

Investigating the thyroid nodule

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Thyroid nodules are common: 4-7% of the adults have a palpable nodule, and up to 50-70% will have nodules on high definition ultrasonography, which may cause considerable concern to patients. In this article, we present an evidence based guide to investigating and managing thyroid nodules and we discuss the myths about nodules. Where relevant, we also highlight the differences between the two most widely used guidelines on this topic: the recently issued second edition of the British Thyroid Association's guidelines on thyroid cancer¹ and the American Thyroid Association's guidelines.² These guidelines were formulated by two large committees of experts, who reviewed all the available evidence, which mainly consists of prospective and retrospective cohorts; where there was no evidence, expert consensus opinion was used.

What is the risk of a thyroid nodule being malignant?

Traditional teaching states that 20-40% of thyroid nodules are malignant.³ However, this pertains to a highly selected group of patients, with solitary cold nodules on scintigraphy.⁴ The risk of malignancy for a thyroid nodule identified on ultrasonography is much lower: 4-7%.^{5,6}

When to refer a patient with a thyroid nodule to secondary care

Little evidence is available on referral times. Relying on expert opinion, the British Thyroid Association's guidelines say that most thyroid nodules are benign and therefore do not require urgent referral to secondary care.¹ This advice includes patients with a new thyroid lump that has been growing over a period of months and patients with a sudden onset of pain in a nodule (which is usually due to a bleed into a cyst).¹ They recommend that such patients should be referred to a specialist thyroid clinic with provisions for ultrasound and fine needle aspiration assessment, where they should be seen within four weeks of referral.¹

Patients who have suspicious features, including painless rapid enlargement over a few weeks, associated cervical lymphadenopathy, and insidious persistent pain, should be referred urgently to a secondary care physician with expertise in the diagnosis and management of thyroid cancer, and seen within two

weeks.¹ Box 1 lists the "red flag" features (worrying signs and symptoms) that suggest a referral might be necessary. Any patient with a thyroid lump and associated stridor should be referred for same day review by a secondary care specialist, as this may be due to recurrent laryngeal nerve involvement secondary to a thyroid carcinoma.¹

What are the first investigations to consider?

Thyroid function tests

All patients with a thyroid nodule should have thyroid function tests,^{1,2} which exclude nodules associated with hyperthyroidism. If hyperthyroidism is present, referral to an endocrinologist for assessment and management should follow.¹ Some evidence from a large prospective cohort suggests that patients with high levels of thyroid stimulating hormone are at an increased risk (adjusted odd ratio 11) of thyroid malignancy.⁷

Fine needle aspiration

Who should perform fine needle aspiration?

Aspiration may be performed by a surgeon, cytopathologist, radiologist, endocrinologist, or an oncologist, provided that they are trained and carry out sufficient numbers to maintain their expertise^{1,6}; 20-35 aspiration procedures a year have been suggested as an adequate number.⁶ Box 2 outlines one of various techniques used for fine needle aspiration.

Box 1 "Red flag" features: worrying signs and symptoms in a patient with a thyroid nodule

- Family history of thyroid cancer
- History of previous irradiation or exposure to high environmental radiation
- Child with a thyroid nodule
- Unexplained hoarseness or stridor associated with goitre
- Painless thyroid mass enlarging rapidly over a period of a few weeks
- Palpable cervical lymphadenopathy
- Insidious or persistent pain lasting for several weeks

Box 2 How to do a fine needle aspiration⁶

- Under aseptic technique, localise the nodule between the fingers or with the ultrasound probe
- Then pass a gauge 25 needle into the solid part of the nodule. Repeat the passes several times while rotating the needle between the finger and thumb. Only aspirate if fluid is obtained, so as to remove the cyst's contents
- Then empty the needle contents into a liquid preservative (such as Cytolyt) if your local laboratory uses liquid based cytology. Alternatively, the sample can be smeared directly on to glass slides. When lymphoma is suspected, sending a sample in cell culture medium for flow cytometry may be very helpful in obtaining the diagnosis²
- Once the fluid component is removed, reassess the nodule by palpation or with ultrasonography, and repeat aspiration if there is any residual mass. Take care not to contaminate the sample with the ultrasound gel when using ultrasound guidance

How accurate is fine needle aspiration cytology for thyroid nodules?

The accuracy of fine needle aspiration cytology varies with the operator performing the aspiration and the cytopathologist reporting it.⁶ Even if the operator is experienced and the sample is sufficient for diagnosis, the false negative rate for cancer can vary from 1% to 6%, owing to wrong diagnosis or sampling errors.⁶ The latter occur more commonly in nodules smaller than 1 cm or larger than 4 cm.⁸ Therefore, as thyroid cytology is a specialist field, guidelines strongly recommend that cytopathologists reporting fine needle aspiration cytology are experienced in the field.¹

Case series have reported rates of non-diagnostic aspirates (aspirate samples inadequate for reaching a diagnosis) in the order of 15–30%.^{5,9} The rate of a non-diagnostic aspirate seems to be higher for nodules smaller than 1 cm than for nodules 1 cm or larger (22.5% v 16.6%).¹⁰ Repeating the fine needle aspiration will yield an adequate sample in up to half of cases.⁶ As inadequate samples carry as much as a 9% risk of malignancy,^{11–13} aspiration should be repeated, preferably with ultrasound guidance.¹

A core biopsy (with or without ultrasound guidance)¹ or a diagnostic hemithyroidectomy is warranted if two aspiration procedures do not result in a diagnosis.^{12,14} Open biopsies of the thyroid gland are rarely necessary.¹

What is the role of ultrasonography?

High definition ultrasonography can provide valuable information about the characteristics of the nodule and its potential risk of malignancy, particularly if the operator is experienced in thyroid ultrasonography.^{15,16} A large prospective cohort study suggests that the presence of one or more of several features (listed in table 1) increases the likelihood of malignancy,¹⁰ even in the presence of benign results of fine needle aspiration.

Ultrasonography also enables more accurate serial assessments of growth.¹⁷ The American Thyroid Association recommends that all patients have ultrasonography,² whereas the British Thyroid Association's guidelines suggest only that it may be helpful in aiding fine needle aspiration and identifying coexisting non-dominant nodules.¹

Is fine needle aspiration cytology needed if ultrasonography does not show suspicious features?

It is a myth that ultrasonography can be used to determine the risk of malignancy or whether fine needle aspiration is required. A large prospective cohort study¹⁰ of 494 patients found that selection by ultrasonography characteristics alone would have missed 13% of the cancers identified by a combination of ultrasonography and fine needle aspiration cytology. A retrospective study of 441 patients found that fine needle aspiration cytology was more accurate than ultrasonography alone in making a diagnosis of thyroid malignancy.⁴ Ultrasonography alone had a low specificity.

Is fine needle aspiration better with ultrasound guidance? Ultrasound guidance increases the accuracy of fine needle aspiration—from 85% to 95% in a large prospective cohort study.¹⁷ Furthermore, ultrasound guidance of fine needle aspiration or core biopsy has been shown to reduce the rate of inadequate samples from 15% to 3%.¹⁶ In another large cohort the rate of inadequate samples decreased from 47% to 16% for core biopsies with ultrasound guidance.¹⁸ Ultrasound guidance can also help with selecting the most suspicious nodule for biopsy in a multinodular goitre.⁵ We therefore recommend using ultrasound guidance for fine needle aspiration, especially when the first aspiration was inadequate¹ and for small nodules and multinodular goitres.¹² Ultrasound guidance is essential for the biopsy of non-palpable incidental nodules.¹⁹

Should a multinodular goitre be investigated?

Another myth is that the risk of thyroid malignancy is negligible for a patient presenting with multinodular goitre. This view is not supported by evidence. A large, well designed prospective study of 402 patients with non-palpable or single palpable nodules found that 33% of malignant disease was identified in a single nodule and 22% in multinodular goitres.⁵ In a small

Table 1 | Ultrasonography features suggestive of thyroid malignancy. Adapted from Ahuja et al¹⁵

Ultrasound feature	Risk of malignancy
Coarse calcification	Very low
Comet tail sign	Very low
Hypoechoic	Moderate
Absent halo or indistinct margin	Moderate
Intranodular blood flow on colour Doppler	Moderate
Microcalcification	High

TIPS FOR NON-SPECIALISTS

- Suspicious history of thyroid malignancy includes age less than 16 years, family history, previous exposure to irradiation
- Most thyroid nodules need routine referral (seen within four weeks) to a specialist thyroid lump clinic
- Urgent referral (within two weeks) is required only if a painless nodule is growing rapidly (over a few weeks) or is associated with hoarseness or cervical lymphadenopathy
- Immediate (same day referral) is required if a goitre is associated with stridor
- Longstanding thyroid nodules (over many years) that are asymptomatic and have not grown recently can be managed in primary care
- When referring patients, arrange a thyroid stimulating hormone assay but do not delay in arranging ultrasonography or fine needle aspiration biopsy. Refer to a clinician with a special interest in management of thyroid cancer, preferably a one-stop thyroid clinic

study of 68 consecutive papillary thyroid cancers, 52% were in solitary nodules and 48% in multinodular goitres.²⁰

In patients with multinodular goitre, selection of the nodule for aspiration is best guided by ultrasound features.²⁵ A nodule with suspicious ultrasound features should take precedence over a larger nodule with no suspicious ultrasound features.^{21,22} If none of the nodules have suspicious features, it is then reasonable to aspirate the largest nodule.²

Should patients with incidentally detected nodules or nodules smaller than 1 cm be referred or investigated?

Some bodies, including the British Thyroid Association, recommend that patients with non-palpable nodules smaller than 1 cm that are discovered incidentally on imaging of the neck (a group that is rapidly increasing) and with no worrying features can be managed in primary care.¹ The American Thyroid Association's guidelines state that usually no further investigations are required.² This may be due to the perceived low rates of mortality and complications in this subgroup of patients.

However, it is difficult to determine the risk of malignancy using size as the only criterion. One retrospective series of 207 patients who had a total of 472 biopsies with ultrasound guided fine needle aspiration¹⁹ found that the risk of malignancy was 21% in nodules smaller than 1 cm and 17% in nodules 1 cm or larger. This study also found that ultrasound guided fine needle aspiration was as accurate for diagnosing malignancy in nodules smaller than 1 cm as in those 1 cm or larger. In a prospective study of 494 patients, selecting only nodules 1 cm or larger for fine needle aspiration would have missed 39% of the total number of thyroid cancers identified by the ultrasound guided aspiration in all sizes of nodule.

Furthermore, size is not necessarily associated with aggressiveness of malignant disease. A large prospective cohort found that 35% of incidental tumours of 8–15 mm had extracapsular extension and 19% had nodal involvement.¹⁰ A retrospective series of 267 patients with incidentally detected, non-palpable thyroid nodules reported that 44% of the 36 occult thyroid tumours they identified had extracapsular extension,

Table 2 | Management of thyroid nodules according to the THY cytology classification. Where appropriate, the American Thyroid Association's equivalent categories are also shown (prefix ATA). Adapted from the British Thyroid Association's guidelines¹

Diagnostic category	Actions
THY non-diagnostic (ATA non-diagnostic)	Repeat fine needle aspiration with ultrasound guidance. Consider surgery if several results are non-diagnostic, especially if the nodule is solid
THY1 cyst	If the aspirate contains colloid and histiocytes only in the absence of epithelial cells, the THY1 category should be clearly identified as cyst. If the cyst has been aspirated completely with no residual mass, a repeat ultrasound scan alone may be sufficient, with fine needle aspiration only if the cyst recurs. Consider surgery if several results are non-diagnostic
THY2 non-neoplastic (ATA benign)	Repeat fine needle aspiration in three to six months The recent British Thyroid Association's guidelines suggest that in some cases a reliable benign diagnosis can be achieved with one single aspirate only. Furthermore in patients with high clinical risk or in whom ultrasound features suggest malignancy, a lobectomy may be appropriate (even with a THY2 diagnosis)
THY3 (i) follicular lesion, suspected follicular neoplasm (ATA indeterminate follicular)	Discuss at the multidisciplinary case management meeting then proceed to lobectomy
THY3 (ii) for the small number of other cases where cytological findings are worrying but do not fit in the THY2 or THY4 categories	Discuss at the multidisciplinary case management meeting to decide appropriate course of action
THY4 suspicious but non-diagnostic of papillary, medullary, anaplastic carcinoma or lymphoma (ATA suspicious for papillary carcinoma or Hürthle cell neoplasm)	Discuss at the multidisciplinary case management meeting. Ensure that immunohistochemistry has been performed for medullary carcinoma or flow cytometry for lymphoma. Proceed to surgery (lobectomy or total thyroidectomy) if appropriate
THY5 diagnostic of malignancy (ATA suspicious for papillary carcinoma or Hürthle cell neoplasm)	Discuss at the multidisciplinary case management meeting whether to proceed to surgical intervention for differentiated thyroid cancer and medullary thyroid cancer as indicated. Other cancers should be treated appropriately

SOURCES AND SELECTION CRITERIA

We used the terms "nodule", "syndrome", and "thyroid"—with each limited by "ultrasound" and "diagnosis" and "aspiration" separately—to search Medline, Embase, PubMed, Cochrane, CINAHL, and AMED, as well as cross checking with national guidelines, reference lists, textbooks, and personal reference lists. We assessed over 4000 identified abstracts for relevance. We used guidelines published on the Evidence-Based On-Call website (www.eboncall.org) to assess the quality of the evidence in original articles.

50% had nodal metastasis, and 39% were multifocal.²³ All these features affect the staging of the disease and so can potentially affect prognosis. We believe that clinicians should be cautious about the management of patients with small or incidentally diagnosed nodules in primary care. It may be prudent to refer to secondary care for further investigation, such as ultrasound guided aspiration.

Does interval growth predict malignancy?

The rate of growth of nodules is very variable.²⁴ In general, the rate of growth of a nodule does not alone predict the risk of malignancy. A small randomised trial of 74 patients found that 19% of benign nodules grew over a follow-up period of two years.²⁵

Does any evidence suggest that other investigations are required?

Ultrasonography is the only imaging modality routinely indicated for investigating the thyroid nodule¹² except when cervical lymphadenopathy or a fixed thyroid mass is present, in which case magnetic resonance imaging or computed tomography may be used

ADDITIONAL EDUCATIONAL RESOURCES

- British Thyroid Association, Royal College of Physicians. *British Thyroid Association guidelines for the management of thyroid cancer*. 2nd ed. 2007 (www.british-thyroid-association.org/Guidelines/)—Contains an informative section on the management of the thyroid nodule including the THY classification
- Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al. American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer (*Thyroid* 2006;2:109-42)—Discusses the management of the thyroid nodule and cites a large body of evidence on the topic
- Ahuja AT, Evans RM, King AD. *Imaging in head and neck cancer—a practical approach*. (London: GMM, 2003)—Has a good account with illustrative photographs of the features of thyroid malignancy on ultrasound
- UK Endocrine Pathology Society website (www.ukeps.com)—Has two videos showing techniques for fine needle aspiration

to assess the extent and distribution of disease and to plan surgery.^{12 15}

Radioiodine isotope scanning has a limited role in the diagnosis of thyroid cancer.^{w1} The British Thyroid Association does not support its routine use, saying it is "usually non-diagnostic of cancer."¹ The American Thyroid Association recommends its use only in specific situations.²

Testing for serum thyroglobulin plays no role in establishing a diagnosis.¹² Testing for thyroid autoantibodies may be useful if thyrotoxicosis or hypothyroidism has been shown to exclude a diagnosis of autoimmune disease, such as Graves' disease or Hashimoto's thyroiditis respectively. Lymphoma is more likely in patients with Hashimoto's thyroiditis.¹ Evidence is insufficient to recommend screening for medullary cancer in thyroid nodules by testing for calcitonin.^{2 w2 w3}

Management and follow-up of the thyroid nodule

How to interpret results?

Management of the thyroid nodule is determined largely on the results of the fine needle aspiration,¹² because this is the most accurate and cost effective investigation.²⁹ However, it carries a small but important false negative rate (up to 6%).^{6 w4 w5} Therefore clinical and ultrasound features should also be considered when deciding on a management strategy,^{w6} and suspicious clinical features must prompt concern in the context of benign or indeterminate cytology results.

Several cytological classification systems are available for reporting the cytology results of fine needle aspiration. These are based on the type of cells and their number and morphology in the aspirate. The British Thyroid Association's guidelines use the THY classification,¹ and table 2 summarises the association's management recommendations.

The American Thyroid Association's recommendations are similar. They differ mainly with respect to the management of a suspicious or follicular lesion, in which case a radionuclide scan is recommended. The guidelines state that if a hot nodule is found on the radionuclide scan and it coincides with the nodule for which a biopsy has been done on ultrasound, then surgery is not necessary owing to the very low risk of malignancy in a hyperfunctioning nodule.² There is a myth that there is no risk at all of malignancy in this situation, whereas an old report on findings from a

QUESTIONS FOR FUTURE RESEARCH

- New markers are needed for the diagnosis of malignancy on fine needle aspirate or serum, especially for follicular thyroid cancer
- New imaging techniques for the diagnosis of malignancy in thyroid nodules are needed
- Research needs to compare different management strategies (comparison of conservative follow-up versus surgery) for small (<1 cm) thyroid nodules

SUMMARY POINTS

- Thyroid nodules are common, but only about 5% are malignant
- The risk of malignancy is similar for solitary nodules and multinodular goitres
- Urgent referral to secondary care is necessary only if the nodule is growing rapidly (over few weeks) or associated with stridor, hoarseness, or cervical lymphadenopathy
- Needle aspiration biopsy is the most accurate method of investigation. Its accuracy is improved by ultrasound guidance. Ultrasonography can also add useful information and can improve accuracy.
- Management depends mainly on the results of needle aspiration but should also take into consideration the clinical and ultrasound features

small cohort of patients showed that there could be a risk of malignancy of up to 6%.^{w7}

What is the best method of follow-up for a benign lesion?
Owing to a small risk of a false negative result,^{6 w4} both guidelines recommend that nodules diagnosed initially as benign with fine needle aspiration cytology should remain under follow-up.¹² Expert opinion would suggest that serial investigation is effective and clinically useful.¹¹ A report of the results of 1564 repeated ultrasound guided fine needle aspirations out of 7394 calculated that the probability of a benign lump being accurately diagnosed as benign from a single aspirate is 90%.¹⁴ In patients in whom a lump was diagnosed as benign twice, from two separate aspirates, the probability of accurate diagnosis increased significantly to 98%. A case series of 235 patients found that a second fine needle aspiration decreased the false negative rate from 5.2% to 1.2%.^{w8} The British Thyroid Association therefore recommends a repeat biopsy three to six months after an initial diagnosis of benign disease.¹

On the other hand, for cases with benign cytology, the American Thyroid Association recommends follow-up 6–18 months later with ultrasonography (or palpation in an easily palpable nodule). It recommends repeating fine needle aspiration, preferably with ultrasound guidance, if growth is detected.² If no growth is detected, it recommends further review at longer intervals.² We believe that the recommendations of the British Thyroid Association would lessen the likelihood of a false negative result and would enable the clinician to discharge the patient, rather than continue follow-up for a prolonged period of time.

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