidologists in Europe and North America. It is not a particularly valuable investigative tool. It gives no indication of function of nodules and simply indicates whether nodules are solid or cystic or, most commonly, a mixture of both components. Although ultrasound may demonstrate unexpected nodules that are impalpable, the relevance of these is uncertain as nodular change within the thyroid is part of the ageing process. Features that increase the likelihood that a nodule is a carcinoma include diffuse microcalcification, hypoechogenicity, an irregular margin and regional lymphadenopathy. However, there are no ultrasound characteristics that definitely exclude carcinoma and, therefore, render biopsy unnecessary. The technique is also operator-dependent.

FINE NEEDLE ASPIRATION

This is the most useful single investigation in the patient with a solitary palpable thyroid nodule. In the past, most euthyroid patients with a clinically solid single nodule underwent surgery, particularly if the lesion failed to concentrate isotope – the so-called ‘cold’ nodule – or was solid on ultrasound. As only 5% of solitary nodules are malignant, mainly papillary and follicular carcinomas, most patients underwent an unnecessary operation. As

a result of FNA about 25% of patients require surgery (Table 1). About 2–3% of patients have a false-positive aspirate, and it is wise not to give the patient a definite answer on the basis of the cytological appearance but simply indicate the need to examine the entire lesion in the knowledge that any aspirate of a solid nodule is only sampling two to three follicles. There is a similar false-negative rate, but the clinical impression should always override a negative report, e.g. a teenage girl in whom a benign thyroid nodule would not be anticipated or an elderly patient in whom there has been rapid growth of a nodule. It is not usually possible to differentiate between follicular adenoma and carcinoma on cytological grounds, as the distinction depends upon features such as vascular or capsular invasion. Expression of galectin-3 by follicular cells obtained by FNA favours a diagnosis of carcinoma but, unfortunately, 20% of follicular cancers are galectin-3 negative.

Cystic lesions will yield clear straw-coloured fluid or chocolate-coloured fluid if there has been haemorrhage into the nodule. Identifying the derivation of a cyst may not be possible as the aspirate is often acellular or contains mainly macrophages but no epithelial cells. Cysts often recur within hours of aspiration. It is reasonable to reaspirate, but further accumulation is an indication for surgery as there may be a microfocus of papillary carcinoma in the cyst wall or the nodule may represent a papillary carcinoma that has undergone cystic degeneration. An injection of ethanol, as a sclerosing agent, has been used to prevent cyst recurrence with some success.

The material from the mid-line thyroglossal cyst is often thick and cheese-like and difficult to aspirate.

The aspiration of crystal clear fluid is diagnostic of a parathyroid cyst, and the measurement of parathormone in the aspirate is a useful confirmatory test.

Technique

Fine needle aspiration is a simple procedure that nonetheless requires an experienced operator for good results. The skin overlying the nodule should be cleaned with an alcohol wipe. Local anaesthesia is not necessary. A 21-gauge needle is attached to a 20-ml syringe held in a pistol grip to allow suction with one hand, the other fixing the nodule. The plunger of the syringe should be withdrawn by 1–2 ml before inserting the needle into the nodule. Once the needle is in the nodule, negative pressure should be exerted by withdrawing the plunger to the 10 ml mark. The tip of the needle is then moved back and forward several times over a distance of 2–4 mm until material, which will often be blood-stained, appears in the hub of the needle.

It is important that no significant fluid enters the syringe as this will dilute the cellular element of the specimen. The negative pressure is then released. The needle is withdrawn, disconnected from the syringe, and the plunger of the syringe pulled back to 5 ml before reconnecting to the needle. The contents of the needle are then expelled onto two slides. Smears are made immediately. One slide is allowed to dry in air and the second is fixed in alcohol. Two passes are usually sufficient to obtain adequate material.

It is unusual for an experienced clinician to resort to ultrasound-guided aspiration in a patient with a palpable nodule.

TUMOUR MARKERS

The measurement of serum calcitonin is indicated in patients with a family history of medullary carcinoma or other components of the multiple endocrine neoplasia type 2 syndrome. Measurement cannot be justified in all patients with a solitary nodule as less than 0.5% will have a raised calcitonin concentration due to medullary carcinoma of thyroid.

FURTHER READING

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Although the measurement of serum thyroglobulin is useful in the follow-up of patients previously treated for differentiated thyroid carcinoma, it is of no value in identifying the cause of a thyroid nodule.

THE THYROID INCIDENTALOMA

The ageing thyroid undergoes nodular change and it is not surprising that such nodules, usually less than 1 cm in diameter, are increasingly identified during imaging of the neck for unrelated disorders. Ultrasound-guided FNA of these nodules has shown a similar prevalence of thyroid carcinoma to that in larger palpable nodules. Although clinically evident thyroid carcinoma must have small beginnings, there is no evidence that these incidentalomas will grow rapidly and reduce life expectancy in older patients with significant co-morbidities. The management of these impalpable, and unexpected, nodules is usually one of masterly inactivity.

KEY POINTS

- Nodular thyroid disease is usually benign.
- Single or multiple autonomously functioning nodules demonstrated by isotope imaging and associated with a low serum thyroid-stimulating hormone concentration are benign.
- Thyroid ultrasound, although widely used, cannot distinguish reliably between benign and malignant thyroid nodules.
- Fine needle aspiration of a single thyroid nodule will reliably detect malignant disease, and has reduced significantly the referral rate for surgery.
- Measurement of the tumour marker, serum calcitonin, is only justified in patients with nodular thyroid disease and a family history of medullary carcinoma or other features of multiple endocrine neoplasia type 2.
- Investigation of non-palpable thyroid nodules, identified by chance during imaging, is not usually indicated.