Management of the thyroid nodule

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Abstract

Thyroid nodules are common, and a frequent reason for referral to secondary care. Clinical assessment and investigation should aim to address: functional status of the thyroid; exclusion of malignancy; and the presence of other symptoms (e.g. tracheal or oesophageal compression). A combination of neck ultrasound and fine-needle aspiration cytology (FNAC) can usually help establish a plan of management, allowing conservative management of most patients, and surgical treatment for those with suspected or confirmed thyroid cancer. The limitations of FNAC include a relatively high rate of inadequate/non-diagnostic samples, and the inability of cytology to distinguish between benign and malignant follicular neoplasms. Surgery may therefore be required to establish the diagnosis in patients with indeterminate nodules, in addition to its role in treatment for compressive symptoms or thyrotoxicosis.

Keywords Fine-needle aspiration cytology; follicular neoplasm; thyroid cancer; thyroid function; thyroid nodule; ultrasound

Thyroid nodules are very common, and a frequent reason for surgical consultation. The thyroid naturally tends to become nodular with increasing age, and clinically significant thyroid nodules are also more frequent in females compared to males. In Western society, prevalence has been estimated to be as high as 35–65% if sensitive methods of detection, such as ultrasound or assessment of the thyroid gland at autopsy, are used, but up to 2–6% of the population may have a palpable thyroid nodule.[1]

The majority of thyroid nodules are benign, usually representing part of the spectrum of multi-nodular goitre (degenerate, haemorrhagic or hyperplastic nodules, cysts).

However, some are neoplastic.

Benign neoplasms:

- follicular adenoma, including Hurthle cell adenoma.

Malignant neoplasms:

- papillary thyroid cancer (and its sub-types)
- follicular thyroid cancer (including Hurthle cell cancer)
- medullary thyroid cancer (arising from the neuro-endocrine C-cells)
- anaplastic thyroid cancer
- primary Thyroid Lymphoma
- metastases to the thyroid from cancer elsewhere.

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Most thyroid nodules present as a neck lump. This is usually the thyroid nodule itself, although occasionally the palpable abnormality is a lateral neck lymph node metastasis in a patient with thyroid cancer. Thyroid nodules are also often discovered as an incidental finding on imaging performed for another reason, such as:

- Ultrasound scanning of the neck for other pathology, e.g. to assess non-thyroid neck lumps, or for duplex scanning of the carotid arteries.
- Positron-emission tomography (PET-CT), often used in staging of other cancers.
- Chest X-ray or computed tomography (CT) of the chest performed for respiratory symptoms (a common presentation of retro-sternal nodules and goitres).
- MRI for assessment of the cervical spine.

Clinical evaluation

Assessment of thyroid nodules should aim to answer the following questions:

- What is the functional status of the thyroid?
- Is the nodule benign or malignant?
- Is the nodule causing any other symptoms (which might necessitate treatment, even if benign)?

The clinical history should therefore concentrate on eliciting any symptoms suggestive of thyroid dysfunction; risk factors for malignancy; symptoms suggestive of cancer; and compressive symptoms.

Dysfunction

Symptoms of hyperthyroidism may include weight loss (typically with a normal or increased appetite), sweating, tremor, anxiety, tiredness/disturbed sleep, and palpitations (usually with a rapid heart rate). Conversely, hypothyroidism might be implied by unexplained weight gain, lethargy, dry skin, and frequently a decline in cognitive function. It should be recognized, however, that symptoms might be lacking, even when thyroid function is abnormal, hence a biochemical assessment of thyroid function will always be necessary.

Risk factors for thyroid malignancy

Age: there is a bi-modal distribution of incidence of thyroid cancer with age, with a small peak in childhood/early adolescence, and a later peak after age 50 years.[2] Conversely, most benign nodules present between ages 30–50 years. Hence, the probability of an individual nodule proving malignant is highest at the extremes of the age distribution.

Gender: the incidence of thyroid cancer has an approximately 2.3–2.6:1 female:male ratio, whereas for benign disease this ratio is closer to 4–4.7:1.[2–4]

Hence, the probability of a thyroid nodule proving malignant in a man is paradoxically greater than in a woman.

Family history: genetic predisposition to thyroid cancer may be revealed by a careful family history. Around 20–25% of medullary thyroid cancer (MTC) is associated with germ-line mutations in the RET-oncogene, as part of multiple endocrine neoplasia type 2 (MEN2) or familial medullary thyroid cancer (FMTC).[5,6]

The former is associated with phaeochromocytomas and primary hyperparathyroidism. A history in a family member, of

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thyroid cancer (especially at an early age), or of premature sudden death (suggesting phaeochromocytoma) should raise the suspicion of MEN2.

Other familial syndromes[6] can increase the risk of both papillary and follicular cancers, including familial papillary thyroid cancer (fPTC), Cowden's syndrome (other features include multiple skin and mucous membrane hamartomas, breast cancer, macrocephaly and mental retardation), and familial adenomatous polyposis (FAP), typically associated with multiple intestinal polyps and colorectal cancer.

History of radiation exposure: radiation significantly increases the risk of thyroid cancer, particularly in young individuals. A history of external beam radiotherapy to the head, neck or upper chest/breast should specifically be sought (most commonly for Hodgkin's lymphoma or breast cancer).

Past history of cancer elsewhere: clinically significant metastases to the thyroid are uncommon, but can occur in patients with previous lung, breast, colorectal or renal cancer, or melanoma.

Symptoms suggestive of cancer

Few features of the history are specific for thyroid malignancy. However, the following raise suspicion:

- Hoarseness of the voice: in association with a thyroid mass, this is suggestive of vocal cord palsy, secondary to invasion of the recurrent laryngeal nerve. Benign lesions almost never compromise this nerve (although hoarseness may be due to unrelated, benign disease).
- A rapidly enlarging mass, growing steadily and swiftly over a few weeks: very suggestive of more aggressive forms of thyroid cancer, as detailed below. (In contrast, a lump appearing over 24–48 hours is likely to represent a bleed into a thyroid cyst, most of which are benign).
- Symptoms of local invasion of structures in the neck: pain in the ipsilateral ear (referred otalgia), stridor, dysphagia or haemoptysis.

Compressive symptoms

Even benign thyroid masses, if large enough, can cause compression of the cervical oesophagus or trachea, causing difficulty swallowing, a sensation of tightness in the neck, or of difficulty/noisy breathing.

Summary of key features in the history

- Features of hypo/hyperthyroidism
- Hoarseness of voice
- Family history
- Past history of head/neck irradiation
- Compressive features – noisy breathing, dysphagia

Physical examination should comprise:

Assessment of thyroid functional status

Hyperthyroidism may be manifest by resting tachycardia, agitation, tremor, palmar sweating, and signs of weight loss; while bradycardia, dry skin and hair, obesity and slow mentation may imply hypothyroidism.

Neck examination

This should determine whether or not the presenting lump is within the thyroid, and if so whether the lump is clinically:

- A solitary nodule.
- A dominant nodule within a multi-nodular gland ('dominant' implying the largest, most symptomatic or most suspicious nodule).
- A smooth, symmetrical goitre (usually suggestive of autoimmune thyroiditis).

Examination of the neck should also look for lymphadenopathy and assess for tracheal deviation.

Red flag signs for malignancy include a fixed hard mass, cervical lymphadenopathy, stridor, and hoarseness.

Investigation

A blood test for thyroid function should be performed. Serum thyroid stimulating hormone (TSH) alone is adequate, if the patient is clinically euthyroid, and there is no suspicion/history of pituitary disease. If TSH level is outside the reference range, free thyroxine (T4) and free tri-iodothyronine (T3) should be measured.

Optimal further investigation depends upon the clinical picture. The following scenarios are most frequently observed:

The euthyroid, solitary (or dominant) thyroid nodule

These are patients with a normal TSH and a solitary thyroid mass or a 'dominant' or large nodule in a background multinodular goitre. The risk of the dominant nodule being malignant is similar to that for solitary nodules,[7] hence management is similar. The main clinical concern is to establish whether or not the lesion is malignant. First-line investigations are an ultrasound scan of the neck, with or without fine-needle aspiration cytology.

Ultrasound

When undertaken by an appropriately trained and experienced sonographer, ultrasound can reliably be used to guide subsequent management.

Sonographic features of a thyroid nodule can be used to assess the likelihood of malignancy.[5] Features such as spongiform texture, cysts without solid components, iso-echogenicity, hypoechoic halo, avascular nodules or nodules with peripheral vascularity are typically benign; whereas irregular margins, intra-nodular vascularity, micro-calcifications and associated cervical lymphadenopathy are indicators of malignant pathology.

The British Thyroid Association guidelines[5] for the management of thyroid cancer suggest that the cumulative sonographic features of thyroid nodules should be summarized in a U1–5 classification, as follows:

- U1 Normal thyroid
- U2 Benign
- U3 Equivocal
- U4 Suspicious
- U5 Malignant

Lesions classified as benign (U2) do not necessarily require fine-needle aspiration to confirm benignity, unless there are suspicious clinical features such as increasing size of the lesion,

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