THE ASYMPTOMATIC THYROID NODULE

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Two key features need to be clarified when dealing with a thyroid nodule: its function and its nature. A nodule may be present in a patient who is hyperthyroid, euthyroid or hypothyroid and may be benign or malignant. An asymptomatic thyroid nodule, presupposes a euthyroid patient with no pressure effects. Furthermore an asymptomatic nodule may be palpable or non-palpable. Non-palpable nodules are the most common and are discovered incidentally due to increasing neck imaging¹.

Asymptomatic thyroid nodules are not an uncommon presentation. The fear of cancer and cosmetic concerns often prompt patients to seek medical attention. Physicians are now faced with a considerable load of patients with incidental nodules that may not be of any clinical significance.

In the United States (an iodine replete country), 4% of the population has a palpable thyroid nodule and up to 50% older than 50 years have incidental nodules on ultrasound and at post mortem².

Only 5% of all thyroid nodules are malignant³. Papillary carcinoma, the most favourable histological type, is the most common cancer subtype (80%)⁴,⁵.

The relevant further investigations in these incidentally discovered nodules include thyroid function test, imaging and cytology depending on risk profile of the patient.
INVESTIGATIONS

Risk Profile for Thyroid Cancer

A nodule in the young (< 20 years) and elderly (> 60 years) is considered at high risk for malignancy. Radiation exposure, whether accidentally or post-treatment of head and neck cancers is a risk factor for thyroid cancer. A firm solitary nodule in a male patient is more likely to be malignant than a multinodular goitre in a female.

A family history of previous thyroid cancer in a first-degree relative is important. Multiple Endocrine Neoplasia (MEN type 2A and 2B) needs to be investigated to rule out medullary thyroid cancer (MTC). Genetic screening of a family with MTC is important to address the risk of cancer before it develops.

A geographic iodine deficient area predisposes to certain thyroid cancers. There is a prevalence of follicular cancer in iodine deficient areas whereas papillary cancer is by far more prevalent in iodine rich areas.

Signs and symptoms suggestive of malignant infiltration (rapid growth, hoarse voice, cervical lymphadenopathy) do not apply to an asymptomatic thyroid nodule.

Thyroid Function Test (TFT)
Thyroid-stimulating hormone (TSH) is the most sensitive and allows differentiation between hyperthyroid, euthyroid and hypothyroidism. A free thyroxine (FT4) level will then subdivide between clinical and subclinical hypothyroidism and hyperthyroidism.

Tumour markers such as Thyroglobulin are not useful in the initial evaluation of thyroid pathology. Thyroglobulin may be raised by both benign and malignant conditions. However, after total thyroidectomy for differentiated thyroid cancer (DTC), any rise in thyroglobulin may represents recurrence and/or metastases.
IMAGING MODALITIES

Ultrasound$^{2,5}$

Ultrasound is the imaging modality of choice. It does not accurately discriminate benign from malignant nodules but may identify suspicious features (Table 1) that need further characterisation by ultrasound-guided fine needle aspiration (FNA).

Furthermore, it provides information on the regional lymph nodes that may be suggestive of metastases. Currently, there is a trend to report thyroid imaging in the TIRADS$^{6}$ format (thyroid image reporting and data system). The American Thyroid Association (ATA) published the 2015 guidelines on a nodule's risk of malignancy based on the sonographic pattern (Table 2).

Table 1. Sonographic Features of Thyroid Nodule

<table>
<thead>
<tr>
<th>Sonographic features</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcification</td>
<td>Micro calcification (axial)</td>
<td>Micro calcification (coarse or spiculated)</td>
</tr>
<tr>
<td>Border</td>
<td>Regular</td>
<td>Irregular, extra thyroidal extension</td>
</tr>
<tr>
<td>Halo</td>
<td>Thin</td>
<td>Thick or no halo</td>
</tr>
<tr>
<td>Vascularity</td>
<td>Peripheral</td>
<td>Central</td>
</tr>
<tr>
<td>Consistency</td>
<td>Cystic</td>
<td>Solid or mixed</td>
</tr>
<tr>
<td>Echogenicity</td>
<td>Hypo/iso/hyper echoic</td>
<td>Hypo echoic or heterogeneous</td>
</tr>
<tr>
<td>Diameter</td>
<td></td>
<td>Taller than wide (&lt; 1cm)</td>
</tr>
<tr>
<td>Nodes</td>
<td>No suspicious nodes</td>
<td>Suspicious nodes</td>
</tr>
</tbody>
</table>

Table 2. ATA Guidelines 2015 – Ultrasound Pattern and suggested FNA Cutoffs

<table>
<thead>
<tr>
<th>Ultrasound suspicion</th>
<th>Risk of cancer</th>
<th>Ultrasound pattern</th>
<th>Indication for FNA</th>
<th>Strength of recommendation</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>70-90%</td>
<td>Microcalcification, hypoechoic, irregular margin, taller than wider, extra thyroid extension</td>
<td>≥ 1cm</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>Intermediate</td>
<td>10-20%</td>
<td>Hypoechoic, solid, regular margin</td>
<td>≥ 1cm</td>
<td>Strong</td>
<td>Low</td>
</tr>
<tr>
<td>Low</td>
<td>5-10%</td>
<td>Hyper/isoechoic, solid, regular margin, partially cystic with eccentric solid area</td>
<td>≥ 1.5cm</td>
<td>Weak</td>
<td>Low</td>
</tr>
<tr>
<td>Very low</td>
<td>&lt;3%</td>
<td>Spongiform, partially cystic no suspicious features</td>
<td>≥ 2cm or No FNA (follow up)</td>
<td>Weak</td>
<td>Moderate</td>
</tr>
<tr>
<td>Benign</td>
<td>&lt;1%</td>
<td>Cyst</td>
<td>No FNA</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
Radionucleotide Thyroid scans\(^5\)
Radionucleotide scans have a limited role in the evaluation of the euthyroid nodule and are more commonly used in the work up of Differentiated Thyroid Cancers (DTC) post total thyroidectomy to detect metastases and residual thyroid tissue in the neck.

CT scans, MRI, Fluorodeoxyglucose–Positron Emission Tomography (FDG-PET) Scan\(^1,5\)
There is no indication for these in the asymptomatic thyroid nodules. However they may on occasion reveal an incidental nodule. These should be managed as any other asymptomatic thyroid nodule. Patient risk profile should be taken into consideration. Ultrasound follow-up and FNA when indicated. Special mention is made about nodules identified by FDG-PET because the risk of malignancy is high (33.3%).

X-Ray
It is usually done as a routine preoperative investigation to assess the degree of tracheal deviation but it adds no value in the work up of asymptomatic thyroid nodule. Occasionally incidental mediastinal goitre is identified in a patient without any obvious thyroid nodule in the neck or related symptoms.

Cytology: FNA
The FNA is the gold standard in the evaluation of the thyroid nodule\(^7\). The report is standardised by using the Bethesda classification (Table 3). The Bethesda system has reduced the need for surgery in approximately 20-50% of patients with a benign FNA. The false negative rate is reduced when ultrasound guided FNA is routinely available\(^8\). Surgery (lobectomy or total thyroidectomy) for a benign goitre (THY 2) is only considered for pressure symptoms and cosmesis.
**Table 3. Bethesda Distribution and Risk of Cancer**

<table>
<thead>
<tr>
<th>Category</th>
<th>%</th>
<th>% (Risk of cancer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>THY 1 Inconclusive</td>
<td>~10%</td>
<td>1-5%</td>
</tr>
<tr>
<td>THY 2 Benign goitre</td>
<td>~65%</td>
<td>2-4%</td>
</tr>
<tr>
<td>THY 3 AUS or FLUS</td>
<td>9-24%</td>
<td>5-15%</td>
</tr>
<tr>
<td>THY 4 Follicular/ Hurthle cell neoplasm</td>
<td>15-30%</td>
<td></td>
</tr>
<tr>
<td>THY 5 Suspect for malignancy</td>
<td>~4%</td>
<td>60-75%</td>
</tr>
<tr>
<td>THY 6 Definitely malignancy</td>
<td>~6%</td>
<td>97-100%</td>
</tr>
</tbody>
</table>

*FLUS: Follicular lesion of unknown significance. AUS: Atypical cell of unknown significance.*

Failed or inadequate cytology mandates repeat FNA (preferably sonar guided). Atypical nodules and follicular neoplasms (THY 3 and 4) are treated by a diagnostic lobectomy to rule out cancer. Nodules that are suspect or definitely malignant (DTC) need surgery (either total thyroidectomy or lobectomy). Patient in the indeterminate category (THY 3, THY 4 and THY 5) are still undergoing surgery that yields benign histopathology in the majority of cases; molecular testing is aiming at addressing this shortcoming of FNA.

Logistical and capacity constraints may constrain the ability to perform all FNAs under ultrasound guidance, but a non-palpable nodule or a nodule in a difficult location are indications for ultrasound guided FNA. The same applies to a repeat FNA, a nodule that is increasing in size and a nodule that is mainly cystic.

**Molecular testing**

Molecular testing is classified as follow:

1. Somatic mutations (BRAF V600E, RAS, RET/PTC, PAX8-PPAR-γ).
2. Gene expression analysis (HMGA2, UbcH10).

This is an emerging modality that aims at distinguishing benign from malignant diseases. There is controversy on its role in surgical decision-making.
Molecular testing is inappropriate when there is already an indication for or against surgery (THY 1, THY 2, THY 5 and THY 6). It is believed to be of most value in the patients with Bethesda THY 3 and THY 4 where the current management of Bethesda THY 3 and THY 4 is diagnostic lobectomy where majority of cases (up to 80%) are benign on final histopathology\(^\text{12}\).

Molecular testing is expected to decrease surgery in these categories. Molecular testing should not be used in isolation but in combination with other factors (cytology, risk profile, ultrasound pattern). Further validation is required to gain wide acceptance, as its current sensitivity and specificity are not yet adequate\(^\text{7,13}\).

It is anticipated that molecular testing will be incorporated in the Bethesda classification to prevent unjustified surgery especially in THY 3 and THY 4 lesions. ThyraMIR™ microRNA gene-expression classifier and the genetic-mutation panel ThyGenX® (Interspace Diagnostics) are newly available combinations of molecular tests that are promising\(^\text{14}\).

**MANAGEMENT OF ASYMPOTOMATIC THYROID NODULES**

**ATA Guidelines 2015\(^\text{9}\)**

*Palpable nodule: Nodule > 1cm*

The palpable nodules are offered FNA preferably under ultrasound guidance to target the sonographically suspicious nodule (Table 1).

The decision to FNA the patient takes into consideration the risk profile and the sonographic features\(^\text{9}\). It is important to recognise that guidelines can be adjusted to suit a patient specific consideration.
*Incidental (non-palpable) nodule: < 1cm*

A subcentimetre nodule does not require a FNA. Investigating the incidental nodule is futile because most of these nodules are benign and there is a concern of superfluous surgery with potential complications. Moreover even when micropapillary cancer (<1cm) is identified, it is of little significance and is unlikely to affect the patient outcome¹.

**CONCLUSION**

Due to the increased use of imaging, more and more incidental thyroid nodules are detected, the significance of which is questionable. The majority of these patients should be considered for follow up and reassurance. It is important to recognise a small subgroup of patients who may need further investigation to rule out malignancy. Even when nodules are reported to harbor malignancy, the extent of thyroidectomy should be individualised to avoid aggressive surgery on patients with low risk profile.

**REFERENCES**


