Guideline-Integrated Approach to Thyroid Nodule Workup

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The approach to thyroid nodule work-up is challenging for the radiologist. Thyroid nodules are extremely common affecting approximately 50% of North Americans as measured by autopsy, and 40% by ultrasound. However, only 4.5-6% of these are found to be malignant.

The percentage of clinically significant malignancy is even lower, at 2%. Thus, the balance between over-investigation and delayed diagnosis of a malignant nodule remains problematic. Moreover, the imaging presentation of many thyroid nodules is nonspecific with overlap between malignant and benign nodules, further complicating the issue.
This exhibit will provide a review of:

- Relevance of Clinical History and Endocrine Profile for Nodule Workup
- Key Features of Benign and Malignant Nodules
- Predictive Values of Imaging Characteristics
- Algorithm for Radiological Management of Thyroid Nodule
Physical exam is not sensitive, but a handful of historical elements raise the suspicion of malignancy including history of rapid growth of a neck mass, childhood:

- Head and neck irradiation (e.g. Chernobyl and Fukushima émigrés)
- Total body irradiation for bone marrow transplantation
- Family history of thyroid cancer
- Thyroid cancer syndromes (MEN 2, FAP, Cowden Syndrome)
Serum TSH is an independent risk factor for predicting malignancy in a thyroid nodule. At serum concentrations above 5.5 mU/L, the risk approaches 30%. When cancer is known, higher TSH is generally associated with advanced stage.

Radionuclide scintigraphy should be reserved for patients with depressed TSH levels.
Key Features of Malignant Nodules

- Microcalcifications
- Marked Hypoechogenicity
- Spiculated/Irregular Margins
- Taller-than-Wide
Microcalcifications

- There is no single feature that can be used to identify malignant nodules. However, microcalcifications are the most specific characteristic of a malignant nodule and FNA is required.

- Calcifications can be seen in benign nodules, but tend to be coarse or “eggshell” in appearance. However, they are also seen in malignancy.
Surgically proven papillary carcinoma. (A) Contrast-enhanced CT demonstrates primarily hypodense nodule with punctate microcalcifications (arrow). (B) Ultrasound demonstrates a nodule with hypoechogenicity and punctate echogenic foci consistent with microcalcifications, which correspond with histopathologic psammoma bodies. Both are sonographic features associated with malignancy. Unless these calcifications are clumped, there is usually no posterior shadowing. (C) Color doppler ultrasound demonstrates absence of intranodular flow.
**Key Features of Malignant Nodules**

- **Marked Hypoechogenicity**
  - Hypoechogenicity is predictive of malignancy (Fig 1). Markedly hypoechoic nodules require FNA, even those <1 cm.

- **Spiculated / Irregular Margin**
  - Another appearance which mandates FNA is irregular or spiculated margin. These are likely to be follicular neoplasm, where capsular invasion will indicate malignancy when present.
Key Features of Malignant Nodules

• **Taller-than-Wide**
  - Another appearance which mandates FNA is irregular or spiculated margin. These are likely to be follicular neoplasm, where capsular invasion will indicate malignancy when present.

• **Other Features**
  - Other features that are highly suggestive of malignancies include lymphadenopathy, particularly when morphologically-irregular lymph nodes or intranodular vascularity is present.
Pathologically-proven papillary thyroid cancer. This taller-than-wide nodule possesses (A) markedly hypoechoic and B) hyperechoic components with irregular and partly ill-defined margins, as well as (C) peripheral and central vascularity.
Key Features of Benign Nodules

- Simple Cystic Appearance
- Spongiform
- Tiny Multiple Nodules
Key Features of Benign Nodules

**Simple Cystic Appearance**
- Simple cyst is predictive of benign nodule. Approximately 80% of thyroid neoplasms have no or very little cystic component.
- Colloid cyst may contain punctate echogenic foci with ring-down artifact that is often described as “comet tail” and represents cholesterol crystals. They often occupy dependent portions of the nodule.
Benign Nodules

Histologically-proven multinodular goiter. (A) Contrast enhanced CT demonstrates diffusely enlarged thyroid gland containing multiple cystic nodules. Although the imaging appearance is suggestive of multinodular goiter, it is not specific. (B) T1-weighted MR image shows some cysts are hyperintense which may represent colloid or hemorrhage, but the imaging appearance remains nonspecific. (C & D) Ultrasound shows primarily cystic nodules that contain solid debris and septations, giving a spongiform appearance, and cholesterol crystals with “comet tail” (arrows).
Key Features of Benign Nodules

- **Spongiform**
  - Benign nodules may exhibit sponge-like cystic areas (Fig 3). These produce the appearance of a heterogeneous nodule, with visible septations. Although spongiform appearance is characteristics of benign nodules, current guidelines recommend FNA if they exceed 2 cm.

- **Tiny Multiple Nodules**
  - Multiple tiny hypoechoic nodules in both lobes of the thyroid highly suggest Hashimoto’s thyroiditis. However, the disease slightly elevates future cancer risk. Multinodular goiter may also give this appearance.
Benign Nodules

Ultrasonography of a simple cyst in (A) axial and (B) transverse projections. This appearance is classic for a benign nodule and does not require FNA even with thick septations or internal debris.
Key Features of Indeterminate Nodules

- More Suspicious (Consider FNA if >1cm)
  - Mild to Moderate Hypoechogenicity
  - Coarse Microcalcifications

- Less Suspicious (Consider FNA if >2cm)
  - Cystic with Solid Component
  - Homogeneously Iso- or Hyperechoic
Mild to Moderate Hypoechogenicity
- Mild to moderate hypoechogenicity (compared to the background thyroid but not strap muscles). Mild to moderate hypoechogenicity is less worrisome than marked hypoechogenicity, but many guidelines recommend FNA if the nodule exceeds 1 cm.

Coarse Microcalcifications
- Fine microcalcifications are far more commonly associated with malignancy than coarse ones are. However, when a nodule exceeds 1 cm many recommendations suggest FNA in the setting of coarse microcalcifications.
Follicular nodule with acute and chronic inflammatory changes. This predominantly solid nodule with cystic components and coarse calcifications underwent FNA for size larger than 1 cm.
Cystic with Solid Component

- Cystic nodules with a solid component and spongiform nodules qualify only at this size, however features such as an irregular wall/mural nodes, vascularity or microcalcifications are almost invariably present in malignancy.

Homogeneously Iso- or Hyperechoic

- A homogeneously iso- or hyperechoic nodule with a smooth or ill-defined margin is also indeterminate. Though most of these nodules are benign, they may uncommonly represent follicular or papillary carcinoma.
Indeterminate Nodules

Pathologically-confirmed benign follicular nodule. Ultrasound demonstrated a mostly isoechoic and (A) predominantly solid nodule (B) with few cystic components. There are echogenic foci that can represent small macrocalcifications. This is an indeterminate nodule larger than 2 cm, which required FNA.
Atypia of uncertain significance by pathology. This is a case of (A-C) mostly isoechoic solid nodule with (D) peripheral and central vascularity. While greater than 2 cm, this nodule possesses only nonspecific but concerning features. Review of clinical history and endocrine profile could aid decision to perform FNA.
A practice based on integration of the guidelines from American Thyroid Association (2009) and the American Association of Clinical Endocrinologists (2006) is summarized in the flowchart below. Features present in malignant nodules with their reported predictive values. Of note the Korean Society of Thyroid Radiology guidelines (2011) do not advocate for immediate FNA of lesions with intranodular vascularity.

<table>
<thead>
<tr>
<th>Features</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microcalcification</td>
<td>26.1 – 59.1</td>
<td>85.8 – 95.0</td>
<td>24.3 – 70.7</td>
<td>41.8 – 94.2</td>
</tr>
<tr>
<td>Hypoechogenicity</td>
<td>26.5 – 87.1</td>
<td>43.4 – 94.3</td>
<td>11.4 – 68.4</td>
<td>73.5 – 93.8</td>
</tr>
<tr>
<td>Solid</td>
<td>69.0 – 75.0</td>
<td>52.5 – 55.9</td>
<td>15.6 – 27.0</td>
<td>88.0 – 92.1</td>
</tr>
<tr>
<td>Intranodule vascularity</td>
<td>54.3 – 74.2</td>
<td>78.6 – 80.8</td>
<td>24.0 – 41.9</td>
<td>85.7 – 97.4</td>
</tr>
<tr>
<td>Taller than wide</td>
<td>32.7</td>
<td>92.5</td>
<td>66.7</td>
<td>74.8</td>
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## Fine Needle Aspiration

### Features of nodules  |  Threshold size for FNA
---|---
**High-risk history**  |  
- With suspicious sonographic features  > 5 mm (Strongly recommends; based on good evidence)
- Without suspicious sonographic features  > 5 mm (No recommendation)

**Cervical lymphadenopathy**  |  All (Strongly recommends; based on good evidence)

**Microcalcifications in nodule**  |  ≥ 1 cm (Recommends; based on fair evidence)

**Solid nodule**  |  
- AND hypoechoic  > 1 cm (Recommends; based on fair evidence)
- AND iso- or hyperechoic  ≥ 1 – 1.5 cm (Recommends; based on expert opinion)

**Mixed cystic-solid nodule**  |  
- WITH suspicious US features  ≥ 1.5 – 2.0 cm (Recommend; based on fair evidence)
- WITHOUT suspicious US features  ≥ 2.0 cm (Recommends; based on expert opinion)

**Spongiform nodule**  |  ≥ 2.0 cm (Recommends; based on expert opinion)

**Purely cystic nodule**  |  FNA not indicated (Based on fair evidence)

* High risk history: thyroid cancer in first degree relatives; exposure to ionizing radiation in childhood or adolescence; prior thyroid cancer; PET positive nodule; history or family history of thyroid cancer syndrome; elevated serum calcitonin.

Thresholds for FNA given various sonographic findings in our practice, based on the American Thyroid Association guidelines. Size is used as a threshold for some imaging features.
Suggested nodule management algorithm based on summary of current practice guidelines.
Evidence-based guidelines are available for work-up of thyroid nodules.

Imaging features of malignant and benign thyroid diseases are often nonspecific. Microcalcifications, hypoechogenicity, irregular margins, taller-than-wide, invasion of normal structures and lymphadenopathy are highly suggestive of malignancies.

Indolent thyroid cancer can disguise itself as benign disease, particularly adenoma.

Clinical history and endocrine profile should be used to determine the need for FNA in indeterminate nodules.