When should a dominant thyroid nodule be subjected to surgery?

Controversies of Surgery: 6-7 October 2017

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Introduction

• “Thyroid nodule”: A discrete lesion within the thyroid gland that is radiologically distinct from the surrounding normal thyroid parenchyma. ¹, ²

• Prevalence:
  • General population: 4-8%. ³-⁶
  • U/S and at autopsy: 50-70%. ⁷-⁹

• Thyroid nodule
  • Single dominant nodule (solitary thyroid nodule)
  • Dominant nodule in a multinodular goiter.

• The rate of malignancy: 4-12%
  • palpable thyroid nodules as well as non-palpable incidentalomas. ¹¹-¹³
Indications for surgery

• Symptomatic thyroid nodules:
  • A very large goiter
  • Compression symptoms
    • Tracheal
    • Oesophageal
  • Patient’s request (mainly for cosmesis)
  • Non-resolving hyperthyroidism
    • failed medical treatment
    • failed radio-active iodine ablation (RAI)
      • RAI is contra-indicated). 5

• Malignancy

• Suspicion of malignancy?
Factors that increase the suspicion of malignancy \(^6, 16-18\)

- Age less than 20 or greater than 70 years
- History of neck irradiation
- Family history of thyroid cancer
- Rapid growth
- Nodules larger than 4 cm in size (19.3% risk of malignancy)
- Firm and irregular consistency on palpation
- Fixation of the nodule to adjacent tissues
- Ipsilateral cervical lymphadenopathy
- Vocal fold paralysis
Recommendations

• Multiple guidelines on the work-up of the thyroid nodule for malignance and whether to operate or not.
• The American Thyroid Association (ATA)-2015
• American Association of Clinical Endocrinologists (AACE)-2016
• American College of Endocrinology (ACE)
• Associazione Medici Endocrinologi Medical guidelines (AME)
• British Thyroid Association (BTA)-2014
• European thyroid cancer consensus- 2006\textsuperscript{1,16,17,18}
Initial investigations:

- European thyroid cancer consensus group, BTA, AACE, ACE and AME suggest
- Thyroid stimulating hormone (TSH) and U/S of the thyroid as the initial investigations.
ATA-2015

• TSH
• Radioisotope scanning, $^{123}$I or $^{99m}$Tc pertechnetate scan
• Any nodularity requires an ultrasound
• Hyperfunctioning nodule (hot nodule): cytology is NOT required
• Isofunctioning (“warm” nodule): managed according the ultrasound criteria.$^1$,$^{20}$
• Non-functioning nodule (“cold” nodule): cytology required$^1$
Ultrasound (U/S) of the thyroid

• U/S very accurate
• Possibly even more accurate than cytology.\textsuperscript{9,22}
• Cervical lymph nodes assessment under U/S has the highest sensitivity
Ultrasound features to consider/include on assessment of thyroid nodules\textsuperscript{16}.

<table>
<thead>
<tr>
<th>Relevant nodule size</th>
<th>Solid, cystic, mixed solid/cystic, micro-cystic/spongiform</th>
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</thead>
<tbody>
<tr>
<td>Nodule composition</td>
<td>?Ring down sign- colloid</td>
</tr>
<tr>
<td>Cystic component</td>
<td>Markedly hypo-echoic, hypo-echoic, iso-echoic, hyper-echoic</td>
</tr>
<tr>
<td>Echogenicity</td>
<td>Micro-calcification, macro-calcification, rim/egg shell</td>
</tr>
<tr>
<td>Margin</td>
<td>Well defined, irregular/lobulated, spiculated</td>
</tr>
<tr>
<td>Taller than Wide</td>
<td>Anterior-Posterior diameter &gt; Transverse diameter</td>
</tr>
<tr>
<td>Halo</td>
<td>Regular/continuous, interrupted, absent</td>
</tr>
<tr>
<td>Colour flow</td>
<td>Central, peripheral, mixed, none</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>Suspected malignancy –? metastases: anatomical location/levels</td>
</tr>
<tr>
<td>Extent</td>
<td>Retrosternal extension/tracheal deviation</td>
</tr>
</tbody>
</table>
Ultrasound (U/S) of the thyroid

- Kim Criteria: high sensitivity of malignancy.\textsuperscript{16,23}
  - marked hypo-echogenicity
  - irregular or micro-lobulated margins
  - micro-calcification
  - taller-than-wide shape (AP > TR)
Comparison of the risk of malignancy in the different Ultrasound Classification Systems for Thyroid Nodules

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>&lt;1%</td>
<td>Not defined</td>
<td></td>
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<tr>
<td>&lt;3%</td>
<td>Not defined</td>
<td></td>
<td></td>
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<tr>
<td>5-10%</td>
<td>equivocal. Not defined</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-20%</td>
<td>Not defined</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High suspicion.</td>
<td>U5. Malignant.</td>
<td>3. High-risk thyroid lesion. 50-90%</td>
<td>TR5. Highly suspicious. Not defined</td>
</tr>
<tr>
<td>&gt;70-90%</td>
<td>Not defined</td>
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Significance of U/S

• Society U/S classification (risk of malignancy)
• Size of the nodule
• Indications for Fine needle aspiration (FNA) cytology
## Comparison of ultrasound size limit indications for thyroid nodule FNA

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<tbody>
<tr>
<td>Benign. No FNA</td>
<td>U1. No FNA</td>
<td>1. ≥2cm and increasing in size</td>
<td>≥1cm</td>
<td>TR1. No FNA</td>
</tr>
<tr>
<td>Very low suspicion. ≥2cm</td>
<td>U2. No FNA</td>
<td></td>
<td></td>
<td>TR2. No FNA</td>
</tr>
<tr>
<td>Low suspicion. ≥1.5cm</td>
<td>U3. Any size</td>
<td></td>
<td></td>
<td>TR3. ≥2.5cm</td>
</tr>
<tr>
<td>Intermediate suspicion. ≥1cm</td>
<td>U4. Any size</td>
<td>2. ≥2cm</td>
<td></td>
<td>TR4. ≥1.5cm</td>
</tr>
<tr>
<td>High suspicion. ≥1cm</td>
<td>U5. Any size</td>
<td>3. ≥1cm</td>
<td></td>
<td>TR5. ≥1cm</td>
</tr>
</tbody>
</table>
Thyroid nodule biopsy

- FNA
  - sensitivity of 89% to 98% and a specificity of 92%.\(^{33}\)

- The **Bethesda system** for reporting thyroid cytopathology
  - 2007
  - National Cancer Institute Thyroid FNA State of the Science Conference held in Bethesda, USA
  - Different cytopathology categories were decided upon.\(^{39}\)

- UK uses the **Thy numerical diagnostic categories** as defined by Royal College of Pathologists.\(^{16,40}\)

- The AACE/ACE/AME uses the **Thyroid Imaging and Reporting system** from the Italian consensus from 2014.\(^{18}\)
Comparison of the Bethesda and Thy numerical diagnostic categories

<table>
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</thead>
<tbody>
<tr>
<td>I. Nondiagnostic or Unsatisfactory</td>
<td>Thy1 – non-diagnostic. Thy1c. Cyst fluid samples</td>
<td>TIR 1. Nondiagnostic TIR 1c. Nondiagnostic cystic</td>
</tr>
<tr>
<td>II. Benign</td>
<td>Thy2 – non-neoplastic. Thy2c.-Cyst samples containing abundant colloid,</td>
<td>TIR 2. Non-malignant</td>
</tr>
<tr>
<td>III. Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance</td>
<td>Thy3 – neoplasm possible. This is subdivided into Thy3a and Thy3f: Thy3a – There are atypical features present but not enough to place into any of the other categories.</td>
<td>TIR 3. Indeterminate TIR 3A. Low-risk indeterminate lesion-</td>
</tr>
<tr>
<td>IV. Follicular Neoplasm or Suspicious for a Follicular Neoplasm</td>
<td>Thy3f – when a follicular neoplasm is suspected.</td>
<td>TIR 3B. High-risk indeterminate lesion-</td>
</tr>
<tr>
<td>V. Suspicious for Malignancy</td>
<td>Thy4 – suspicious of malignancy but definite diagnosis of malignancy is not possible.</td>
<td>TIR 4. Suspicious for malignancy</td>
</tr>
<tr>
<td>VI. Malignant</td>
<td>Thy5 – diagnostic of malignancy.</td>
<td>TIR 5. Malignant</td>
</tr>
</tbody>
</table>
Follicular cells - Benign (II/Thy 2)?

• “Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc.)”\textsuperscript{39}

• Minimum of 6 groups of benign follicular cells, each group composed of a minimum of 10 cells with or without colloid;
  
  Or

• Any FNA specimen that contains abundant colloid, even if less than 6 groups of follicular cells on 1 or more smears.\textsuperscript{16,18,39}

• Arranged as macrofollicles or macrofollicle fragments.\textsuperscript{39}
The indeterminate group: Bethesda III/IV or Thy 3a/3f

• Cytological features
  • follicular adenoma = follicular carcinoma?

• Certain FNA features may suggest carcinoma- “follicular neoplasm” (Bethesda IV or 3f).³⁹
  • abundant follicular cells arranged in sheets, microfollicular or trabecular pattern
  • minimal background colloid

• Follicular carcinoma -> histological sample
  • vascular or capsular invasion
  • cellular characteristics are assessed.⁵

• U/S features have to correlated with the cytological findings
When to subject a dominant nodule to surgery?

- **I/Thy 1:**
  - ATA, BTA, AACE/ACE/AME – repeat FNA

- **II/Thy 2:**
  - ATA, AACE/ACE/AME – No surgery
  - BTA - if high suspicion – repeat FNA or MDT

- **V/Thy 4:**
  - ATA, AACE/ACE/AME – Surgery
  - BTA: repeat U/S guided FNA

- **VI/Thy 5:**
  - ATA, BTA, AACE/ACE/AME - Surgery
When to subject a dominant nodule to surgery with a Bethesda III/IV or Thy 3a/3f?

• ATA:
  • correlate U/S features and clinical risk factors
    • Observe
    • Repeat FNA
    • Surgery

• AACE/ACE/AME:
  • Repeat FNA and correlate with U/S features and clinical risk factors
    • Observe
    • Surgery

• BTA:
  • Repeat FNA, if still indeterminate
    • Surgery

• European consensus
  • Surgery
Further investigations

• Elastography
• 99mTc-sestamethoxyisobutylisonitrily (sestaMIBI) scan
• 18F-fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET scan)
Molecular testing

• Group of mutation tests (BRAF, NRAS, HRAS, KRAS, RET/PTC1, RET/PTC3, PAX8/PPARc)
• Sensitivity: 44-100%.\textsuperscript{59-60}
• May not assist to reliably exclude carcinoma.

Limitations:
• Similar for cytological interpretation, i.e. an inadequate sample.
• ATA recommendation
  • Clinical Laboratory Improvement Amendments/ College of American Pathologists (CLIA/CAP)-certified molecular laboratories, or a similar international standard.
• The long term outcome lacking
• Not part of the routine work-up.\textsuperscript{1,18}
Conclusion

• Symptomatic
• Step-wise approach
• Order of the investigations may differ
• U/S and cytopathology
• Different thyroid society’s criteria: similar/differences.
• Indeterminate group: further investigations that may assist
• Be aware of the limitations of these investigations.

• Surgery or not?:
  • history
  • clinical findings
  • appropriate investigations
  • recommendation guidelines
References


References


References


Introduction

• A single dominant (2.7 to 30%) > single nodule within a multinodular gland (1.4 to 10%)\textsuperscript{6}.

Calcitonin as an initial investigation?

• European consensus recommends serum calcitonin
• BTA do not recommend unless medullary thyroid cancer is suspected.¹,¹⁶,
• ATA and AACE do not have recommendations
## American College of Radiology- TIRADS classification (2017)

<table>
<thead>
<tr>
<th>Composition (Choose 1)</th>
<th>Echogenicity (Choose 1)</th>
<th>Shape (Choose 1)</th>
<th>Margin (Choose 1)</th>
<th>Echogenic foci (Choose all that apply)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic or almost completely cystic 0 points</td>
<td>Anechoic 0 points</td>
<td>Wider-than-tall 0 points</td>
<td>Smooth 0 points</td>
<td>None or large comet-tail artefacts 0 points</td>
</tr>
<tr>
<td>Spongiform 0 points</td>
<td>Hyperechoic or isoechoic 1 point</td>
<td>Taller-than-wide 3 points</td>
<td>Ill-defined 0 points</td>
<td>Macrocalfcifications 1 point</td>
</tr>
<tr>
<td>Mixed cystic and solid 1 point</td>
<td>Hypoechoic 2 points</td>
<td>Lobulated or irregular 2 points</td>
<td>Peripheral (rim) calcifications 2 points</td>
<td></td>
</tr>
<tr>
<td>Solid or almost completely solid 2 points</td>
<td>Very hypoechoic 3 points</td>
<td>Extra-thyroidal extension 3 points</td>
<td>Punctate echogenic foci 3 points</td>
<td></td>
</tr>
</tbody>
</table>

Add points from all categories to assess TIRADS level:

- 0 points - TR1
- 2 points - TR2
- 3 points - TR3
- 4 to 6 points - TR4
- ≥7 points - TR5
Nodules less than the cut-off size

- The AACE/ACE/AME, BTA and European group
  - history with high clinical suspicion of thyroid malignancy should be considered for FNA.\textsuperscript{16,17,18}

- AACE/ACE/AME: consider FNA for high-risk thyroid nodules ≤1cm only when suspicious U/S signs are present,

- ≤5 mm should be monitored rather than biopsied.\textsuperscript{18}
Comparison of Bethesda and Thy numerical diagnostic categories Malignancy rate and Management\textsuperscript{16,39}

<table>
<thead>
<tr>
<th>Bethesda categories</th>
<th>Thy numerical diagnostic categories</th>
</tr>
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<tbody>
<tr>
<td><strong>Bethesda categories</strong></td>
<td><strong>Malignancy rate\textsuperscript{16}</strong></td>
</tr>
<tr>
<td>I.</td>
<td>1-4%</td>
</tr>
<tr>
<td>II.</td>
<td>0-3%</td>
</tr>
<tr>
<td>III.</td>
<td>5-15%</td>
</tr>
<tr>
<td>IV.</td>
<td>15-30%</td>
</tr>
<tr>
<td>V.</td>
<td>60-75%</td>
</tr>
<tr>
<td>VI.</td>
<td>97-99%</td>
</tr>
</tbody>
</table>
Further investigations

- Elastography: is a new dynamic U/S technique
  - measures tissue stiffness.
  - mixed positive and negative predictive values
  - AACE/ACE/AME

- 99mTc-sestamethoxyisobutylisonitril (sestaMIBI) scan
  - cold nodule with a non-diagnostic FNA.
  - negative predictive value = 100%
  - positive predictive value = 27%

- 18F-fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET scan)
  - not a routine test for thyroid nodule work-up.
  - cannot diagnose malignancy in thyroid nodules
  - negative predictive value of 95-100%\(^6,57,58\)