Outcomes from the diagnostic approach of thyroid lesions using US-FNA and LBC in clinical practice

Emmanouel Mastorakis
MD PhD Cytopathologist
Director in Cytopathology Laboratory

Regional General Hospital “Venizelion”, Heraklion, Crete, Greece

40th European Congress of Cytology
Liverpool, UK October 2-5, 2016
Regional Hospital “Venizelion”, Heraklion Crete - Greece
Cytopathology Laboratory
- 1989 establishment
- 1998 – 2016 FNA Thyroid samples evaluation
13,000 cases examined
Objective

high quality - adequate cytologic specimens

This depends upon choosing aspiration technique for adequate samples

preparation method that will minimize cell loss and also preserve morphologic detail

accurate diagnosis

retain FNA as the most sensitive and most specific diagnostic tool available in the evaluation of thyroid lesions
U/S predictors for thyroid malignancy

- Solid composition
- Hypoechogenicity
- Microcalcifications
- Irregular margin
- Taller than wide shape (a-p > trans diam.)
- Increased blood flow
- Evidence of extracapsular extension

2003 The US guided FNA was introduced

Aspirations performed at Radiology Department / US unit

Not on-site evaluation of specimens’ adequacy

2-3 passes
2005 the LBC ThinPrep® was applied
Hyperplastic

ThinPrep® Pap stain
Hyperplastic

ThinPrep® Pap stain
Lymphocytic thyroiditis

ThinPrep Pap stain
• PTC ThinPrep® Pap stain
MTC  CALCITONIN (+)
THYROGLOBULIN (-)
MTC Liquid Based Cytology ThinPrep Pap stain

ICC Calcitonin (+) – Thyroglobulin(-)

Histology
Objective the interdisciplinary cooperation

cytopathologists
endocrinologists
thyroid surgeons
Terminologies

PSC 1997 Papanicolaou Society Cytopathology

*PSC : Papanicolaou Society of cytology; Working group : Thyroid 2006;16*

- Inadequate
- Benign
- Presence of atypical cells
- Suspicious for malignancy
- Malignant

Cibas and Ali, Am J Clin Pathol 2009

The Bethesda System for reporting Thyroid Cytopathology: uniform terminology for FNA results

TBSRTC

2010
Diagnostic terminology for reporting thyroid fine needle aspiration cytology: European Federation of Cytology Societies thyroid working party symposium, Lisbon 2009

# Thyroid FNA

## Bethesda Classification Scheme

**The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC): Implied Risk of Malignancy and Recommended Clinical Management**

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>Risk of Malignancy (%)</th>
<th>Usual Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-diagnostic or Unsatisfactory</td>
<td>0-3%</td>
<td>Repeat FNA with ultrasound guidance</td>
</tr>
<tr>
<td>Benign</td>
<td></td>
<td>Clinical follow-up</td>
</tr>
<tr>
<td>Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance (AUS/FLUS)</td>
<td>~5-15%</td>
<td>Repeat FNA</td>
</tr>
<tr>
<td>Follicular Neoplasm or Suspicious for a Follicular Neoplasm (Specify if Hurthle type or Oncocytic)</td>
<td>15-30%</td>
<td>Surgical lobectomy</td>
</tr>
<tr>
<td>Suspicious for Malignancy</td>
<td>60-75%</td>
<td>Near-total thyroidectomy or surgical lobectomy</td>
</tr>
<tr>
<td>Malignant</td>
<td>97-99%</td>
<td>Near-total thyroidectomy</td>
</tr>
<tr>
<td>YEAR</td>
<td>FNA - CYTOPREPARATORY METHOD- ANCILLARY</td>
<td>CASES</td>
</tr>
<tr>
<td>------</td>
<td>----------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>1998</td>
<td>NON GUIDED FNA-DIRECT SMEAR</td>
<td>72</td>
</tr>
<tr>
<td>2008</td>
<td>Introduction of ancillary techniques</td>
<td>682</td>
</tr>
<tr>
<td>2010</td>
<td>Introduction of TBSRTC and molecular cytology</td>
<td>853</td>
</tr>
<tr>
<td>2011</td>
<td>US GUIDED FNA- LBC- IMMUNOCYTOLOGY- MOLECULAR</td>
<td>1146</td>
</tr>
<tr>
<td>2012</td>
<td>US GUIDED FNA- LBC- IMMUNOCYTOLOGY- MOLECULAR</td>
<td>1271</td>
</tr>
<tr>
<td>2013</td>
<td>US GUIDED FNA- LBC- IMMUNOCYTOLOGY- MOLECULAR</td>
<td>1545</td>
</tr>
<tr>
<td>2014</td>
<td>US GUIDED FNA- LBC- IMMUNOCYTOLOGY- MOLECULAR</td>
<td>1695</td>
</tr>
<tr>
<td>2015</td>
<td>US GUIDED FNA- LBC- IMMUNOCYTOLOGY- MOLECULAR</td>
<td>1510</td>
</tr>
</tbody>
</table>
Mean diameter of malignant nodules

The last years the mean diameter is 0.94cm±0.5 max=4cm, min=0.1cm)
TBSRTC IV follicular neoplasm

ThinPrep® Pap stain

Cell block H/E
MOLECULAR TESTING: A useful adjunct to cytology

Regional hospital “Venizelion”
Cytopathology Laboratory

- PTCs > 90% of malignant nodules
- Detection of BRAF V600E mutation
- LBC residual material (PreservCyt® solution)
BRAFV 600E (GTG > GAG)

BRAF mutation is a genetic alteration that is Thymine (T) to Adenine (A) transversion at nucleotide 1799, leading in a valin-to-glutamate substitution at residue 600(V600E)

- BRAF (V600E) mutation is frequent in PTCs
- mutation rate 29% to 83% (PTC) average level of 45%
- not been detected in benign nodules

In many cancer types, including thyroid cancer, BRAF mutation seems to play a critical role in cell proliferation, survival and cellular dedifferentiation.

This genetic alteration appears to be associated with more aggressive biological behavior of the tumor extrathyroidal extension, lymph node or distant metastases, increased tumor recurrence.
molecular detection of BRAF V600E

particular importance in cases of
  • indeterminate
  • suspicious cytology
    (reported in 15-20% of nodules)
    increasing the diagnostic accuracy and sensitivity of FNA

additional tool

preoperative treatment plan after thyroidectomy.

ambiguos cases
Diagnosis of malignancy (PTCs)

Preoperative prognostic information
Clinical management
National and Kapodistrian University of Athens Greece
University Hospital “ATTIKON”
Department of Cytopathology
Prof. Petros Karakitsos
Abraham. Pouliakis PhD
Aris Spathis Biologist PhD

General Hospital “VENIZELION”
Heraklion Crete Greece
Department of Cytopathology
Emmanuel Mastorakis MD PhD

Interlaboratory cooperation

Links για μεταφραστικά γραφεία και πιστοποιημένους μεταφραστές.
Καθορίστε προτιμώμενο τομέα σας:
Γενικές μεταφράσεις, μεταφράσεις των επιχειρήσεων, του εμπορίου μεταφράσεις, μεταφράσεις δίκαιο, τεχνικές μεταφράσεις, μεταφράσεις ιατρικών, μεταφράσεις επιστήμη, προσαρμογή λογισμικού, ιστοσελίδα localization, άλλους τομείς ...

Partnership
Search Hotels
The Bethesda System for Reporting Thyroid

I. NONDIAGNOSTIC or UNSATISFACTORY
Cyst fluid only
  Virtually acellular specimen
  Other (obscuring blood, clotting artifact, etc.)

II. BENIGN
  Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc.)
  Consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical context
  Consistent with granulomatous (subacute) thyroiditis
  Other

III. ATYPIA OF UNDETERMINED SIGNIFICANCE or FOLLICULAR LESION OF UNDETERMINED SIGNIFICANCE

IV. FOLLICULAR NEOPLASM or SUSPICIOUS FOR A FOLLICULAR NEOPLASM
   - specify if Hurthle cell (oncocytic) type

V. SUSPICIOUS FOR MALIGNANCY
  Suspicous for papillary carcinoma
  Suspicous for medullary carcinoma
  Suspicous for metastatic carcinoma
  Suspicous for lymphoma
  Other

VI. MALIGNANT
  Papillary thyroid carcinoma
  Poorly differentiated carcinoma
  Medullary thyroid carcinoma
  Undifferentiated (anaplastic) carcinoma
  Squamous cell carcinoma
  Carcinoma with mixed features (specify)
  Metastatic carcinoma
  Non-Hodgkin lymphoma
  Other
The Bethesda System for Reporting Thyroid

I. NONDIAGNOSTIC or UNSATISFACTORY
   Cyst fluid only
   Virtually acellular specimen
   Other (obscuring blood, clotting artifact, etc.)

II. BENIGN
   Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc.)
   Consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical context
   Consistent with granulomatous (subacute) thyroiditis
   Other

III. ATYPIA OF UNDETERMINED SIGNIFICANCE or FOLLICULAR LESION OF UNDETERMINED SIGNIFICANCE

IV. FOLLICULAR NEOPLASM or SUSPICIOUS FOR A FOLLICULAR NEOPLASM
   - specify if Hürthle cell (oncocytic) type

V. SUSPICIOUS FOR MALIGNANCY
   Suspicious for papillary carcinoma
   Suspicious for medullary carcinoma
   Suspicious for metastatic carcinoma
   Suspicious for lymphoma
   Other

VI. MALIGNANT
   Papillary thyroid carcinoma
   Poorly differentiated carcinoma
   Medullary thyroid carcinoma
   Undifferentiated (anaplastic) carcinoma
   Squamous cell carcinoma
   Carcinoma with mixed features (specify)
   Metastatic carcinoma
   Non-Hodgkin lymphoma
   Other
The Bethesda System for Reporting Thyroid

I. NONDIAGNOSTIC or UNSATISFACTORY
Cyst fluid only
  Virtually acellular specimen
  Other (obsuring blood, clotting artifact, etc.)

II. BENIGN
  Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc.)
  Consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical context
  Consistent with granulomatous (subacute) thyroiditis
  Other

III. ATYPIA OF UNDETERMINED SIGNIFICANCE or FOLLICULAR LESION OF UNDETERMINED SIGNIFICANCE

IV. FOLLICULAR NEOPLASM or SUSPICIOUS FOR A FOLLICULAR NEOPLASM
  - specify if Hürthle cell (oncocytic) type

V. SUSPICIOUS FOR MALIGNANCY
  Suspicious for papillary carcinoma
  Suspicious for medullary carcinoma
  Suspicious for metastatic carcinoma
  Suspicious for lymphoma
  Other

VI. MALIGNANT
  Papillary thyroid carcinoma
  Poorly differentiated carcinoma
  Medullary thyroid carcinoma
  Undifferentiated (anaplastic) carcinoma
  Squamous cell carcinoma
  Carcinoma with mixed features (specify)
  Metastatic carcinoma
  Non-Hodgkin lymphoma
  Other
366/15 TBSRTC - PTC BRAF (V600E)

L Lobe: Papillary carcinoma/classic-follicular 0.4 cm

R Lobe: Hyperplastic Nodule

367/15 Benign TBSRTC-2

ThinPrep® Pap stain
2015 TBS-6  PTC BRAF (V600E)

L Lobe: Papillary carcinoma / tall cell  0.3 cm
The Bethesda System for Reporting Thyroid

I. NONDIAGNOSTIC or UNSATISFACTORY
   - Cyst fluid only
   - Virtually acellular specimen
   - Other (obscuring blood, clotting artifact, etc.)

II. BENIGN
   - Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc.)
   - Consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical context
   - Consistent with granulomatous (subacute) thyroiditis
   - Other

III. ATYPIA OF UNDETERMINED SIGNIFICANCE or FOLLICULAR LESION OF UNDETERMINED SIGNIFICANCE

IV. FOLLICULAR NEOPLASM or SUSPICIOUS FOR A FOLLICULAR NEOPLASM
   - Specify if Hurthle cell (oncocytic) type

V. SUSPICIOUS FOR MALIGNANCY
   - Suspicious for papillary carcinoma
   - Suspicious for medullary carcinoma
   - Suspicious for metastatic carcinoma
   - Suspicious for lymphoma
   - Other

VI. MALIGNANT
   - Papillary thyroid carcinoma
   - Poorly differentiated carcinoma
   - Medullary thyroid carcinoma
   - Undifferentiated (anaplastic) carcinoma
   - Squamous cell carcinoma
   - Carcinoma with mixed features (specify)
   - Metastatic carcinoma
   - Non-Hodgkin lymphoma
   - Other
BRAF V600E mutation analysis performed on 329 cases
pathological TNM (pTNM) staging system

• **Primary tumor (T)**
  
  **TX:** Primary tumor cannot be assessed  
  **T0:** No evidence of primary tumor  
  **T1:** Limited to thyroid, 2 cm or less in greatest dimension  
  **T1a:** Limited to thyroid, 1 cm or less  
  **T1b:** Limited to thyroid, more than 1 cm but not more than 2 cm  
  **T2:** Limited to thyroid, greater than 2 cm, but not more than 4 cm  
  **T3:** Limited to thyroid and > 4 cm OR any tumor with minimal extrathyroid extension (e.g. extension to sternothyroid muscle or perithyroid soft tissues)  
  **T4a:** Moderately advanced disease  
  Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus or recurrent laryngeal nerve  
  **T4b:** Very advanced disease  
  Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels  
  **Anaplastic carcinoma** - all are considered T4 tumors  
  **T4a:** Intrathyroidal anaplastic carcinoma  
  **T4b:** Anaplastic carcinoma with gross extrathyroid extension

• **Regional lymph nodes (N)**
  
  **NX:** Regional lymph nodes cannot be assessed  
  **N0:** No regional lymph node metastasis  
  **N1:** Regional lymph node metastasis  
  **N1a:** Metastasis to Level VI (pretracheal, paratracheal and prelaryngeal/Delphian lymph nodes)  
  **N1b:** Metastasis to unilateral, bilateral or contralateral cervical (Levels I, II, III, IV or V) or retropharyngeal or superior mediastinal lymph nodes (Level VII)

• **Distant metastasis (M)**
  
  **M0:** No distant metastasis  
  **M1:** Distant metastasis
<table>
<thead>
<tr>
<th>Pathological Stage (pTNM)</th>
<th>Number (Percentage)</th>
<th>V600E Positive</th>
<th>Total Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT1a</td>
<td>141 (42.86%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT1b</td>
<td>40 (12.16%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT2</td>
<td>2 (0.61%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT3</td>
<td>146 (44.38%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>329 (100%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 67.89% (N=222) of the cases V600E mutation
- Out of the total (N=141) of pT1a 85 (60.28%) were V600E positive,
- Out of the total (N=40) of pT1b 25 (62.5%) were V600E positive
- Out of the total (N=144) of pT3 110 (76.39%) were V600E positive
BRAF mutation and LN Metastasis

V600E mutation
higher probability for metastasis
(22.97%) of cases

BRAF WT
lower probability
(13.33%) of cases

SURGICAL MANAGEMENT Neck Dissection-Compartments
PTC VARIANTS in 329 cases

Distribution of the number of variants found in the studied population:
- 1 variant: 66%
- 2 variants: 30%
- 3 variants: 3%
- 4 variants: 1%

Percentages of diagnoses according to primary variant:
- Classic Papillary: 73%
- Follicular: 18%
- Oncocytic: 6%
- Tall cell: 2%
- Columnar cell: 1%
The BRAF mutation status and existence of PTC VARIANT

- **Classical Papillary**
  - 62.86% of WT had Papillary Component
  - 77.93% of V600E had similar component

- **Follicular**
  - 55.24% of WT had Follicular Component
  - 36.49% of V600E had similar component.

- **Tall Cell**
  - 5.71% of WT had Tall Cell Component
  - more than the double (13.76%) of V600E had similar component.

- **Encapsulation**
  - 1.8% of V600E cases had encapsulation and more than the triple 6.67% of the WT cases had encapsulation.
Cytopathology Laboratory
General Hospital “Venizelion”, Heraklion, Crete, Greece

1998-2003

- diagnostic accuracy of reporting results in thyroid cytology challenge
2016
diagnostic approach of thyroid lesions
CYTOLOGY
Leading Role
thank you
Heraklion Crete Greece

ευχαριστούμε