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PLEASE RESPOND WITHIN 48 HOURS
Evaluation of the thyroid nodule

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ABSTRACT

The annual incidence of thyroid cancer worldwide is 1 case per 100 000 men and 2.6 cases per 100 000 women. Most thyroid nodules are asymptomatic and are discovered incidentally on physical examination, self-palpation or incidentally on imaging studies performed for unrelated reasons. Although the majority of both palpable and non-palpable thyroid nodules are benign, ~5% may represent thyroid cancer. Thyroid-stimulating hormone, thyroid ultrasound and fine-needle aspiration biopsy are key tests to guide management. Physicians caring for patients with thyroid nodules need to develop a rational, cost-effective approach to ordering and interpreting imaging and diagnostic tests in the evaluation of the thyroid nodule.

Although thyroid cancer represents under 1% of all malignancies worldwide, it is currently one of the most rapidly increasing malignancies in the Western world. Thyroid nodules can be palpated in 4–7% of patients and can be detected by imaging in as many as 50% of the general population, with ~5% of these nodules representing cancer. Newly available imaging modalities are identifying these often asymptomatic and non-palpable nodules, making it imperative that primary care doctors understand how to interpret diagnostic studies, understand indications for referral, and manage the long-term survivors of thyroid cancer. Three major endocrine societies (American Association of Clinical Endocrinologists (AACE), British Thyroid Association (BTA) and European Thyroid Association (ETA)) have updated their recommendations in the past 5 years, and their recommendations are reviewed here. A rational, cost-effective approach is vital to guide the primary care doctor’s evaluation and management of this important issue.

INCIDENCE

Approximately 275 000 new thyroid nodules are detected annually in the USA. Nodules are four to eight times more common in women and increase in frequency with increasing age, decreased iodine intake, and history of radiation exposure to head and neck. The annual incidence of thyroid cancer worldwide is 1 case per 100 000 men and 2.6 cases per 100 000 women. However, Central America, Japan and Micronesia have incidence rates two to three times higher for unknown reasons. Interestingly, the incidence of thyroid cancer diagnoses has been increasing at an alarming rate in the Western world, from 2.7 to 7.7 per 100 000 people in the USA and from 2.3 to 3.5 per 100 000 people in the UK in the past 30 years. It has been noted that the increase in diagnoses is predominately driven by the increased incidence of small (<1 cm) papillary thyroid cancers. Given that mortality from thyroid cancer (0.5 per 100 000) has not changed over this time and that there has not been a concomitant increase in retrosternal thyroid cancers (which would not be detected by ultrasound surveillance), experts believe that newer surveillance techniques leading to earlier diagnosis of subclinical disease may be responsible for this increase in cancer incidence. It is not clear, however, whether the recent increase in diagnostic CT with iodinated contrast in Western countries has a causative role.

HISTORY AND PHYSICAL EXAMINATION

Most thyroid nodules are asymptomatic and are discovered incidentally on physical examination, self-palpation or imaging studies such as carotid ultrasound, CT or MRI of the neck performed for unrelated reasons. History taking and examination should focus on eliciting high-risk features for thyroid malignancy (box 1). Male sex as well as extremes of age (<20, >70) increase the likelihood of malignancy. History of exposure to head and neck radiation, either as a result of treatment of tonsillar and thymic disease or from exposure to nuclear fallout, is an important risk factor. A family history of benign or malignant thyroid disease, familial medullary thyroid carcinoma, familial polyposis coli, Gardner syndrome (colon polyposis with bone and soft tissue cancers) and Cowden syndrome (hamartomas, fibrocystic breast disease and breast cancer) should be reviewed. Symptoms of airway compression, hoarseness and dysphagia often suggest local invasion. Rate of change of any palpable thyroid mass should be obtained. Masses that have appeared or grown over the course of hours are usually the result of haemorrhage into an existing nodule. However, growth over the course of weeks is concerning for malignancy. Symptoms of hypothyroidism and hyperthyroidism should be elicited; however, they are present in <1% of patients.

Physical examination should include size, consistency (firm, cystic, rubbery) and movement with swallowing. Fixation suggests cellular invasion secondary to malignancy. Patients with a thyroid mass should be assessed for vocal cord paralysis. An inspection for mucosal neuromas or marfanoid habitus may suggest multiple endocrine neoplasia type 2b (MEN2b). In addition to palpation of the thyroid gland, a thorough examination of lymph nodes in the head and neck should be performed. Indicators of thyroid malignancy include a hard, fixed lesion, cervical lymphadenopathy, hoarseness and thyroid nodule >4 cm. Pemburton’s sign (distension of the external jugular veins and facial plethora or symptoms of dyspnoea while the arms of the patient are above
Box 1 Factors associated with increased risk of malignancy

- Male sex
- Age <20 or >70 years
- Family history of multiple endocrine neoplasia type 2b or medullary thyroid cancer
- History of head and neck radiation
- Rapid tumour growth
- Firm or hard consistency
- Fixed nodule
- Cervical adenopathy
- Hoarseness, dysphonia, dysphagia, dyspnoea or cough

LABORATORY EVALUATION

Serum thyroid-stimulating hormone (TSH) should be measured in all patients with thyroid nodules. If it is low, concentrations of free thyroxine and free triiodothyronine should be checked to document the severity of the hyperthyroidism (fig 1). Suppressed TSH concentrations suggest an autonomously functioning nodule or a toxic multinodular goitre. On the other hand, if serum TSH is raised, serum concentrations of thyroperoxidase antibody should be checked to diagnose Hashimoto thyroiditis. Raised TSH does not exclude the need for biopsy because ~5% of thyroid cancers are lymphomas, which can be associated with Hashimoto thyroiditis. Controversy exists over the use of serum calcitonin in the diagnostic evaluation of the thyroid nodule. AACE and BTA guidelines do not recommend routine screening of calcitonin for all thyroid nodules, but consider it to be useful in patients with high suspicion of MEN2b or medullary thyroid cancer (MTC). However, ETA in 2006 came out in favour of routine serum calcitonin screening of all patients with thyroid nodules, citing the high sensitivity of calcitonin for MTC, a recommendation that has been supported by recent cost-effectiveness analyses by Cheung et al. Raised TSH suggests MTC, although renal failure, Hashimoto thyroiditis and hypergastrinaemia may cause false-positive results. Patients diagnosed as having MTC should be evaluated for concurrent pheochromocytoma and hyperparathyroidism as well as screened for the RET proto-oncogene, with consideration of referral to a genetics counsel-

IMAGING STUDIES

Isotope scanning

Thyroid scintigraphy is used for assessment of thyroid function and detection of autonomously functioning thyroid tissue. Based on the pattern of radioiodine uptake, nodules are classified as cold (decreased uptake), hot (increased uptake in nodule with suppression of uptake in surrounding tissue) or warm (uptake similar to surrounding tissue). Hot nodules rarely represent malignancy, whereas cold nodules have a malignancy risk of 5–8%. As the vast majority of thyroid nodules are cold (~85%), and only a small minority of these are malignant, the predictive value of scintigraphy for malignancy is low. Therefore, the AACE recommendations include thyroid scintigraphy only in cases where TSH concentrations are suppressed (or are low-normal in areas of iodine deficiency) or where ectopic thyroid tissue or retrosternal goitre is suspected. ETA recommends scintigraphy for all patients with multinodular goitre.

Ultrasonography

High-resolution ultrasound is extremely sensitive for detection of thyroid nodules missed on physical examination or other imaging techniques. In patients with a palpable thyroid nodule, additional nodules with features requiring biopsy are detected by ultrasound in 24%, prompting AACE to recommend ultrasound evaluation of all palpable thyroid nodules. In addition, ultrasound screening is recommended for all patients at high risk of thyroid malignancy (history of familial thyroid cancer or MEN2b or significant radiation exposure) and for patients with multinodular goitre. Ultrasound evaluation is not recommended as a screening test in patients with normal thyroid on palpation and low risk of cancer. Along with size determination, ultrasound can detect features of nodules that increase the likelihood of malignancy, including hypoechogenicity, microcalcification, irregular margins and chaotic vascular patterns, as well as extracapsular invasion and lymph node involvement. The presence of at least two suspicious sono-

Other diagnostic imaging

MRI and CT scan should not be routinely used because they are seldom diagnostic for malignant lesions in nodular thyroid disease. However, in cases of retrosternal goitre, where ultrasound evaluation may be limited by anatomical factors, MRI or CT scan may be necessary. Furthermore, CT contrast medium contains iodine and can reduce subsequent uptake of radioiodine, limiting the utility of scintigraphy until cleared. Gadolinium-enhanced MRI can provide useful information without subsequent compromise of radioiodine uptake of the remaining thyroid tissue. Evaluation of glucose metabolism by positron emission tomography may help to distinguish benign from malignant nodules, but its use is limited by cost and availability.

FNAB

FNAB is the safest, most effective and most reliable technique available to distinguish between benign and malignant thyroid nodules. It is a highly accurate, inexpensive outpatient procedure and has become an integral part of evaluation of the thyroid nodule. The diagnostic accuracy of FNAB approaches 95% in skilled hands with experienced cytopathologi-

biopsy, and complications are rare. The addition of ultrasound guidance decreases the rate of non-diagnostic FNAB from 16% to 4%.

Biopsy results are classified as non-diagnostic (referred to as Thy1 by BTA), benign or non-neoplastic (Thy2), follicular lesion/suspected follicular neoplasm (Thy3), suspicious (Thy4) or malignant (Thy5) (fig 2).

Inadequate or non-diagnostic (AACE) or Thy1 (BTA) (4–16% of aspirates)
This represents a lack of cellular material for an adequate diagnosis and is usually the result of biopsy of a cystic nodule with few or no follicular cells. Ultrasound-guided re-aspiration from the peripheral portion of the cystic lesion should be performed if the initial test result is non-diagnostic. Re-aspiration yields satisfactory results in 50% of cases. A small percentage (5%) of thyroid nodules remain non-diagnostic despite good initial technique, re-biopsy and FNAB with ultrasound guidance. In those cases, surgical excision is recommended.5 14

Benign (AACE) or Thy2 (BTA) (70% of all aspirates)
Differential diagnoses include benign colloid nodules, Hashimoto thyroiditis, macrofollicular adenoma, lymphocytic thyroiditis, granulomatous thyroiditis and benign cyst. Management options for benign nodules include observation only with regular follow-up, suppressive thyroxine therapy, surgery, percutaneous ethanol injection and radioactive iodine therapy. BTA additionally advises a repeat biopsy in 3–6 months to confirm diagnosis.14

Observation only with regular follow-up
Patients with benign nodules who choose conservative therapy should be reassessed every 6–18 months for symptoms suggesting malignancy or change in size on examination. Ultrasound re-evaluation is recommended 6–12 months after the initial diagnosis and “regularly” thereafter by the AACE (grade D recommendation- inconclusive evidence); ultrasound re-evaluation is optional in BTA guidelines.14 If the nodule size is stable, the intervals between subsequent ultrasound evaluations can be extended. If there is evidence of growth either clinically or by ultrasound, repeat biopsy should be performed. In patients with growing nodules that are benign on repeat biopsy, surgical intervention should be considered, based on the patient’s symptoms or preferences.

Suppressive levothyroxine therapy
Use of thyroid hormone replacement to suppress serum TSH (below 0.3 mU) for management of thyroid nodules is controversial. Its use is aimed at shrinking palpable thyroid nodules and preventing the appearance of new nodules.20 A recent meta-analysis has shown no significant difference in the size of nodules after 6–12 months of suppressive therapy.21 As thyroid hormone suppression induces a clinically significant reduction in thyroid nodule volume in only a minority of patients and is associated with hyperthyroid risks, AACE and BTA guidelines do not recommend routine use of suppressive levothyroxine therapy.14

Surgical treatment
Surgical indications for a benign thyroid nodule include symptoms of dysphagia, dyspnoea, hoarseness, neck pressure, hyperthyroidism from a functioning nodule and nodule growth.
despite benign findings on FNAB. For a solitary benign nodule, lobectomy plus isthmectomy is sufficient. For bilateral nodules, a near-total thyroidectomy is appropriate.

Percutaneous ethanol injection

A number of studies suggest a benefit of percutaneous ethanol injection by ultrasound guidance in the treatment of benign, non-functioning solid and cystic thyroid nodules. Ethanol causes coagulative necrosis and small-vessel thrombosis. Prospective, randomised trials showed that percutaneous ethanol injection is significantly superior to aspiration alone in inducing reduction of nodule volume. A reduction of >50% of baseline volume is obtained in almost 90% of cases. This procedure requires prior documentation of benign cytology. The rate of recurrence of cystic lesions is very low. AACE considers

Key learning points

- Thyroid nodules are palpated in 4–7% of patients and can be detected by imaging in 50% of the general population.
- Most thyroid nodules are benign and ~5% represent malignancy.
- Serum thyroid-stimulating hormone (TSH) should be measured in all patients with thyroid nodules.
- Ultrasonography is recommended in all patients with thyroid nodules with normal or raised TSH.
- Fine-needle aspiration biopsy is the most cost-effective and accurate method for evaluating thyroid nodules.
percutaneous ethanol injection a first-line non-surgical treatment for recurrent cystic nodules of the thyroid gland after FNAB has ruled out a malignant lesion.9

Radioiodine iodine therapy
Radioiodine can be used for treatment of a functioning ("hot") nodule with or without biochemical evidence of hyperthyroidism. It is contraindicated in pregnancy and lactation. The aim of radioiodine treatment is ablation of autonomously functioning areas to achieve euthyroidism. This treatment is successful in 85–100% of patients with hyperfunctioning thyroid nodules or toxic multinodular goitre.24 The main side effect is hypothyroidism, occurring in 10% of patients within 5 years of treatment. Antithyroid drugs should be withdrawn 3 weeks before radioiodine iodine treatment and should not be administered for 3–5 days after treatment.

Suspicious or indeterminate (AACE) or Thy3 and Thy 4 (BTA) (10–20% of aspirates)
Thy3 differential diagnoses include follicular lesion/suspected follicular neoplasms. Although some of these are tumours, many prove to be hyperplastic nodules on excision. Thy4 represents nodules with findings suspicious, but not diagnostic, of malignancy. Differential diagnoses include Hurthle cell tumours and atypical papillary tumours or lymphoma. Suspicious or indeterminate results indicate a cytology pattern that may or may not be malignant, requiring analysis of full histological tissue architecture to rule out malignancy.25 As ~20% of indeterminate FNAB specimens are found to be malignant at surgical intervention, current AACE recommendations are surgical excision of all indeterminate nodules.5 BTA suggests that these cases be reviewed by a multidisciplinary team to guide further treatment, and similarly recommends surgery for all suspected cancers.14

Malignant (AACE) or Thy5 (BTA) (5% of aspirates)
Differential diagnosis includes primary thyroid or secondary (metastatic) cancers. The most common malignant lesion encountered is papillary thyroid cancer. If cytological results are positive, surgical intervention is always necessary for surgical candidates. The extent of thyroid surgery is controversial. For most patients, especially those with differentiated cancers >1 cm in size, familial disease, multifocal disease, capsular invasion or lymph node involvement, near-total thyroidectomy along with removal of lymph nodes from the central compartment is recommended.6 Postoperative 131I ablation is administered for high-risk patients, especially those with gross residual disease, metastatic disease or nodal involvement. Postoperative administration of levothyroxine after complete resection of thyroid cancer to suppress TSH concentration (<0.1 mU) has been shown to improve disease-free survival in locally advanced papillary cancers.26

CONCLUSIONS
For patients presenting with a thyroid nodule, exclusion of cancer is the important clinical concern. Initial evaluation should include a serum TSH assay (to determine the functional status of the nodule) and ultrasound (to look for other non-palpable nodules and to determine high-risk features that require biopsy). If serum TSH is suppressed, radionuclide scanning should be performed. FNAB is essential for distinguishing between benign and malignant nodules. Patients with malignant or indeterminate biopsy results should be referred for surgery. Patients with non-diagnostic biopsy results should have a repeat ultrasound-guided biopsy. For non-functioning, benign nodules, no treatment is necessary, but serial follow-up should be performed, and repeat FNAB can be considered.

MULTIPLE CHOICE QUESTIONS (ANSWERS AFTER THE REFERENCES)
1. A 35-year-old woman undergoes routine physical examination and her doctor notices 1.5 × 1 cm soft, mobile nodule on the left thyroid lobe. What is the next diagnostic test?
A. FNAB
B. TSH
C. Thyroglobulin level
D. Thyroperoxidase antibodies

2. A 45-year-old man presents to his doctor for follow-up of a 1.2 × 1.8 cm thyroid nodule identified incidentally on MRI of his neck ordered for neck pain. He has no family history of thyroid disease or MEN2b. Serum TSH = 0.0005 mU (normal 0.5–5 mU). What is the next best test to order?
A. FNAB
B. Thyroid ultrasound
C. Radionuclide scintigraphy
D. Serum calcitonin assay

3. A 53-year-old man with normal TSH underwent FNAB of a 2 × 1.5 cm nodule. Pathology results were read as suspicious for follicular neoplasm. What is the next step in management of this patient?
A. Wait and watch

Key references

Future research questions
- Do newer techniques to identify thyroid nodules prolong survival in patients screened?
- Is routine serum calcitonin screening in patients undergoing evaluation for thyroid nodule cost-effective?
- Is the recent increase in the use of CT scanning related to the increased incidence of thyroid cancers?

Topics:

Review
B. Refer for surgery  
C. Radioiodine therapy  
D. Levothyroxine suppression

4. A 29-year-old woman presents to her doctor with a concern about thyroid cancer because her friend was recently diagnosed with a benign nodule. She denies any family history of thyroid disease and has no history of exposure to head and neck radiation. What screening test should be offered to her?

A. TSH  
B. Ultrasound  
C. FNAB  
D. Physical examination

Competing interests: None.

REFERENCES

26. Cooper DS, Specker B, Ho M, et al. Thyrotopin suppression and disease progression in patients with differentiated thyroid cancer: results from the National Thyroid Cancer Treatment Cooperative Registry. Thyroid 1998;8:737–44.

Answers
1. (B); 2 (C); 3 (B); 4 (D)