Differentiating between benign and malignant thyroid nodules

An evidence-based approach in general practice

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Background
The widespread use of imaging techniques has led to more frequent detection of thyroid nodules, and while the majority are benign, the risk of malignancy in an adult ranges from 7% to 15%. General practitioners (GPs) must be able to evaluate thyroid nodules and refer cases when appropriate.

Objectives
The aim of this article is to bring GPs up to date on the evidence-based management of thyroid nodules, with specific focus on neoplastic nodules, while highlighting significant changes in the 2015 American Thyroid Association guidelines.

Discussion
Thyroid nodules frequently occur in the general population. Differentiating between a benign and malignant nodule can be challenging, and community guidelines have standardised investigation, management and follow-up procedures. The key tests for risk stratification of thyroid nodules include serum thyroid-stimulating hormone testing, ultrasonography and fine-needle aspiration. GPs should be aware of the latest evidence-based recommendations for the appropriate management of a thyroid nodule.

THYROID NODULES are discrete lesions present within the thyroid gland that are radiologically distinct from the adjacent parenchyma (Table 1).[1] They are palpable in 4–7% of the population and have been detected using ultrasonography in up to 67% of adults.[2] While the majority of nodules are benign, the risk of malignancy reaches approximately 7–15%.[1] Given the prevalence of thyroid nodules and their underlying risk, it is imperative that general practitioners (GPs) are able to appropriately assess thyroid nodules. Not only is the morbidity associated with a missed diagnosis potentially significant, but given the prevalence of the condition, excessive or unnecessary investigations lead to a significant economic burden on the healthcare system.

Evaluation of the thyroid nodule

Thyroid nodules have diverse presentations. Most are a lump in the neck that is noticed by either the patient or the GP without any associated symptoms. Many are incidentally detected on imaging tests while examining for unrelated conditions. Larger nodules can cause compressive symptoms including dyspnoea, globus and dysphagia. Any symptom suggestive of invasion, including dysphonia or dysphagia, should raise the suspicion for an underlying malignancy.

A thorough history and examination are vital in formulating a complete risk assessment of a thyroid nodule. A history of childhood head and neck irradiation significantly increases the likelihood of a thyroid nodule being malignant.[1] While the majority of thyroid malignancies are sporadic, a number of familial conditions can predispose to thyroid thyroid malignancies, including multiple endocrine neoplasia type 2 (MEN2) and familial nonmedullary thyroid cancer (FNMTC). MEN2 is associated with medullary thyroid cancer and FNMTC, which effects two or more first degree relatives and can occur in isolation or as part of a syndrome such as familial adenomatous polyposis, Cowden's syndrome, Gardner's syndrome and Carney's complex type 1.

Clinical examination should involve inspection and palpation of the thyroid gland and examination of the cervical lymph nodes. The nodule should be assessed for size, consistency and mobility. When the patient swallows, the thyroid and nodule should move in an upward direction. The presence of a firm, fixed nodule or ipsilateral cervical lymphadenopathy are late features suggestive of malignancy and should not delay further assessment.

Laboratory tests

A thyroid-stimulating hormone (TSH) serum level should be obtained in all patients suspected as having a thyroid nodule on examination or in whom one was incidentally discovered. While the majority of patients will be euthyroid, a suppressed TSH level indicates a hyperfunctioning nodule, which t, if confirmed, has an exceedingly small risk of malignancy.[1] Further evaluation of a patient with suppressed TSH levels is best managed by an endocrinologist.

Serum thyroglobulin levels are neither sensitive nor specific for the detection of thyroid cancer and should not be ordered in the evaluation of thyroid nodules.[1]

Serum calcitonin levels are expensive to obtain and should only be requested when a medullary thyroid carcinoma is suspected.

Radionuclide imaging

The 2015 American Thyroid Association (ATA) guidelines recommend that only patients with a TSH level below the normal range should undergo a radionuclide test to establish whether there is an overactive gland or a hyperfunctioning nodule.[1] Iodine-123 (^{123}I) is the recommended radionuclide; however, in Australia, imaging with technetium-99^{m} pertechnetate (^{99m}Tc) is more accessible, easier, faster and less expensive to perform. A study directly comparing the results of the two types of scintiscans showed a high degree of correlation, particularly when differentiating between hot and cold nodules.[3] In general practice, radionuclide scans should not be routinely ordered to evaluate thyroid nodules unless indicated by a low TSH result, and ^{99m}Tc should be the imaging modality of choice.

Ultrasonography

Ultrasonography is the imaging modality of choice for thyroid nodules. High-resolution machines can detect nodules as small as 1–3 mm with sensitivity of approximately 95%. All patients who are suspected of having a thyroid nodule or nodular goitre or in whom a nodule has been incidentally detected on another imaging modality should be referred for ultrasonography of the neck and thyroid. It is recommended that the thyroid nodule is not imaged in isolation on ultrasonography.[1]

The ultrasound assessment provides valuable information regarding the size and sonographic features of the nodules, which form the basis for risk stratification and guidance on fine-needle aspiration (FNA). Numerous ultrasonography-based risk stratification systems have been used, and attempts to unify assessment and decision-making for FNA continue. The 2015 ATA guidelines take a new approach to risk stratification. Thyroid nodules are categorised into five groups based on the sonographic pattern that provides an estimate of the malignancy risk and FNA guidelines (Table 2). As ultrasonography reports do not yet consistently contain risk stratification of nodules, GPs should be aware that the sonographic features with the highest specificity for thyroid cancer include microcalcifications, irregular margins and a taller than wide shape (ie greater anteroposterior diameter than transverse diameter) on an axial recumbent image.[1] If it is unclear from the ultrasound or report whether an FNA is required, the patient should be referred to a specialist who manages thyroid nodules, commonly an endocrinologist.

Fine-needle aspiration

FNA is a valuable tool in the assessment of benign and malignant nodules and has reduced the need for unnecessary thyroidectomies. When considering only technically satisfactory specimens,

Table 1. Types of thyroid nodules

	Types
Non-neoplastic	Hyperplastic Colloid Inflammatory
Thyroid cysts*	
Neoplastic	
Benign	Follicular adenoma
Malignant	Papillary Follicular Medullary Anaplastic Lymphoma Metastasis

**Nearly uniformly benign*

Table 2. Classification and estimated malignancy risk of thyroid nodules[1]

Nodule classification	Ultrasound features
Benign: • Malignancy risk: <1% • FNA not required	Cystic nodules with no solid component
Very low suspicion: • Malignancy risk: <3% • Monitor with observation • Consider FNA for nodules ≥2 cm	Spongiform or partially cystic nodules
Low suspicion: • Malignancy risk: 5–10% • FNA recommended for nodules ≥1.5 cm	Solid isoechoic or hyperechoic solid nodule OR Partially cystic nodule with eccentric solid areas
Intermediate suspicion: • Malignancy risk: 10–20% • FNA recommended for nodules ≥1 cm	Solid hypoechoic nodule with smooth margins
High suspicion: • Malignancy risk: >70–90% • FNA recommended for nodules ≥1 cm	Solid hypoechoic nodule OR Solid hypoechoic component of a partially cystic nodule PLUS one or more of the following: • Irregular margins (infiltrative, microlobulated) • Microcalcifications • Taller-than-wide shape • Rim calcifications with small extrusive soft tissue component • Evidence of extrathyroidal extension

FNA, fine needle aspiration

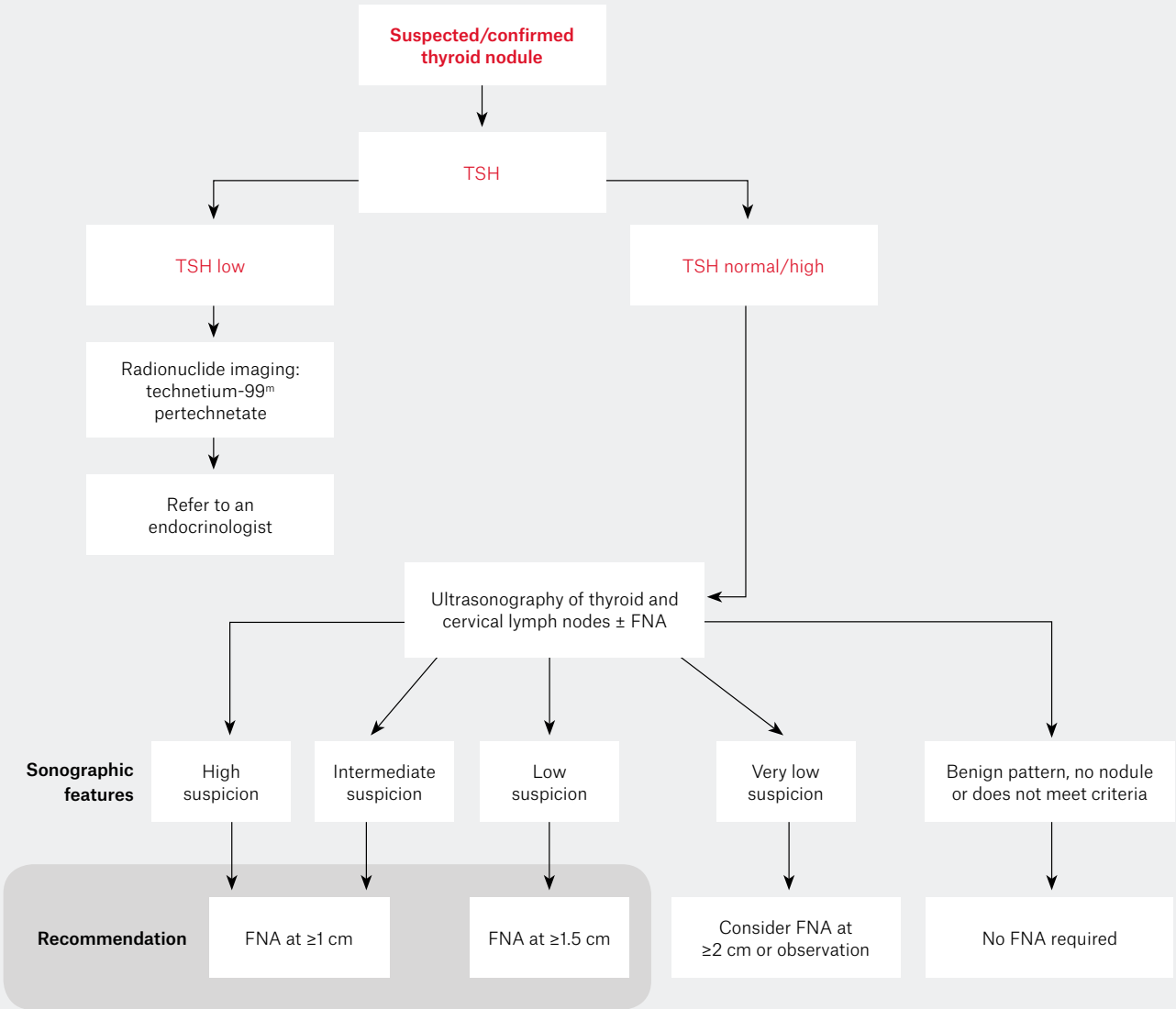

Figure 1. Suggested algorithm for the initial management of thyroid nodules in general practice[1]
FNA, fine-needle aspiration; TSH, thyroid-stimulating hormone

the diagnostic accuracy of FNA when performed by an experienced operator is approximately 95%, although this figure is dependent on how each cytology category is used in the calculation[4] The decision to perform FNA of a nodule depends on the sonographic pattern and size (Figure 1, Table 2). The new recommendation is that all cytology results should be reported using the Bethesda system for classification of thyroid nodules, which aligns with the Thy classification system adopted by the Royal College of Pathologists in the UK.[5] This classification provides an estimate of the malignancy risk for each category and provides a recommended management plan.

Management

The primary goal of a GP is to differentiate between a benign and a malignant nodule. Cytology plays a key part in determining the most appropriate management and follow-up of thyroid nodules.

The majority of thyroid nodules encountered in general practice will have benign cytology and can be monitored with a repeat ultrasound scan at a time interval determined by the sonographic features (Figure 2). A non-diagnostic or unsatisfactory test should have a repeat

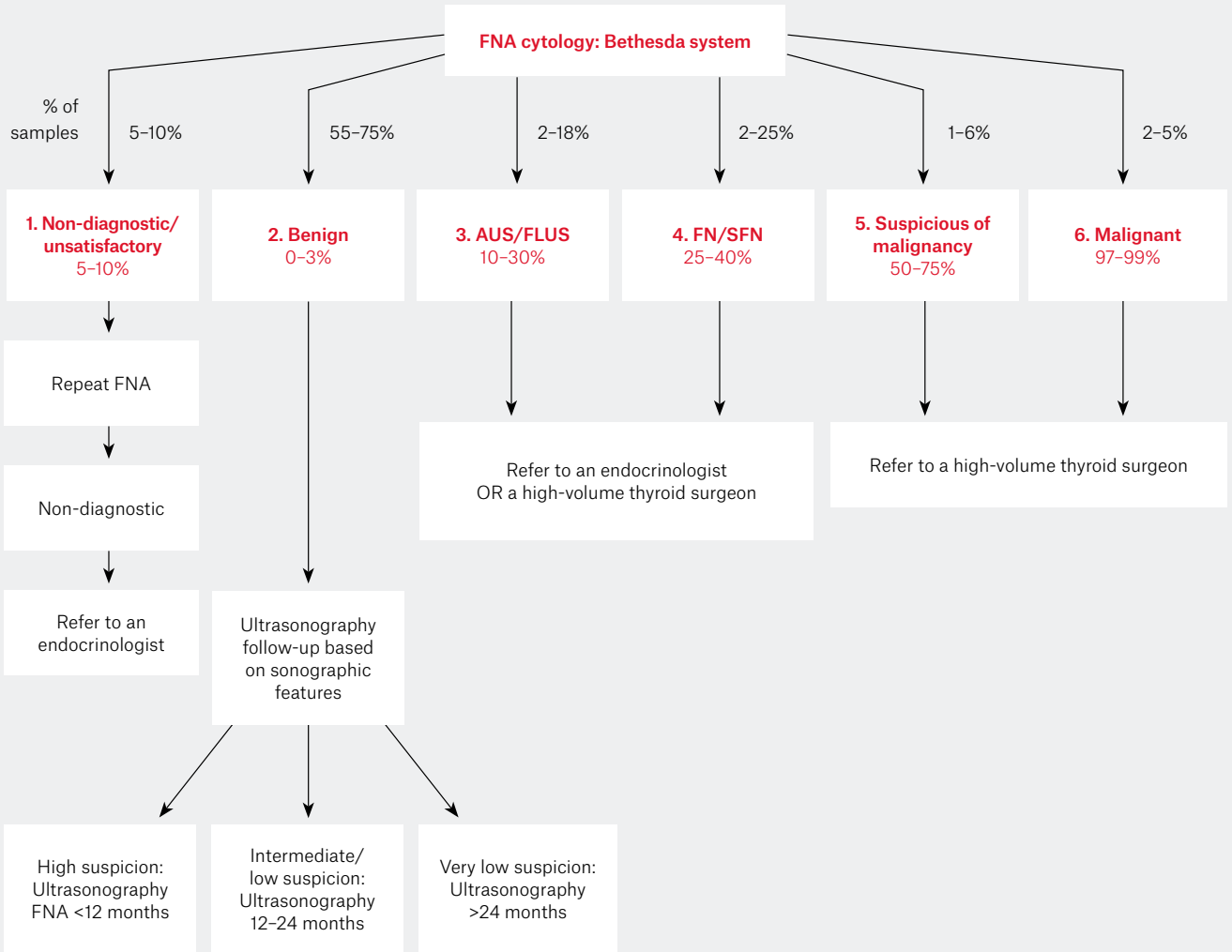

Figure 2. Bethesda diagnostic categories for thyroid cytopathology with associated malignancy risk and suggested management options in general practice[1]

AUS/FLUS, atypia of undetermined significance/follicular lesion of undetermined significance; FN/SFN, follicular neoplasm/suspicious for follicular neoplasm; FNA, Fine-needle aspiration; TSH, thyroid-stimulating hormone; FNA, fine-needle aspiration

ultrasound-guided FNA or be referred on for further assessment.

With the exception of benign cytology, all other results should be referred to an endocrinologist or thyroid surgeon for further assessment. Management of indeterminate cytology can be complex. Many endocrinologists are now experienced in interpreting and performing thyroid ultrasonography and FNA and can offer expertise in interpreting indeterminate cytology. Any malignancy or suspected malignancy should be referred directly to a high-volume thyroid surgeon.[1]

A significant proportion of thyroid nodules do not meet FNA criteria, and ultrasound features guide follow-up. Highly suspicious nodules should have repeat ultrasonography within 6–12 months, and low-risk and intermediate-risk nodules within 12–24 months. Nodules classified as very low risk and <1 cm have been shown to grow very little over five years and do not require routine ultrasonographic follow-up.[1,6]

Incidentaloma

An incidentaloma is a non-palpable, asymptomatic thyroid nodule that is detected via imaging and has the same malignancy risk as a palpable nodule.[1] Computed tomography and magnetic

resonance imaging scans cannot give precise structural details, and nodules detected using these techniques should be assessed further with ultrasonography. As a large proportion of incidentalomas will be under 1 cm, it is important they are managed according to the guidelines, to avoid over-investigation. Approximately 1–2% of FDG-PET scans show focal thyroid uptake, and a recent meta-analysis showed that 35% of those were noted to be malignant. Because of the increased risk of malignancy, the new recommendation is for patients to undergo ultrasound-based FNA for all focal nodules >1 cm detected on FDG-PET.[1,7] Nodules <1 cm that do not meet FNA criteria should be monitored.

Paediatric thyroid nodules

The incidence of paediatric thyroid nodules that are palpable is approximately 1.8–5.1% with the use of ultrasonography.[8] However, in a review of 1134 children, the overall malignancy rate was 26%, compared with 5–10% in adults.[8] The ATA guidelines suggest paediatric nodules should be evaluated in a similar manner to those in adults, with some important exceptions. As children and their thyroid glands are proportionally smaller, FNA should be based on clinical context and sonographic features rather than on the absolute size of the nodule. In cases of indeterminate cytology, because of the increased risk of malignancy, referral to a thyroid surgeon for hemi-thyroidectomy is recommended over a repeated FNA.[8,9]

Pregnancy

Nodules that are detected during pregnancy should be assessed on the basis of serum TSH levels. If the TSH level is normal or elevated, FNA should be performed. Thyroid cancer does not behave more aggressively during pregnancy, and age-matched, non-pregnant women have a similarly excellent prognosis.[10] These patients should be referred to a thyroid surgeon for discussion regarding delaying surgery or timing surgery to minimise fetal and patient risks.

Conclusion

Thyroid nodules are increasingly encountered in general practice because of the widespread use of imaging. Serum TSH, ultrasonography and FNA remain the initial investigations in general practice, with radionuclide scans reserved for patients with low TSH. The majority of nodules are benign and require follow up on the basis of the sonographic features, while malignant nodules should be referred to a high-volume thyroid surgeon. The difficulty arises when the ultrasound or cytological findings are unclear; these patients should be under the care of an endocrinologist.

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