The common case of thyroid nodular disease: a practical approach to care

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Appropriate investigations are needed in patients presenting with thyroid nodules to determine the risk of malignancy and any need for surgical intervention. Most thyroid nodules are benign but require long-term follow up after the initial assessment.

Key points

- **Thyroid nodules are very common and often asymptomatic.**
- **Nodules may require fine-needle aspiration (FNA) biopsy depending on their size and ultrasound characteristics.**
- **If the thyroid-stimulating hormone (TSH) level is low then a thyroid nuclear uptake scan is appropriate to assess for warm or hot nodule(s), which generally do not require FNA biopsy.**
- **The Bethesda system of thyroid FNA cytology results now reports six categories, each with different management implications.**
- **Thyroid malignancy is uncommon but surgery is sometimes required for diagnostic clarification and total thyroidectomy is required if malignancy is confirmed.**

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The management of patients with thyroid nodules can be a source of confusion for GPs, endocrinologists, thyroid surgeons and radiologists. Ultrasound screening studies suggest that thyroid nodules are present in more than 50% of the population aged over 60 years. The likelihood of malignancy is low at about 5 to 10% and is the same for single and multiple nodules. Nodules may be detected clinically and/or by ultrasound, and they are frequently impalpable. The recently published guidelines from the American Thyroid Association have shed some evidence-based light on this complex management dilemma.[1,2]

Approach to diagnosis

A careful history and physical examination is required in patients presenting with thyroid nodules (Figure 1), with specific attention to risk factors such as a family history of thyroid cancer, a past history of autoimmune thyroid disease or exposure to significant ionising neck irradiation. Local symptoms such as dysphagia, choking and cough should be sought. The flowchart on page 29 shows the approach to diagnosing and managing patients with thyroid nodules.

Thyroid function tests and ultrasound are routinely performed. Thyroid ultrasound (Figure 2) should be performed in all patients with a suspected nodule found on clinical examination or on other imaging modalities such as CT, MRI or PET scans. A reduced thyroid-stimulating hormone (TSH) level is common in patients with nodular disease (usually with a normal free thyroxine [T4] level) and reflects mild autonomy of one or more nodules. If the TSH level is low, free T4 and free T3 levels are measured, and highly specific thyroid receptor antibodies are also worthwhile measuring to exclude Graves' disease. A thyroid nuclear uptake scan (Figure 3) is useful to clarify 'hot' versus 'cold' nodules in a patient with a low TSH level, and helps to decide which nodule(s) requires fine-needle aspiration (FNA) biopsy. A thyroid nuclear scan is not required if the TSH level is within the normal range.

Measurement of thyroid antibodies, such as antibodies to thyroid

Figure 1. Patient with a large right-sided thyroid nodule.

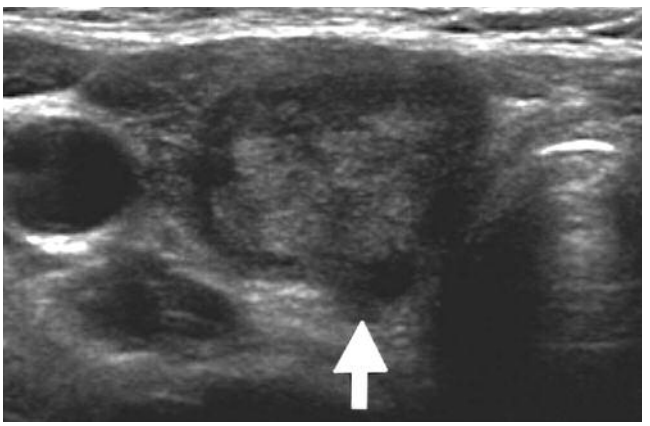


Figure 2. Thyroid ultrasound showing a nodule in the right lobe (arrow) with an irregular border. This nodule requires a FNA biopsy (see Table).

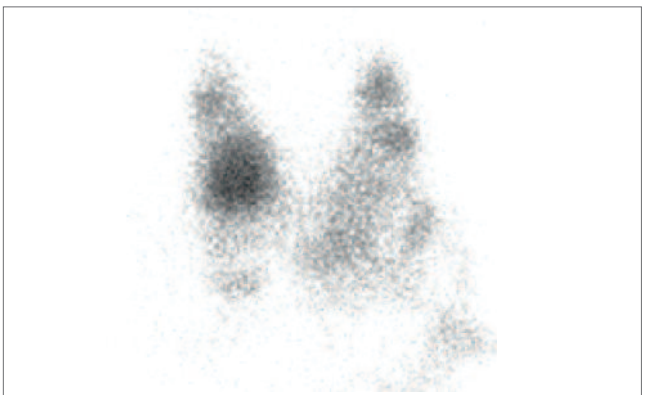


Figure 3. Tc 99m thyroid nuclear uptake scan in a patient with multinodular goitre and a low serum thyroid-stimulating hormone level, showing isotope uptake in several nodules, most marked in the hot right-sided nodule. The nodule did not require FNA biopsy because it had no worrying ultrasound features, but the patient was given low-dose radioiodine therapy as her free T4 level was elevated and she had symptoms of thyrotoxicosis.

peroxidase and thyroglobulin, do not add to the management in patients with thyroid nodules; although if there is a past history or family history of autoimmune thyroid disease then these tests guide the frequency of ongoing TSH monitoring. Currently, the routine measurement of calcitonin, which is associated with medullary thyroid cancer, is not warranted.

In summary, ultrasound provides anatomical information and nuclear scanning provides functional information. Functioning or 'hot' nodules rarely require FNA biopsy. A 'warm' nodule may display isotope uptake without suppression of the remaining thyroid and may require FNA biopsy if there is concern based on the ultrasound or clinical features. CT and MRI scans have limited resolution within the thyroid gland and are only performed to clarify whether there is tracheal compression or retrosternal extension in the context of obstructive symptoms.

A new problem that is encountered with the advent of new scanning technologies is the presence of asymptomatic thyroid uptake on PET scanning (1 to 2% of fluorodeoxyglucose PET scans), because PET positive thyroid nodules have a higher likelihood of malignancy (33%) and patients will need to be referred to an endocrinologist or endocrine surgeon.

When to perform a FNA biopsy

Any nodule greater than 1 cm in diameter requires a baseline FNA biopsy unless it is clearly a simple cyst with no solid component. Most FNA biopsies are currently carried out by radiologists under ultrasound guidance and some practices have a cytopathologist in attendance to ensure an adequate sample is obtained at the first attempt; this may necessitate multiple passes.

If there are multiple nodules then ultrasound features come into play because it is technically difficult and traumatic for the patient to have multiple simultaneous biopsies (more than two at any one time is unpleasant for the patient). If there are multiple nodules with no suspicious ultrasound features then it is reasonable to biopsy the largest nodule and perform serial ultrasound scans thereafter.

Ultrasound features of concern are listed in the box on page 30. A nodule of less than 1 cm in diameter will sometimes require FNA biopsy if there are several ultrasound features of concern or if it is growing rapidly.

The big unanswered question is what is the best ongoing follow up for patients with thyroid nodules? If the FNA biopsy result is benign, when should the next one be carried out and how often should ultrasounds be performed?

Management of thyroid nodules

FNA results are now classified by the Bethesda system of thyroid cytopathology (see Table). A suggested approach to management of patients with thyroid nodules in keeping with the American Thyroid Association guidelines is presented in the flowchart on page 29.

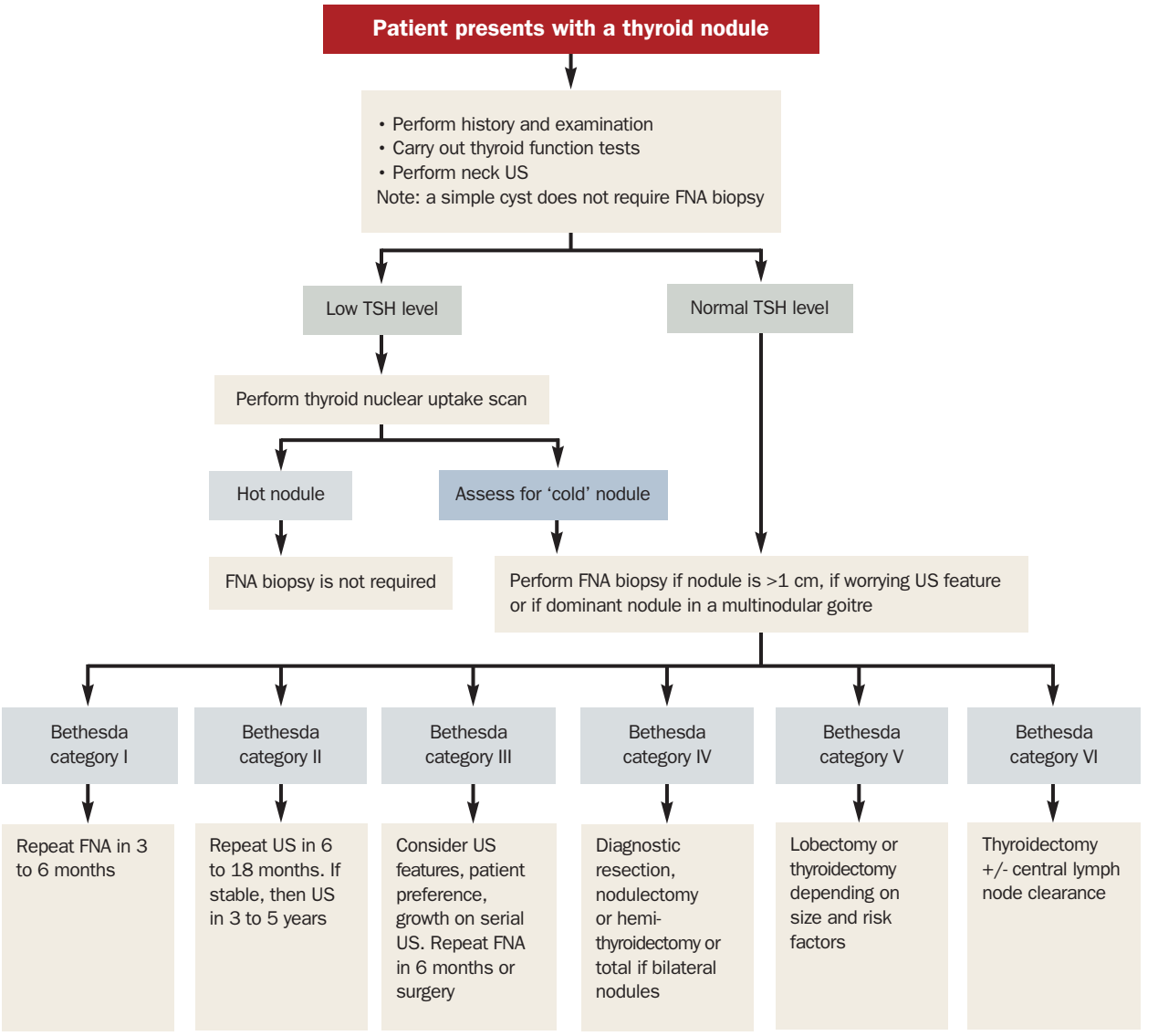
More than 90% of thyroid nodules are benign. A benign nodule (Bethesda category II) is managed conservatively unless there are

local or obstructive symptoms. In the latter case, a minimally invasive nodulectomy or hemithyroidectomy is performed with the aim of avoiding the need for thyroxine replacement if possible. The American Thyroid Association guidelines suggest serial ultrasound scans within six to 18 months after initial FNA biopsy for benign thyroid nodules. If the size of the nodule is stable then it may be possible to extend the next follow-up clinical examination or ultrasound to three to five years.

A nondiagnostic or insufficient result (Bethesda category I) requires a repeat biopsy in three to six months. An adequate sample is vital regardless of the cytological classification system.

An atypical FNA biopsy result is now classified as category III or 'atypia of uncertain significance' with a risk of malignancy of about 5 to 15%. This category has created confusion and can usually be managed by repeat FNA biopsy unless there are suspicious ultrasound features or rapid growth, when surgery would be recommended. Bethesda category IV is atypical with a risk of malignancy of up to 30% and surgery is required. A total thyroidectomy is the appropriate initial operation if cytology is malignant, clinical features are highly suspicious for malignancy (categories V and VI) or there are multiple nodules on both sides of the gland with at least one category IV cytology or above. A category V case will

Approach to managing the patient with a thyroid nodule



ABBREVIATIONS: FNA = fine-needle aspiration; TSH = thyroid-stimulating hormone; US = ultrasound.

Ultrasound features associated with increased risk of malignancy

- Hypoechoic
- Increased intranodular vascularity
- Irregular infiltrative margins
- Presence of microcalcifications (as opposed to 'egg shell' calcification)
- Incomplete halo
- Nodule is taller than wider on ultrasound criteria

Table. The Bethesda system for reporting thyroid fine-needle aspiration biopsy results

Level	Diagnostic category
I	Nondiagnostic or unsatisfactory
II	Benign
III	Atypia of undetermined significance
IV	Suspicious for follicular neoplasm
V	Suspicious for malignancy
VI	Malignant

sometimes be managed by hemithyroidectomy so that precise histopathology is obtained.

Some studies suggest that for nodules over 4 cm in diameter, consideration should be given to surgery regardless of the FNA biopsy result because FNA biopsy may be inaccurate due to sampling error. If the nodule is very firm, fixed to surrounding structures, associated with regional lymphadenopathy or vocal cord paresis then malignancy is more likely, particularly in elderly patients.

Low-dose radioiodine treatment is sometimes needed for patients with benign functioning nodules if there is biochemical and/or clinical thyrotoxicosis (Figure 3).

Thyroid cancer

Most thyroid cancers are derived from the thyroid follicular cells and are classified as papillary (80%) or follicular (10 to 15%). People with thyroid cancer have an excellent long-term prognosis after combined surgery and radioactive iodine therapy.

A rare form of thyroid cancer is the follicular cell-derived anaplastic carcinoma, which is aggressive, usually occurs in elderly patients and is rapidly fatal. The rare medullary thyroid cancer arises from the calcitonin-producing C cells and can be familial in 25% of cases. Total thyroidectomy with bilateral central with or without lateral neck dissection performed by an experienced endocrine surgeon is important in patients with medullary thyroid cancer as radioactive iodine therapy is ineffective.

Thyroid disease during pregnancy

The American Thyroid Association has recently made recommendations for management of thyroid disease during pregnancy and the postpartum period. Thyroid nodules detected in women during pregnancy can be watched and biopsied in the postpartum period, unless there are ultrasound features suspicious for malignancy or rapid growth.

Surgery for thyroid cancer detected in women during pregnancy can be performed with 'less risk' in the second trimester if there is major clinical concern, or delayed to the postpartum period if the cancer is in its early stages. If surgery is delayed until the postpartum period, then an ultrasound should be performed in each trimester to determine change. Radioactive iodine therapy should never be used during pregnancy, and breastfeeding must be discontinued for several months before use of radioactive iodine treatment.

Summary

Thyroid nodules are very common and are detected either clinically or incidentally found during a radiological procedure. Appropriate workup and investigation are needed to determine the risk of malignancy and the need for surgical intervention. In many cases, thyroid FNA biopsy is required. If there is concern regarding the possibility of malignancy then thyroid surgery is necessary.

Most thyroid nodules are benign but importantly require long-term follow up after the initial assessment. Thyroid nodules found during pregnancy create unique challenges and need careful consideration regarding the timing of investigations and management. **ET**

References

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2. Stagnaro-Green A AM, Alexander E, Azizi F, et al. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid 2011; 21: 1081-1125.

COMPETING INTERESTS: None.