



# Cytology and molecular biology for thyroid nodules

## From diagnostic categories to clinical actions



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# Take-home Messages

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# REPORTING CATEGORIES

We suggest the use of five diagnostic categories and three sub-categories:

- **TIR 1.** Non diagnostic
  - **TIR 1c:** consistent with Cystic lesion
- **TIR 2.** Negative for malignant cells
- **TIR 3.** Indeterminate
  - **TIR 3A**
  - **TIR 3B**
- **TIR 4.** Suspicious of malignancy
- **TIR 5.** Positive for malignant cells

# TIR 1: Non diagnostic



- Consider repeat FNA under US-guidance
- Suggest repeat FNA after at least one month to avoid artefacts
- When repeat FNA is still non-diagnostic, use clinical and US data for clinical decision

# TIR 1: Non-diagnostic



- Clinical and US surveillance for small nodules with benign appearance
- Surgery for clinically suspicious nodules, due to the non-negligible rate of malignancy of TIR-1 nodules
- Microhistology by US-guided core-needle biopsy (CNB) may be useful when FNA is repeatedly non-diagnostic

# TIR 1C: Cystic lesion



- Most thyroid cysts are benign
- Routine repeat FNA is not required
- Repeat FNA:
  - on mixed nodules with a solid component, vascular signals or thick irregular margins
  - before PEI treatment
  - in case of growth or structural changes

# TIR 2: Negative for malignant cells

- Clinical and US follow-up
- Repeat FNA only in case of nodule growth or suspicious structural changes

Nodule growth is defined as an increase of nodule diameters  $> 20\%$  or a volume enlargement  $> 50\%$  .

- Repeat FNA for candidates of US-guided interventional procedures

# TIR 3: Indeterminate

- TIR 3 cytologic results have an overall 20% risk of malignancy
- Stratification of malignancy risk may spare from surgery TIR 3 lesions at low cancer risk
- A classification of TIR 3 nodules into two subclasses (TIR 3A and TIR 3B) at different risk of malignancy is recommended

# TIR 3: Indeterminate

## TIR 3A

- Cellular microfollicular/Hurthle cell pattern in a background of poor colloid amount with degenerative/regressive features
- Partially compromised specimens (blood contamination) with mild cytologic or architectural alterations
- *Expected lower risk of malignancy*

## TIR 3B

- Monotonous, repetitive microfollicular pattern with scanty or absent colloid (“follicular proliferation”)
- *More likely follicular neoplasm; expected higher risk of neoplasia.*



# TIR 3A

- Lower risk of malignancy: a patient-tailored management is required.
- Nodule size and US appearance, thyroid function, and patient's symptoms, comorbidities and preferences should be considered for the choice of surgery or clinical surveillance
- The conservative strategy requires a repeat FNA showing a TIR 2 or reiterating a TIR 3A result

# TIR 3A



- If repeat FNA confirms TIR 3A, close follow-up is recommended
- CNB may be used when indicated
- Immunohistochemical panel and molecular markers may be considered in selected cases

# TIR 3A



- Immunohistochemical markers: Galectin-3, HBME-1, Cytokeratin 19
- Molecular markers: BRAF-1, Ret/PTC, PAX8/PPA $\gamma$  and RAS

These markers currently show the most promising results

# TIR 3B



- Surgery is usually recommended
- Routine frozen section examination is not recommended
- Repeat FNA is usually not helpful. CNB may be considered in selected TIR 3B lesions only (small lesions in subjects at high surgical risk)
- In occasional cases when surgery is not performed, molecular testing and/or close follow-up is appropriate

# Molecular Testing in Thyroid Nodules



- 20% of thyroid FNAs are cytologically indeterminate
- The majority undergo surgical excision; 80% have benign histology
- Clearly, this is not a cost-effective practice & ways to improve diagnostic accuracy seem necessary

# Molecular Testing in Thyroid Nodules



## Veracyte Affirma Gene Expression (GEC) Classifier

- Gene expression from mRNA on FNA washings
- Alexander et al, NEJM 2012, showed that for 265 nodules, NPV was 92%
- Cost \$3200

# Molecular Testing in Thyroid Nodules

## Asuragen Panel

- done on FNA specimens
- Panel includes BRAF, RAS, RET/PTC, & PAX8/PPARg
- Nikiforov et al, JCEM 2011, reported on 1056 nodules
- With positive mutations, risk of cancer was 88% to 95%; sensitivity was only 60%
- Cost \$650

# Molecular Testing in Thyroid Nodules



## Cleveland Clinic mRNA Assay

- Milas et al, Ann Surg 2010, reported on 54 nodules with FN/SFN a sensitivity of 76% & specificity 96%
- Test performed on blood sample
- Available thru CCF
- Cost \$300



# Molecular Testing in Thyroid Nodules



- We need better tests for suspicious thyroid FNA
- Current tests are useful but additional studies are needed
- Until more info is available, we continue to use US & cytology to manage our “indeterminate” patients.

# TIR-4: Suspicious



- Surgery with ( optional ) frozen section examination due to the high risk of PTC
- For a better pre-surgical diagnostic characterization FNA repetition or CNB may be considered in cases with poor cellularity
- In this setting, ancillary techniques may increase diagnostic accuracy.

# TIR-5: Positive for malignant cells



- Surgery almost always indicated
- Schedules alternative to surgery may be appropriate in different malignancies (anaplastic carcinoma, lymphoma, thyroid metastasis).

UK RCPATH	Consensus 2013	USA BETHESDA	
Diagnostic category		Terminology	Clinical management
<b>Thy1/Thy1c</b> Non-diagnostic for cytological diagnosis Unsatisfactory, consistent with cyst	<b>TIR 1</b>  <b>TIR 1c</b>	<b>I. Non-diagnostic</b>	Reaspirate with US guidance after at least 3 months
<b>Thy2/Thy2c</b> Non-neoplastic	<b>TIR 2</b>	<b>II. Benign</b>	Clinical follow-up at 6-8 months intervals
<b>Thy 3a</b> Neoplasm possible – atypia/ non-diagnostic	<b>TIR 3A</b>	<b>III. Atypia of undetermined significance or follicular lesion u.s.</b>	Low TSH: radioisotope scan. Repeat US-guided FNA in 6 months Consider ancillary techniques
<b>Thy3f</b> Neoplasm possible - suggesting follicular neoplasm	<b>TIR 3B</b>	<b>IV. Follicular neoplasm or suspicious for a follicular neoplasm</b>	Surgical consultation
<b>Thy 4</b> Suspicious of malignancy	<b>TIR 4</b>	<b>V. Suspicious of malignancy</b>	Surgical consultation
<b>Thy5</b>	<b>TIR 5</b>	<b>VI. Malignant</b>	Surgical consultation

The diagnostic categories and most of clinical actions  
are based on the final draft of the

## **2013 Italian Consensus for the Classification and Reporting of Thyroid Cytology**

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# Thank You!



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