Is preoperative RAS or BRAF K601E mutations cytologic detection useful for clinical management of indeterminate thyroid nodules, according to the new WHO classification?

Ravella, Lucie¹; Lopez, Jonathan²,³; Descotes, Françoise²; Giai, Joris⁴,⁵; Lapras, Véronique⁶; Denier, Marie-Laure⁶; Borson-Chazot, Françoise⁷; Lifante, Jean-Christophe⁸; Decaussin-Petrucci, Myriam¹,⁹

¹ Pathology department, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Pierre Bénite, France.
² Biochemistry and molecular biology department, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Pierre Bénite, France.
³ Cancer Research Center of Lyon, Team EMT and cancer cell plasticity, Lyon 1 University
⁴ CNRS, UMR 5558, Laboratoire de Biométrie et Biologie Evolutive, Équipe Biostatistique-Santé, F-69622, Villeurbanne, France; Université Lyon 1, F-69622, Villeurbanne, France.
⁵ Hospices Civils de Lyon, Service de Biostatistique et Bioinformatique, F-69003, Lyon, France.
⁶ Radiology department, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Pierre Bénite, France.
⁷ Endocrinology department, Groupeement hospitalier Est, Hospices Civils de Lyon, Bron, France.
⁸ Endocrine Surgery department, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Pierre Bénite, France.
⁹ Cancer Research Center of Lyon, INSERM1052 CNRS5286, Lyon 1 University
Introduction

Thyroid nodules: high prevalence
50% of patients older than 50 years

Thyroid cancer: only 5% of nodules

Objective of diagnostic evaluation ➔ determine its nature

➢ FNA: the most cost-effective and accurate preoperative diagnostic modality to evaluate thyroid nodules
Cytology

Reliable diagnosis in 60%-80% of cases

Introduction

Cibas, The Bethesda System for Reporting Thyroid Cytopathology, 2017
Indeterminate nodules
20-30% of FNA results

- **Bethesda III / AUS**: Atypia of undetermined significance
- **Bethesda IV / FN**: Follicular neoplasm
- **Bethesda V / SM**: Suspicious for malignancy
## Introduction

### Indeterminate nodules

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Risk of malignancy (%)</th>
<th>Usual management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondiagnostic or Unsatisfactory</td>
<td>5–10&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Repeat FNA with ultrasound guidance</td>
</tr>
<tr>
<td>Benign</td>
<td>0–3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Clinical and sonographic follow-up</td>
</tr>
<tr>
<td>Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance</td>
<td>~10–30&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Repeat FNA, molecular testing, or lobectomy</td>
</tr>
<tr>
<td>Follicular Neoplasm or Suspicious for a Follicular Neoplasm</td>
<td>25–40&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Molecular testing, lobectomy</td>
</tr>
<tr>
<td>Suspicious for Malignancy</td>
<td>50–75</td>
<td>Near-total thyroidectomy or lobectomy</td>
</tr>
<tr>
<td>Malignant</td>
<td>97–99</td>
<td>Near-total thyroidectomy or lobectomy</td>
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Cibas, The Bethesda System for Reporting Thyroid Cytopathology, 2017
Introduction

Molecular testing

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<tr>
<td>Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance</td>
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- Improve diagnostic accuracy

*BRADF, RAS*
# Introduction

## Thyroid oncogenesis

- Follicular adenomas (20-30%)
- Follicular thyroid carcinomas (30-45%)
- Follicular variant of papillary thyroid carcinomas (30-45%)
- NIFTP (30-54%)

- Entities difficult to discriminate as benign or malignant based on cytology
- Often categorized as indeterminate on FNA

## Molecular testing

*RAS*
Introduction

Molecular testing

**BRAF K601E**

- Rare
- Follicular variant of PTC
- Follicular adenomas
- NIFTP
  - « Ras-Like »
Clarify the uncertainty regarding the clinical and surgical management of RAS and BRAF K601E-positive cytologically indeterminate thyroid nodules

- Histological characteristics
- Risk of malignancy
- Risk of “surgical pathology”
Materials and methods

- Records from Lyon Sud University Hospital 1/2013 - 1/2019
- Indeterminate nodules
- RAS BRAF K601E

Cytologic Review
Bethesda 2017

Histological Review
WHO 2017
Materials and methods

FNA classified as **AUS** (B III), **FN** (B IV) and **SM** (B V)

2017 Bethesda system

Cytologic Review
Materials and methods

Benign
- Follicular adenoma
- Oncocytic adenoma

Histological Review
Materials and methods

**Benign**
- Follicular adenoma
- Oncocytic adenoma

**Malignant**
- Invasive follicular variant of PTC (IFVPTC)
- Encapsulated follicular variant of PTC with capsular/vascular invasion (EFVPTC)
- Classic and other type of PTC
- Follicular carcinoma (FC)

Histological Review
Materials and methods

**Benign**
- Follicular adenoma
- Oncocytic adenoma

**Malignant**
- Invasive follicular variant of PTC (IFVPTC)
- Encapsulated follicular variant of PTC with capsular/vascular invasion (EFVPTC)
- Classic and other type of PTC
- Follicular carcinoma (FC)

**Indolent**
- NIFTP
  (non-invasive neoplasms with papillary-like features)
- TUMP
  (tumor of uncertain malignant potential)
Materials and methods

**Benign**
- Follicular adenoma
- Oncocytic adenoma

**Malignant**
- Invasive follicular variant of PTC (IFVPTC)
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- Classic and other type of PTC
- Follicular carcinoma (FC)

**Indolent**
- NIFTP (non-invasive neoplasms with papillary-like features)
- TUMP (tumor of uncertain malignant potential)

Risk of malignancy (ROM)
Risk of surgical pathology
Materials and methods

Benign
- Follicular adenoma
- Oncocytic adenoma

Malignant
- Invasive follicular variant of PTC (IFVPTC)
- Encapsulated follicular variant of PTC with capsular/vascular invasion (EFVPTC)
- Classic and other type of PTC
- Follicular carcinoma (FC)

Indolent
- NIFTP
  (non-invasive neoplasms with papillary-like features)
- TUMP
  (tumor of uncertain malignant potential)

Surgical nodules
- Risk of « surgical pathology »
- Surgical management
**Materials and methods**

**Benign**
- Follicular adenoma
- Oncocytic adenoma

**Malignant**
- Invasive follicular variant of PTC (IFVPTC)
- Encapsulated follicular variant of PTC with capsular/vascular invasion (EFVPTC)
- Classic and other type of PTC
- Follicular carcinoma (FC)

**Indolent**
- NIFTP (non-invasive neoplasms with papillary-like features)
- TUMP (tumor of uncertain malignant potential)

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**Benign nodules**
- non surgical
  - Watchful waiting

**Surgical nodules**
  - Risk of « surgical pathology »
  - Surgical management
## Results

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>69 indeterminate RAS- or BRAF K601E- positive nodules</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Average age</strong></td>
<td><strong>44</strong></td>
</tr>
<tr>
<td><strong>Average size of the nodules</strong></td>
<td><strong>25 mm</strong></td>
</tr>
<tr>
<td><strong>17 lymph node dissection</strong></td>
<td><strong>No metastase</strong></td>
</tr>
<tr>
<td><strong>1 focal extra-thyroidal extension (fat tissue)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>No recurrences to date</strong></td>
<td></td>
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</table>
Results

69 indeterminate RAS- or BRAF K601E- positive nodules

28  AUS / Bethesda 3
16  FN / Bethesda 4
25  SM / Bethesda 5
Results

28 AUS / Bethesda 3
16 FN / Bethesda 4
25 SM / Bethesda 5

69 indeterminate RAS- or BRAF K601E- positive nodules

Histological Review

Adenoma 39%
Results

69 indeterminate RAS- or BRAF K601E- positive nodules

- 28 AUS / Bethesda 3
- 16 FN / Bethesda 4
- 25 SM / Bethesda 5

Histological Review

- NIFTP / TUMP 32%
- Adenoma 39%
Results

69 indeterminate RAS- or BRAF K601E- positive nodules

- 28 AUS / Bethesda 3
- 16 FN / Bethesda 4
- 25 SM / Bethesda 5

Histological Review

- NIFTP / TUMP 32%
- Adenoma 39%
- Carcinoma 29%
Results

69 indeterminate RAS- or BRAF K601E- positive nodules

- 28 AUS / Bethesda 3
- 16 FN / Bethesda 4
- 25 SM / Bethesda 5

Risk of surgical pathology 61%

Risk of malignancy 29%

Histological Review
Results

69 indeterminate RAS- or BRAF K601E- positive nodules

- 28 AUS / Bethesda 3
- 16 FN / Bethesda 4
- 25 SM / Bethesda 5

Histological Review

Adenoma 31%
Results

69 indeterminate RAS- or BRAF K601E-positive nodules

- 28 AUS / Bethesda 3
- 16 FN / Bethesda 4
- 25 SM / Bethesda 5

Histological Review

- NIFTP / TUMP 31%
- Adenoma 31%
Results

69 indeterminate RAS- or BRAF K601E- positive nodules

- 28 AUS / Bethesda 3
- 16 FN / Bethesda 4
- 25 SM / Bethesda 5

Histological Review

- NIFTP / TUMP 31%
- Adenoma 31%
- Carcinoma 38%
Results

69 indeterminate RAS- or BRAF K601E- positive nodules

28
AUS / Bethesda 3

16
FN / Bethesda 4

25
SM / Bethesda 5

Risk of surgical pathology 69%

Risk of malignancy 38%

Histological Review
Results

69 indeterminate RAS- or BRAF K601E- positive nodules

- 28 AUS / Bethesda 3
- 16 FN / Bethesda 4
- 25 SM / Bethesda 5

Histological Review

Adenoma 4%
Results

69 indeterminate RAS- or BRAF K601E- positive nodules

- 28 AUS / Bethesda 3
- 16 FN / Bethesda 4
- 25 SM / Bethesda 5

Histological Review

NIFTP / TUMP 28%
Adenoma 4%

4%
Results

69 indeterminate RAS- or BRAF K601E- positive nodules

- 28 AUS / Bethesda 3
- 16 FN / Bethesda 4
- 25 SM / Bethesda 5

Histological Review

- NIFTP / TUMP 28%
- Carcinoma 68%
- Adenoma 4%

69 indeterminate RAS- or BRAF K601E- positive nodules
Results

69 indeterminate RAS- or BRAF K601E- positive nodules

- 28 AUS / Bethesda 3
- 16 FN / Bethesda 4
- 25 SM / Bethesda 5

Risk of surgical pathology 96%
Risk of malignancy 68%

Histological Review
Results

69 indeterminate RAS- or BRAF K601E- positive nodules

- AUS / Bethesda 3: 28 (Risk of surgical pathology: 61%, Risk of malignancy: 29%)
- FN / Bethesda 4: 16 (Risk of surgical pathology: 69%, Risk of malignancy: 38%)
- SM / Bethesda 5: 25 (Risk of surgical pathology: 96%, Risk of malignancy: 68%)
Most of tumors demonstrated an exclusive follicular growth pattern
Preoperative detection of \textit{RAS} and \textit{BRAF} \textit{K601E} mutations can contribute to cancer risk assessment.

\textbf{Discussion}

Our study: RAS or BRAF K601E-positive nodules

<table>
<thead>
<tr>
<th>Risk of malignancy</th>
<th>Risk of surgical pathology</th>
</tr>
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<tbody>
<tr>
<td>44%</td>
<td>22%</td>
</tr>
<tr>
<td>75%</td>
<td>25%</td>
</tr>
</tbody>
</table>

\textbf{Literature}: Non mutated nodules

\textbf{Original Article}

Molecular testing of \textit{BRAF}, \textit{RAS} and \textit{TERT} on thyroid FNAs with indeterminate cytology improves diagnostic accuracy


Cytopathology, 2017
Discussion

Preoperative detection of RAS and BRAF K601E mutations can contribute to cancer risk assessment.
Preoperative detection of RAS and BRAF K601E mutations can contribute to cancer risk assessment.

Risk of malignancy: 75%
Risk of surgical pathology: 45%
RAS: 29%
BRAF K601E: 38%
SM: 96%
Conclusion

*RAS* or *BRAF* K601E-positive indeterminate thyroid nodules

- Risk of surgical pathology: 75%
  - surgical management
**Conclusion**

*RAS or BRAF K601E-positive indeterminate thyroid nodules*

- **Risk of surgical pathology**: 75%
  - Surgical management

- **Follicular variant of thyroid tumors**
  - NIFTP, EFVPTC
  - Without lymph node metastasis or extra-thyroidal extension
  - Lobectomy
Thank you for your attention