When should a dominant thyroid nodule be subjected to surgery?

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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[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.[9,22]
- Cervical lymph nodes assessment under U/S has the highest sensitivity

Ultrasound features to consider/include on assessment of thyroid nodules[16].

Relevant nodule size	
Nodule composition	**Solid, cystic, mixed solid/cystic, micro-cystic/spongiform**
Cystic component	**?Ring down sign- colloid**
Echogenicity	**Markedly hypo-echoic, hypo-echoic, iso-echoic, hyper-echoic**
Calcifications	**Micro-calcification, macro-calcification, rim/egg shell**
Margin	**Well defined, irregular/lobulated, spiculated**
Taller than Wide	**Anterior-Posterior diameter > Transverse diameter**
Halo	**Regular/continuous, interrupted, absent**
Colour flow	**Central, peripheral, mixed, none**
Lymphadenopathy	**Suspected malignancy –? metastases: anatomical location/levels**
Extent	**Retrosternal extension/tracheal deviation**

Ultrasound (U/S) of the thyroid

- Kim Criteria: high sensitivity of malignancy.[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[1,16,18,32]

ATA (2015)	BTA (2014)	AACE/ACE-AME (2016)	ACR-TIRADS (2017)
Benign. <1%	U1. Normal. Not defined	1. Low-risk lesion. 1%	TR1. Benign. Not defined
Very low suspicion. <3%	U2. Benign. Not defined		TR2. Not suspicious. Not defined
Low suspicion. 5-10%	U3. Indeterminate/ equivocal. Not defined		TR3. Mildly suspicious. Not defined
Intermediate suspicion. 10-20%	U4. suspicious. Not defined	2. Intermediate-risk thyroid lesion. 5-15%	TR4. Moderately suspicious. Not defined
High suspicion. >70-90%	U5. Malignant. Not defined	3. High-risk thyroid lesion. 50-90%	TR5. Highly suspicious. Not defined

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[1,16,17,18,32]

ATA (2015)	**BTA (2014)**	**AACE/ACE/AME (2016)**	**European consensus** (2006)	**ACR-TIRADS (2017)**
Benign. No FNA	U1. No FNA	1. ≥2cm and increasing in size	≥1cm	TR1. No FNA
Very low suspicion. ≥2cm	U2. No FNA			TR2. No FNA
Low suspicion. ≥1.5cm	U3. Any size			TR3. ≥2.5cm
Intermediate suspicion. ≥1cm	U4. Any size	2. ≥2cm		TR4. ≥1.5cm
High suspicion. ≥1cm	U5. Any size	3. ≥1cm		TR5. ≥1cm

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[16,39,40]

USA-Bethesda categories (2009)	UK-Royal College of Pathologists (2016)	Italian AME Consensus (2014)
I. Nondiagnostic or Unsatisfactory -	**Thy1 – non-diagnostic**. **Thy1c.** Cyst fluid samples	**TIR 1**. **Nondiagnostic** **TIR 1c. Nondiagnostic cystic**
II. Benign	**Thy2 – non-neoplastic.** Thy2c.-Cyst samples containing abundant colloid,	**TIR 2**. **Non-malignant**
III. Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance	**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..	**TIR 3**. **Indeterminate** **TIR 3A. Low-risk indeterminate lesion**-.
IV. Follicular Neoplasm or Suspicious for a Follicular Neoplasm	**Thy3f – when a follicular neoplasm is suspected**.	**TIR 3B. High-risk indeterminate lesion-**
V. Suspicious for Malignancy	**Thy4 – suspicious of malignancy but definite diagnosis of malignancy is not possible**.	**TIR 4. Suspicious for malignancy**
VI. Malignant	**Thy5 – diagnostic of malignancy.**	**TIR 5. Malignant**

Follicular cells - Benign (II/Thy 2)?

- “Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc.)” [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.[16,18,39]
- Arranged as macrofollicles or macrofollicle fragments.[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-sestamethoxyisobutylisonitryl (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%.[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.[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

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Introduction

- A single dominant (2.7 to 30%) > single nodule within a multinodular gland (1.4 to 10%) [6] .
- But, overall risk of malignancy with a solitary nodule is approximately equal to that of a multinodular gland due to the additive risk of each nodule [7-9]. **Bomeli SR, LeBeau SO, and Ferris RL. Evaluation of a thyroid nodule. Otolaryngol Clin North Am. 2010; 43(2): 229–238. doi:10.1016/j.otc.2010.01.002.**

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)[32]

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

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.[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.[18]

Comparison of Bethesda and Thy numerical diagnostic categories Malignancy rate and Management[16,39]

Bethesda categories		Thy numerical diagnostic categories	
Bethesda categories	**Malignancy rate**[16]	**Thy categories**	**Malignancy rate.**
I.	1-4%	Thy1	4.5-8.5%[43]
II.	0-3%	Thy2	<3%[44]
III.	5-15%	Thy3a	9.5%-43%[45-53]
IV.	15-30%	Thy3f	
V.	60-75%	Thy4	68-70%[45,46]
VI.	97-99%	Thy5	98-99%[46,54]

Further investigations

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

- 99mTc-sestamethoxyisobutylisonitryl (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]