# Thyroid Nodules: What Family Medicine Doctors Should Know

**Sanjeewa Sumathipala**
**Rashed Jassim Al Kubaisi**

Family Medicine Consultant
Primary Health Care Corporation, Qatar.

**Corresponding author:**
Dr Sanjeewa Sumathipala
Family Medicine Consultant
Primary Health Care Corporation, Qatar.
**Email:** sansumathipala@phcc.gov.qa

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## Abstract

Thyroid nodules are a common condition and family medicine clinicians are likely to encounter them not least as incidental findings from a variety of imaging modalities. Most of these nodules are benign but often investigations will need to be undertaken to exclude malignancy. Therefore, family medicine clinicians will need to know how to manage thyroid nodules, including how to assess for malignancy, including an understanding of the investigations required and what follow up is necessary.

Key words: thyroid nodules, family medicine

## Introduction

Thyroid nodules are a common condition and family medicine clinicians need to understand how they are detected and managed. Increasingly, thyroid nodules are being detected incidentally through imaging modalities such as ultrasound (US), magnetic resonance imaging (MRI), computed tomography (CT) scan and positron emission tomography (PET). The importance is to ensure that those which are malignant are treated appropriately.

It is estimated that clinically apparent thyroid nodules occur in 6.4 percent of women and 1.5 percent of men (1). Nearly two-thirds of the population have thyroid nodules when evaluated by ultrasound (2). It is estimated that there is a 10% lifetime probability for developing a thyroid nodule and females are four times more susceptible. The prevalence increases with age, occurring in 1.0%–1.5% of children (3), rising to 76% for those older than 61 years (2). The prevalence at autopsy has been reported between 50% and 65% (4). There are familial risk thyroid syndromes including familial medullary thyroid cancer and familial non-medullary thyroid cancer (5). Papillary thyroid cancer affecting a parent or sibling increases the patient's risk of developing that type of cancer by threefold and sixfold, respectively (6). A history of irradiation to the head or neck, especially if received under the age of 20 years, or older than 70 years, has been reported to cause a rate of development of thyroid nodules of 2% per year, with a peak incidence in 15 to 25 years (5).

**Pathogenesis**

The American Thyroid Association (ATA) defines thyroid nodules as "discrete lesions within the thyroid gland, radiologically distinct from surrounding thyroid parenchyma" (7). The underlying cause for thyroid nodule development has yet to be defined.

Many disorders can cause thyroid nodules including benign processes such as Hashimoto's thyroiditis, or malignancies such as papillary cancer and thyroid lymphoma, as well as metastases most commonly arising from lung, renal and head and neck neoplasms (8).

Genetic mutations, such as the BRAF mutation and RAS driver mutation and iodine deficiency can promote thyroid nodule formation (9). A BRAF mutation can be found in papillary cell cancers, and RAS driver mutation is detected in follicular adenomas, follicular thyroid cancer, and follicular variants of papillary cell cancers (9).

**Types of nodules**

There are several types of thyroid nodules (10). Most thyroid nodules are benign. Colloid and hyperplastic nodules are benign and can occur as solitary nodules or as part of a multinodular goitre. Thyroid cysts and thyroid adenomas are also benign, but surgery is usually required to determine that there is no malignancy present when an adenoma is suspected.

Malignancy is considered to occur in 4.0 to 6.5% of all thyroid nodules (8). The most common thyroid cancer is papillary thyroid carcinoma (PTC), accounting for 80–85% of thyroid malignancies. There is frequently lymph node involvement. Women are more frequently affected, and the peak incidence occurs in the third and fourth decades. Follicular thyroid cancer comprises 10% of thyroid malignancies, spread through the blood stream and develop in a pre-existing follicular adenoma.

Medullary carcinoma produces calcitonin and comprises 5% of thyroid malignancies. It can be familial, as part of multiple endocrine neoplasia (MEN) type II syndrome, or occur sporadically. Anaplastic carcinoma yields the worst prognosis with peak incidence in the sixth to seventh decades. It typically presents late with symptoms such as dyspnea, dysphagia, and laryngeal nerve palsy (11).

**Management**

There are several guidelines available for evaluation of thyroid nodules from organizations such as the American Thyroid Association (ATA) and the British Thyroid Association (9). The guidelines recognize the need to use the findings from a variety of sources, including clinical examination, measurement of serum thyroid stimulating hormone (TSH), ultrasound assessment, fine needle biopsy (FNA) cytological results, and patient preferences as part of the decision making. Newer methods, like molecular marker detection are being developed to reduce the amount of unnecessary surgical interventions.

**Clinical examination.**

A detailed focused history is required including looking for risk factors such as a family history of thyroid malignancy or personal history of irradiation. A physical examination, not just of the thyroid but important related anatomy such as regional lymph nodes (usually deep cervical or supraclavicular region ) is important.

Thyroid nodules when symptomatic can present in a variety of ways, such as a palpable neck mass, anterior neck pain, dysphagia, globus sensation, and voice changes (9). The onset and rate of progression of symptoms are important in terms of risk of thyroid cancer, with persistent hoarseness and rapidly growing thyroid nodules more likely to indicate a malignant cause.

Red flag symptoms have been identified (12):

- Family history of thyroid malignancy
- History of irradiation
- A thyroid nodule in childhood
- A thyroid swelling with unexplained hoarseness or stridor
- Rapidly enlarging thyroid mass over a period of a few weeks
- Palpable cervical lymphadenopathy
- Several weeks of persistently painful thyroid.

Many of the methods of evaluating a thyroid nodule are undertaken in secondary care. According to UK's National Institute for Health and Care Excellence (NICE) (13), immediate hospital admission is required if there are signs of tracheal compression such as severe stridor at rest. An urgent referral, expecting an appointment within 2 weeks is indicated if:

- There is an unexplained thyroid lump
- A thyroid swelling in the presence of unexplained voice changes
- A thyroid swelling associated with cervical lymphadenopathy
- A painless thyroid swelling that is increasing in size
- A thyroid nodule in a child

A non-urgent referral should be considered if:

- There is a thyroid nodule and abnormal thyroid function tests
- A sudden onset of pain in a thyroid lump

Management in primary care can be considered if:

- There are several years of an unchanged nodule or goiter and no red flag features.

**Blood tests**

TSH measurement is recommended by the ATA guidelines for the evaluation of a thyroid nodule (14). A suppressed TSH level (< 0.3 mU/L) suggests an autonomously functioning nodule, and a thyroid scan with iodine-123 should be performed. A hyperfunctional or "hot" nodule is rarely malignant, and biopsy is typically not required (14).

Calcitonin is a tumor marker for medullary thyroid carcinoma (MTC) which develops from calcitonin secreting C tumor cells. Routine serum calcitonin measurement is not recommended in the ATA's guidelines (14). Calcitonin measurement may be of benefit if there is a family history of medullary thyroid carcinoma or MEN type 2.

**Radionuclide thyroid scan/scintigraphy**

Thyroid gland scintigraphy uses radioisotopes of iodine or technetium-99 pertechnetate to detect timed radioisotope uptake by the thyroid gland. There will be greater uptake in a hyperfunctioning nodule than in surrounding normal tissue, and these nodules will appear "hot". In virtually all malignant and benign nodules, the uptake will be lower, and they will appear cold on scintigraphy.

Although ultrasound has largely replaced scintigraphy, the latter can still be utilized to identify hyperfunctioning "hot" nodules when a low TSH is found on initial testing, and which nodule(s) to sample in in presence of multiple nodules (15). However, Radionuclide scintigraphy or radioiodine uptake determination is contraindicated during pregnancy and cannot be used if the patient is breast feeding (16).

**Ultrasound.**

A normal thyroid normally demonstrates an isoechoic homogeneous structure with a fine granularity not exceeding 1 mm (8). Thyroid Ultrasound (US) should be performed on all patients with nodules suspected clinically or incidentally noted on other imaging studies such as CT or MRI scanning (8).

Thyroid ultrasound can be used to confirm the presence of a nodule and sonographic features as well as detecting regional lymphadenopathy. Malignant thyroid nodules appear solid with irregular margins, possess microcalcifications, taller-than-wide shape with hypoechoic echotexture. A nodule being taller than wider has the highest diagnostic odds ratio for malignancy. Purely cystic nodules with a spongiform appearance are more likely to be benign.

**Fine Needle Aspiration**

Fine needle aspiration biopsy (FNA) is held to be the gold standard method for evaluating thyroid nodules (8). There are a variety of cytological results that can be obtained through FNA:

- Nondiagnostic or unsatisfactory
- Benign
- Atypia of undetermined significance or follicular lesion of undetermined significance
- Follicular neoplasm or suspicious for a follicular neoplasm
- Suspicious for malignancy
- Malignant

**Treatment of thyroid nodules.**

80% of biopsied nodules are benign (noncancerous). Typically, they do not require removal unless they are causing symptoms such as dysphagia. Percutaneous ethanol ablation can be considered as a treatment modality for thyroid cysts and certain complex thyroid nodules, and there is no role for TSH suppressive therapy in the management of a benign nodule (17).

Indeterminate results (10–15 % of all FNAs), lacking a distinct cytological diagnosis pose a challenge in terms of next steps for management. Traditionally, an ipsilateral thyroid lobectomy can be performed, preceding to a thyroidectomy if cancer is found. The ATA recommends molecular testing to be considered to establish the risk of malignancy by looking for gene mutations. However, patients who do not undergo surgery must be followed with serial imaging to ensure stability of their nodules (18).

5% of biopsies yield a malignant result and surgery is recommended, typically removal of the lobe containing the biopsied nodule. A suspicious biopsy has a 50-75% risk of malignancy and surgical intervention is normally undertaken (8). Active surveillance can be indicated for low risk papillary microcarcinoma or if the patient has significant co-morbidity or limited life expectation. The management of metastatic thyroid nodules will be influenced by the primary malignancy (8).

The biopsy is typically nondiagnostic or inadequate in less than 5% of cases when an ultrasound is used to guide the FNA (8). A repeat FNA or surgery may be required depending on the risk factors and the growth of the nodule.

Radioactive iodine can be used to treat a hyperfunctioning nodule which has an annual risk of 4% of causing hyperthyroidism (15). Antithyroid drugs, such as propylthiouracil, can be used to treat a patient with hyperthyroidism (hot nodule) but recurrence can occur when the medication is stopped. Surgery may be used for patients with a large thyroid nodule especially if they cause compression of local structures.

**Thyroid nodules in pregnancy**

Thyroid nodules have been reported to be detected in 3% and 21% of pregnancies (16). It is estimated that 10% of thyroid cancers occurring in the child-bearing age are detected during pregnancy or in the first-year post-partum, the most common type being papillary carcinoma (19). The American Thyroid Association (ATA) recommends utilizing a thorough history, physical examination, TSH and thyroid ultrasound in the work up of a thyroid nodule in a pregnant person. Radionuclide scintigraphy is contraindicated during pregnancy (16). A multidisciplinary approach involving obstetricians, pathologists, radiologists, endocrinologists and surgeons is recommended (11).

The timing of surgical intervention is affected by the type of thyroid cancer. Patients with papillary and follicular thyroid cancer can have surgery during the second trimester or post-partum. There is a risk of teratogenicity and of miscarriage if thyroidectomy is undertaken in the first trimester and premature labor if the surgery is undertaken in the third trimester (11). Medullary carcinoma

or anaplastic cancer require surgery during pregnancy. Pregnancy is not thought to be compromised by thyroid cancer (16). There is no significant difference between the overall prognosis and survival rates for thyroid cancer during pregnancy from that in nonpregnant women with similar disease (11).

**Thyroid nodules in children**

Thyroid nodules occur in 1.0%–1.5% of children compared to a prevalence of up to 68% of adults at high resolution ultrasonography (20). A thorough history should be undertaken to include whether there has been exposure to radiation and whether there are first degree relatives with MEN (multiple endocrine neoplasm) type 1 and 2. The same steps are undertaken to diagnose the thyroid nodule in adults and in children, and typically an ultrasound guided FNA is undertaken.

The likelihood of a nodule being malignant is approximately 4-5 times higher than in adult patients (21) with more chance of lymphatic and pulmonary involvement at diagnosis (22). Thyroid nodules are more common in girls, malignant thyroid disease is more common in boys, and typically before the age of 10. Like in adults, the most common thyroid malignancy in children is papillary carcinoma. Approximately 5 percent are medullary thyroid carcinomas, most commonly in association with MEN type 2. Of the benign nodules, the nodular type found in Hashimoto disease is the most common (21).

Children with thyroid nodules can be managed in a similar way to adults (22). Benign thyroid nodules that do not enlarge, a conservative approach, with a "watch and wait" approach can be undertaken. Papillary thyroid cancer is usually multifocal, and so require total or near-total thyroidectomy (23). Children at a high risk for developing medullary thyroid carcinomas can have a total thyroidectomy prophylactically during infancy or early childhood (24).

**Follow up:**

Follow up is determined by a variety of factors, including whether a diagnosis has been reached, the extent of the intervention undertaken and its effect on the thyroid gland, and patient preference. Careful monitoring and repeat biopsies within 1 to 2 months are required with an FNA is inadequate, inconclusive, or indeterminate (25). After subtotal surgery, an ultrasound can be used to monitor the remaining thyroid gland. After surgery, TSH is usually measured annually to detect hypothyroidism. Monitoring of thyroglobulin levels can be used to screen for cancer recurrence after total thyroidectomy for papillary and follicular carcinoma.

**Learning points**

Thyroid nodules are extremely common and can be detected incidentally through a variety of imaging modalities. Although most thyroid nodules are benign, malignancy needs to be identified, initially with a careful history and clinical examination. The presence of risk factors for malignancy as well as ultrasonic features helps to decide which nodules require more investigation or intervention. Fine needle aspiration cytology is the gold standard to evaluate thyroid cancer risk although molecular marker assessment is evolving, especially for indeterminate cytological diagnosis. Benign nodules typically require no further intervention. Malignant nodules often require surgery in the form of a lobectomy or thyroidectomy depending on tumor type and follow up is required to ensure that there is no recurrence. Thyroid nodules detected in pregnancy are assessed in essentially the same manner as for non-pregnant patients, but thyroid malignancy needs to be timed according to the tumor type. Pediatric nodules have a greater chance of malignancy, particularly for boys. Risk factors such as irradiation and the possibility of familial thyroid malignancy needs to be considered.

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