Critical Review and Appraisal of the Latest AJCC System and WHO Classification of Thyroid Tumors

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The Catholic University of Korea
Seoul St. Mary’s Hospital
rates for new thyroid cancer cases have been rising on average 3.8% each year over the last 10 years

Korea's Thyroid-Cancer “Epidemic” — Screening and Overdiagnosis

The trend in thyroid cancer incidence in the United States from 1980 to 2009

Historical aspects of FVPTC

1953
Crile & Hazard, first described FVPTC
Ann Surg 1953;138:33-8

1960
Lindsay S. recognized the entity

1977
Chen KT and Rosai J. defined the FVTPC

1988
WHO classification 2nd Ed.

1998
more accurate diagnosis
Am J Clin Pathol 1999;111:216-222

2016
NIFTP
EFVPTC with distant metastasis

• 3 follicular adenomas → bone metastases 7 to 17 yrs after thyroid resection

• 2 presented initially with bone metastases

Baloch ZW and LiVolsi VA. Mod Pathol 2000;13:861–5
Risk stratification of follicular variant of papillary thyroid carcinoma

- Classic PTC: 20-30% Follicular variant
- Infiltrative
  - Similar to classic PTC
- Encapsulated
  - 1/2 - 2/3
  - Invasion
    - Yes: 1/3
    - No: 2/3
      - Noninvasive EFVPTC
      - Invasive EFVPTC
        - 25%, lymph node metastasis
        - 1%, distant metastasis → death
      - Excellent outcomes:
        - Similar to follicular adenoma
        - “NIFTP”

“noninvasive follicular thyroid neoplasm with papillary-like nuclear features” (NIFTP)
The Increase in Thyroid Cancer Incidence During the Last Four Decades Is Accompanied by a High Frequency of \textit{BRAF} Mutations and a Sharp Increase in \textit{RAS} Mutations

“Less is More”

• **Less diagnosis:** sub-centimeter nodules should not be routinely selected for FNA

• **Lobectomy as the initial surgical approach**

• **Less radioactive iodine treatment**

• **Less stimulated thyroglobulin testing**
The 3rd Edition WHO Classification of Thyroid Tumors

Malignant
- Papillary carcinoma
- Follicular carcinoma
- Poorly differentiated carcinoma
- Undifferentiated (anaplastic) carcinoma
- Squamous cell carcinoma
- Sclerosing mucoepidermoid carcinoma with eosinophilia
- Mucinous carcinoma
- Medullary thyroid carcinoma
- Mixed medullary and follicular cell carcinoma
- Spindle cell tumor with thymus-like differentiation
- Carcinoma showing thymus-like differentiation

Benign
- Follicular adenoma
- Hyalinizing trabecular tumor
- ...
- Secondary tumor of the thyroid

2004
Cell with mutation → Hyperplasia → Dysplasia → In situ cancer → Invasive cancer

10-15 years
Adenoma-Carcinoma Sequence
The 4th Edition WHO Classification of Thyroid Tumors

ICD-O

Benign:
- Follicular adenoma 8330/0
- Hürthle cell adenoma 8290/0

Borderline, uncertain:
- Hyalinizing trabecular tumor 8336/1
- Other Encapsulated Follicular Patterned Thyroid Tumors
  - Follicular Tumor of Uncertain Malignant Potential (FT-UMP) 8335/1
  - Well-Differentiated Tumor of Uncertain Malignant Potential (WDT-UMP) 8348/1
  - Non-invasive Follicular Thyroid neoplasm with Papillary-like nuclear features (NIFTP) 8349/1

Malignant:
- Papillary thyroid carcinoma 8260/3
- Follicular thyroid carcinoma 8330/3
- Hürthle cell carcinoma 8290/3
- Poorly differentiated thyroid carcinoma 8337/3
- Anaplastic thyroid carcinoma 8020/3
- Squamous cell carcinoma 8070/3
- Medullary thyroid carcinoma 8345/3
<table>
<thead>
<tr>
<th>Thyroid Tumor Type</th>
<th>WHO Code</th>
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<tbody>
<tr>
<td>Follicular thyroid carcinoma (FTC), NOS</td>
<td>8330/3</td>
</tr>
<tr>
<td>FTC, minimally invasive</td>
<td>8335/3</td>
</tr>
<tr>
<td><strong>FTC, encapsulated angioinvasive</strong></td>
<td>8339/3</td>
</tr>
<tr>
<td>FTC, widely invasive</td>
<td>8330/3</td>
</tr>
<tr>
<td>Hürthle (oncocytic) cell tumors</td>
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<tr>
<td>Hürthle cell adenoma</td>
<td>8290/0</td>
</tr>
<tr>
<td>Hürthle cell carcinoma</td>
<td>8290/3</td>
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<tr>
<td>Poorly differentiated thyroid carcinoma</td>
<td>8337/3</td>
</tr>
<tr>
<td>Anaplastic thyroid carcinoma</td>
<td>8020/3</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>8070/3</td>
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<tr>
<td>Medullary thyroid carcinoma</td>
<td>8345/3</td>
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## New codes

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tr>
<td>8336/1</td>
<td>Hyalinizing trabecular tumor</td>
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<tr>
<td>8335/1</td>
<td>Follicular Tumor of Uncertain Malignant Potential (FT-UMP)</td>
</tr>
<tr>
<td>8348/1</td>
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</tr>
<tr>
<td>8349/1</td>
<td>Non-invasive Follicular Thyroid neoplasm with Papillary-like nuclear features (NIFTP)</td>
</tr>
<tr>
<td>8339/3</td>
<td>FTC, encapsulated angioinvasive</td>
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</table>
## Renaming entities

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Follicular adenoma, oncocytic type</td>
<td>Hűrthle cell adenoma</td>
</tr>
<tr>
<td>Follicular carcinoma, oncocytic type</td>
<td>Hűrthle cell carcinoma</td>
</tr>
<tr>
<td>Poorly differentiated carcinoma</td>
<td>Poorly differentiated thyroid carcinoma</td>
</tr>
<tr>
<td>Undifferentiated (anaplastic) carcinoma</td>
<td>Anaplastic thyroid carcinoma</td>
</tr>
<tr>
<td>Mixed medullary and follicular cell carcinoma</td>
<td>Mixed medullary and follicular thyroid carcinoma</td>
</tr>
<tr>
<td>Carcinoma showing thymus-like differentiation (CASTLE)</td>
<td>Intrathyroid thymic carcinoma</td>
</tr>
</tbody>
</table>
Hürthle (oncocytic) cell tumors

>75% of the tumor is composed of Hürthle cells

Hürthle cell adenoma 8290/0
Hürthle cell carcinoma 8290/3

Different from non- Hürthle cell thyroid carcinomas
• HCC can spread to cervical nodes
• HCC had larger tumors, higher-stage disease, and lower survival rates
• More common in men
• Older age
Hyalinizing trabecular tumor

- ICD-O code 8336/1
- Benign course, only one case of distant metastasis, rare lymph node metastasis
- Detection of RET/PTC1 rearrangement and RET immunoreactivity
Encapsulated follicular-patterned thyroid tumors

Diagnostic difficulties

• whether the nuclear changes are sufficient to justify a diagnosis of PTC
• uncertainty about the presence of capsular or vascular invasion
Uncertainty about the presence of PTC-type nuclear changes

Follicular variant of papillary thyroid carcinoma
<table>
<thead>
<tr>
<th>% of pathologists</th>
<th>0-9%</th>
<th>10-19%</th>
<th>20-29%</th>
<th>30-39%</th>
<th>40-49%</th>
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</thead>
<tbody>
<tr>
<td>Number of cases (out of 138 total)</td>
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<td>1</td>
<td>12</td>
<td>10</td>
<td>9</td>
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<td>Representative image</td>
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<td><img src="image5" alt="Image" /></td>
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</table>

<table>
<thead>
<tr>
<th>% of pathologists diagnosing</th>
<th>50-59%</th>
<th>60-69%</th>
<th>70-79%</th>
<th>80-89%</th>
<th>90-99%</th>
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<tbody>
<tr>
<td>Number of cases (out of 138 total)</td>
<td>15</td>
<td>34</td>
<td>29</td>
<td>19</td>
<td>8</td>
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<td>Representative image</td>
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<td><img src="image7" alt="Image" /></td>
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<td><img src="image9" alt="Image" /></td>
<td><img src="image10" alt="Image" /></td>
</tr>
</tbody>
</table>
Uncertainty about the presence of capsular or vascular invasion

Minimally invasive follicular thyroid carcinoma
## Uncertainty
### Poor interobserver concordance

<table>
<thead>
<tr>
<th>Encapsulated tumor</th>
<th>Capsular or vascular invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
</tr>
<tr>
<td>Nuclear features of PTC</td>
<td>Present</td>
</tr>
<tr>
<td>Questionable</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td></td>
</tr>
</tbody>
</table>
2017 WHO classification: Encapsulated follicular-patterned thyroid tumors on the basis of presence or absence of nuclear features of PTC and capsular or vascular invasion

<table>
<thead>
<tr>
<th>Encapsulated tumor</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
</tr>
<tr>
<td>Nuclear features of PTC</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>Invasive EFVPTC</td>
</tr>
<tr>
<td>Questionable</td>
<td>WDC, NOS</td>
</tr>
<tr>
<td>Absent</td>
<td>FTC</td>
</tr>
</tbody>
</table>
Tumors of Uncertain Malignant Potential

Encapsulated or well-circumscribed follicular-patterned thyroid tumors with questionable capsular or vascular invasion

ICD-O codes
1) Follicular tumor of uncertain malignant potential 8335/1
2) Well-differentiated tumor of uncertain malignant potential 8348/1
<table>
<thead>
<tr>
<th></th>
<th>Immunohistochemistry</th>
<th>Genetic profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT-UMP</td>
<td>similar to those of follicular adenoma, hyperplasia, minimally invasive FTC</td>
<td>similar to those of follicular neoplasms</td>
</tr>
<tr>
<td>WDT-UMP</td>
<td>may be positive for HBME1, Galectin 3, CK19</td>
<td>intermediate between benign follicular nodule and PTC</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genes</th>
<th>FT-UMP</th>
<th>WT-UMP</th>
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</thead>
<tbody>
<tr>
<td>BRAF</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>RET/PTC3</td>
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<td>0%</td>
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<td>RET/PTC1</td>
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<td>PAX8-PPARG</td>
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<td>7%</td>
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<td>KRAS</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>HRAS</td>
<td>7%</td>
<td>7%</td>
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<tr>
<td>NRAS</td>
<td>0%</td>
<td>13%</td>
</tr>
</tbody>
</table>
Criteria for Capsular Invasion

Fibrous capsule

Not yet (B) Sharp tumor bud invades into but not through the capsule suggesting invasion requiring deeper sections to exclude.

Not yet (F) Follicles aligned perpendicular to the capsule suggesting invasion requiring deeper sections to exclude.

Not yet (I) Mushroom-shaped tumor within but not through the capsule suggests invasion requiring deeper sections to exclude invasion.

“Not yet” (eg, F, G, I) may be acceptable to some pathologists as representing capsular invasion.
**Not yet (F)** Follicles aligned **perpendicular** to the capsule suggesting invasion requiring deeper sections to exclude.
**Questionable capsular invasion**

Fig. 2.16

**Hook-like protrusion** of tumor cells deeply into but not completely through the capsule

**Broad-based bulge** of tumor cells into the capsule that does not extend beyond its outer contour
Vascular invasion (VI)

**** D represents a common but contentious scenario among experts, in light of these new proposed criteria for significant VI. This endothelialized tumor deposit is juxtaposed to the vessel wall. As this is somewhat similar to C, and there is no obvious thrombus, technically this would not count as significant VI. One counterargument is that the endothelialized appearance represents “organization” of a tumor thrombus and is thus still significant. While deeper levels may help, this scenario may still be considered a “judgment call” based on current level of evidence.
Criteria for vascular invasion in 2017 WHO classification

Intravascular tumor cells should be adherent to the vessel walls, either covered by endothelium or in a context of thrombus or fibrin.

Fig. 2.52 Follicular thyroid carcinoma with vascular invasion
Questionable vascular invasion

Irregular outgrowth of neoplastic cells within vascular spaces of the tumor capsule

Tumor cells closely intermixed with vascular spaces of the tumor capsule

Vascular invasion is considered questionable
• when a smooth-contoured tumor cell nest located within a vascular space of the tumor capsule lacks endothelial covering and associated thrombus,
• when a tumor nest in the fibrous capsule abuts a blood vessel
“Well-Differentiated Tumor of Uncertain Malignant Potential (WDT-UMP)”

- by the Chernobyl Pathologists Group in 2000
- Encapsulated tumor composed of well-differentiated follicular cells with questionable PTC-type nuclear changes, no blood vessel invasion, and capsular invasion that is either absent or questionable

“WDT-UMP, however, is not widely accepted as it is not linked to a define clinical management for these patients” Instead, it is important to designate these tumors in the diagnostic line as “EFVPTC” and state if the tumor has vascular or tumor capsule invasion – by Nikiforov YE
<table>
<thead>
<tr>
<th>PTC-Type Nuclear Changes</th>
<th>Capsular Invasion</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obvious</td>
<td></td>
<td>PTC-FV</td>
</tr>
<tr>
<td></td>
<td>Definite</td>
<td>WDC-NOS</td>
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<tr>
<td></td>
<td>Questionable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Absent</td>
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<td>WDT-UMP</td>
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<tr>
<td>Absent</td>
<td>Definite</td>
<td>FC</td>
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<tr>
<td></td>
<td>Questionable</td>
<td>FT-UMP</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>FA</td>
</tr>
</tbody>
</table>
“Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)”

- by international Endocrine Pathology Society working group
- Removing the word “carcinoma” from the nomenclature in an attempt to reduce overtreatment of this indolent tumor
- encompasses non-invasive encapsulated follicular-patterned tumors previously called encapsulated FVPTC as well as WDT-UMP
The International Working Group for re-examination of the encapsulated follicular variant of papillary thyroid cancer
Original Investigation

Nomenclature Revision for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma
A Paradigm Shift to Reduce Overtreatment of Indolent Tumors

Yuri E. Nikiforov, MD, PhD; Raja R. Seethala, MD; Giovanni Tallini, MD; Zubair W. Baloch, MD, PhD;
Fulvio Basolo, MD; Lester D. R. Thompson, MD; Justine A. Barletta, MD; Bruce M. Wenig, MD; Abir Al Ghuzlan, MD;
Kennichi Kakudo, MD, PhD; Thomas J. Giordano, MD, PhD; Venancio A. Alves, MD, PhD;
Elham Khanafshar, MD, MS; Sylvia L. Asa, MD, PhD; Adel K. El-Naggar, MD; William E. Gooding, MS;
Steven P. Hodak, MD; Ricardo V. Lloyd, MD, PhD; Guy Maytal, MD; Ozgur Mete, MD; Marina N. Nikiforova, MD;
Vania Nosé, MD, PhD; Mauro Papotti, MD; David N. Poller, MB, ChB, MD, FRCPath; Peter M. Sadow, MD, PhD;
Arthur S. Tischler, MD; R. Michael Tuttle, MD; Kathryn B. Wall; Virginia A. LiVolsi, MD; Gregory W. Randolph, MD; Ronald A. Ghossein, MD

JAMA Oncol.
Published online April 14, 2016.
### 2015 AFIP fascicle

<table>
<thead>
<tr>
<th>Nuclear features of PTC</th>
<th>Capsular invasion</th>
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<tbody>
<tr>
<td><strong>Present</strong></td>
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</tr>
<tr>
<td><strong>Questionable</strong></td>
<td>Well-differentiated carcinoma, NOS</td>
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<td>Follicular carcinoma</td>
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### 2017 WHO classification

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</table>
NIFTP

Exclusion criteria:
- Invasion
- Papillae > 1%
- Psammoma bodies
- >30% STI growth
- Increased mitoses
- Tumor necrosis

Inclusion criteria:
- Encapsulation/clear demarcation
- Follicular growth pattern
- Nuclear features of PTC

Image and diagnostic criteria for NIFTP from Nikiforov YE, et al. JAMA Oncol 2016
1. Encapsulation or clear demarcation
2. Follicular growth pattern with
   <1% Papillae
   No psammoma bodies
   <30% solid/trabecular/insular growth pattern
No “true” papillae
3. Nuclear score

Nuclear features:

1. Nuclear Size and Shape
   - Enlargement
   - Elongation
   - Overlapping

2. Membrane Irregularities
   - Irregular contours
   - Grooves
   - Pseudoinclusions

3. Chromatin Characteristics
   - Chromatin clearing
   - Margination of chromatin to membrane
   - Glassy nuclei

Degree of prominence:

0 1+ slight 2+ moderate 3+ marked

JAMA Oncol. doi:10.1001/jamaoncol.2016.0386
Nuclear features of PTC (nuclear score of 2-3)
3-point scoring scheme

**Nuclear features:**

<table>
<thead>
<tr>
<th>1. Nuclear Size and Shape</th>
<th>Absent/insufficiently expressed (0)</th>
<th>Present/Sufficient (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Enlargement</td>
<td><img src="image1.jpg" alt="Image" /></td>
<td><img src="image2.jpg" alt="Image" /></td>
</tr>
<tr>
<td>• Elongation</td>
<td><img src="image3.jpg" alt="Image" /></td>
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<tr>
<td>• Overlapping</td>
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<table>
<thead>
<tr>
<th>2. Membrane Irregularities</th>
<th><img src="image7.jpg" alt="Image" /></th>
<th><img src="image8.jpg" alt="Image" /></th>
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<tbody>
<tr>
<td>• Irregular contours</td>
<td><img src="image9.jpg" alt="Image" /></td>
<td><img src="image10.jpg" alt="Image" /></td>
</tr>
<tr>
<td>• Grooves</td>
<td><img src="image11.jpg" alt="Image" /></td>
<td><img src="image12.jpg" alt="Image" /></td>
</tr>
<tr>
<td>• Pseudoinclusions</td>
<td><img src="image13.jpg" alt="Image" /></td>
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<th>3. Chromatin Characteristics</th>
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<tbody>
<tr>
<td>• Chromatin clearing</td>
<td><img src="image17.jpg" alt="Image" /></td>
<td><img src="image18.jpg" alt="Image" /></td>
</tr>
<tr>
<td>• Margination of chromatin to membrane</td>
<td><img src="image19.jpg" alt="Image" /></td>
<td><img src="image20.jpg" alt="Image" /></td>
</tr>
<tr>
<td>• Glassy nuclei</td>
<td><img src="image21.jpg" alt="Image" /></td>
<td><img src="image22.jpg" alt="Image" /></td>
</tr>
</tbody>
</table>

sprinkling sign
Minor diagnostic features:
(C) – Dark colloid in the tumor follicles (T) as compared to the adjacent normal tissue follicles (N);
(D) – Irregularly-shaped follicles with haphazard placement of follicular cell nuclei along the basement membrane of the follicle;

JAMA Oncol. doi:10.1001/jamaoncol.2016.0386
Minor diagnostic features:
(E) – “Sprinkling” of the follicles lined by cells showing the characteristic nuclear features of PTC (arrows) on the background of follicles with benign appearing cells; (F) – Follicles clef from stroma;

JAMA Oncol. doi:10.1001/jamaoncol.2016.0386
Minor diagnostic features:
(G) – Multinucleated giant cells within follicles;
(H) – Intratumoral fibrosis.
FA, Hyperplasia $\rightarrow$ NIFTP $\approx$ EFVPTC $\rightarrow$ Invasive EFVPTC
Algorithm for the evaluation of encapsulated/well circumscribed follicular tumors (with no papillae)

1. Invasive? (Yes or No)
   - Yes: Carcinoma
   - No: Questionable
      - Papillary carcinoma nuclear features (Yes or No)
        - Yes: Use nuclear assessment guide
          - Score 0-1
          - Score 2-3: NIFTP
        - No: Uncertain Malignant Potential
      - No: Adenoma
A meticulous histopathologic examination is of paramount importance, since a deviation from these criteria may affect outcomes.

Exclusion criteria:

- Invasion
- Papillae > 1%
- Psammoma bodies
- >30% STI growth
- Increased mitoses
- Tumor necrosis

- Invasive EFV PTC
- Encapsulated classic PTC
- Encapsulated solid variant of PTC
- Poorly differentiated thyroid carcinoma
BRAFV600E-like PTC

RAS-like PTC

A

V600E BRAF-like

RAS-like

BRAF V600E
BRAF Other
BRAF fusion
H/K/NRAS
EIF1AX
RET
PPARG
NTRK1/3
Other

Somatic Mutation
Fusion

B

MET LTK ALK ALK FGFR2 FGFR2 THADA
RAS-type mutations

- BRAF V600E
- BRAF Other
- BRAF fusion
- H/K/NRAS
- EIF1AX
- RET
- PPARG
- NTRK1/3
- Other

Genetic alterations and their scores are illustrated in the diagram.
Molecular phenotype of NIFTP

- **RAS**
- **BRAF K601E**
- absence of **BRAF V600E**
- **PPARG** fusion
- **THADA** fusion

Most of NIFTPs are driven by clonal genetic alterations → biologically a neoplasm
NIFTP likely represents the “benign” counterpart or precursor of the invasive EFVPTC

Nikiforov YE, et al. JAMA Oncol 2016
Case 1

Male / 59 years
5.0 cm indeterminate nodule

FNA: follicular neoplasm

Lobectomy
Frozen section: follicular neoplasm

> 4 cm
Noninvasive EFVPTC (NIFTP)

No completion thyroidectomy
No RAI
Effect of Lowering the Diagnostic Threshold for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma on the Prevalence of Non-invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features

*Journal of Basic & Clinical Medicine 2017; 6(1):26-28*
Case 2

- 37 y/o male
- 1.4 cm nodule
BRAF V600E

Lymph node metastasis
Case 3
- 33 y/o female
- 0.9 cm nodule
- $BRAF$ V600E
Case 4. 67 y/o male, 0.9 cm nodule, **BRAF V600E**
Case 5. 37 y/o male, 3.5 cm nodule, NRAS Q61R
NIFTP (?) with BRAF V600E mutation

Mod Pathol. 2017 Mar 10. doi: 0.1038/modpathol.2017.9
Potential cases (n=175)

≤1% papillae

Excluded (n=23)
Unmet inclusion criteria

Invasive (n=47)
Noninvasive (n=105)

All PTCs (n=6,269)
Cut-off of papillae

EFVPTC (n=152)

Invasive (n=47)
Noninvasive (n=105)

1.7%

EFVPTC (n=140)

Invasive (n=45)
Noninvasive (n=95)

1.5%

No BRAF V600E
No distant metastasis
LN metastasis: 3% (2/95)

• LN metastasis: 3% (n=3)
• BRAF V600E: 10% (n=10)
• BRAF K601E: 2% (n=2)
• Other BRAF mutation: 2% (n=2)

Seoul St. Mary’s Hospital study 2008 -2014
NIFTP (?) with lymph node metastasis

Mod Pathol. 2017 Mar 10. doi: 0.1038/modpathol.2017.9
Joint Symposium of the Working Group of Asian Thyroid FNA Cytology
25th Thai-Japanese Workshop in Diagnostic Cytopathology
Le Meridien, Chiang Mai, Thailand, January 19, 2018

First row, left-to-right: C.K. Jung (Korea), A. Salilles (Philippines), S.W. Hong (Korea), K. Kakudo (Japan), S. Rangdaeng (Thailand), C.R. Lai (Taiwan), S. Maeda (Japan), S. Hiroi (Japan), P. Sampatanukul (Thailand)

Second row, left-to-right: J.Y. Pyo (Korea), J.F. Hang (Taiwan), S. Watcharadewolfaiya (Thailand), P. Srimun (Thailand), A. Abelardo (Philippines), S. Shrestha (Nepal), A. Bychkov (Thailand), C.Y. Liu (Taiwan), S. Keelewatt (Thailand), T. Hayashi (Japan)
Low Rate of Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features in Asian Practice

Andrey Bychkov,1 Mitsuyoshi Hirokawa,2 Chan Kwon Jung3 Zhiyan Liu4 Yun Zhu5 Soon Won Hong6 Shinya Satoh7 Chiung-Ru Lai8 Lien Huynh9 and Kennichi Kakudo10

Table 1. Incidence of FV-PTC and NIFTP in Asian Institutions

<table>
<thead>
<tr>
<th>PI</th>
<th>Site</th>
<th>Period</th>
<th>PTC, n</th>
<th>FV-PTC n</th>
<th>%</th>
<th>eFV-PTC n</th>
<th>%</th>
<th>NIFTP n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. Hirokawa</td>
<td>Japan, Kobe</td>
<td>2007-2015</td>
<td>9727</td>
<td>271</td>
<td>2.8%</td>
<td>167</td>
<td>1.7%</td>
<td>50</td>
<td>0.5%</td>
</tr>
<tr>
<td>S. Satoh, K. Kakudo</td>
<td>Japan, Fukuoka</td>
<td>2015</td>
<td>386</td>
<td>25</td>
<td>6.5%</td>
<td>20</td>
<td>5.2%</td>
<td>12</td>
<td>3.1%</td>
</tr>
<tr>
<td>C.K. Jung</td>
<td>South Korea, Seoul</td>
<td>2008-2014</td>
<td>6269</td>
<td>240</td>
<td>3.8%</td>
<td>140</td>
<td>2.2%</td>
<td>95</td>
<td>1.5%</td>
</tr>
<tr>
<td>S.W. Hong</td>
<td>South Korea, Seoul</td>
<td>2014</td>
<td>2111</td>
<td>171</td>
<td>8.1%</td>
<td>55</td>
<td>2.6%</td>
<td>5</td>
<td>0.2%</td>
</tr>
<tr>
<td>Z. Liu</td>
<td>China, Shandong</td>
<td>2011-2016</td>
<td>5113</td>
<td>113</td>
<td>2.2%</td>
<td>36</td>
<td>0.7%</td>
<td>16</td>
<td>0.3%</td>
</tr>
<tr>
<td>Y. Zhu</td>
<td>China, Wuxi</td>
<td>2012-2014</td>
<td>2190</td>
<td>187</td>
<td>8.5%</td>
<td>19</td>
<td>0.9%</td>
<td>6</td>
<td>0.3%</td>
</tr>
<tr>
<td>C.R. Lai</td>
<td>Taiwan, Taipei</td>
<td>2010-2011</td>
<td>380</td>
<td>22</td>
<td>5.8%</td>
<td>20</td>
<td>5.3%</td>
<td>18</td>
<td>4.7%</td>
</tr>
<tr>
<td>A. Bychkov</td>
<td>Thailand, Bangkok</td>
<td>2013-2014</td>
<td>163</td>
<td>16</td>
<td>9.8%</td>
<td>9</td>
<td>5.5%</td>
<td>4</td>
<td>2.5%</td>
</tr>
<tr>
<td>L. Huynh</td>
<td>Vietnam, Ho Chi Minh City</td>
<td>2016</td>
<td>265</td>
<td>25</td>
<td>9.4%</td>
<td>10</td>
<td>3.8%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>26,604</td>
<td>1070</td>
<td>4.0%</td>
<td>476</td>
<td>1.8%</td>
<td>206</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

PTC = all primary PTC, including NIFTP; FV-PTC = all PTC follicular variant, including infiltrative and encapsulated (both invasive and noninvasive); eFV-PTC = encapsulated invasive and noninvasive FV-PTC; NIFTP = noninvasive eFV-PTC.

PI, principal investigator; PTC, papillary thyroid carcinoma; FV-PTC, follicular variant of PTC; eFV-PTC, encapsulated follicular variant of PTC; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features.
Western series

- PTC: 85%
- FV-PTC: 20-40%
- NIFTP: 15-20%
- A-M: 5%
- FTC: 5-10%

Asian series

- PTC: 85-90%
- FTC: 5-10%
- A-M: 5%
- NIFTP: 0.5-5%
- FV-PTC: 5-10%

Endocr Pathol. 2018 Feb 23. [Epub ahead of print]
Q1. Have you adopted NIFTP terminology in your practice?

- Use NIFTP only
- Both
- Use only noninvasive eFV-PTC

Overall (n=58):
- 31% Use NIFTP only
- 34% Both
- 35% Use only noninvasive eFV-PTC

Thailand (n=8):
- 100% Use NIFTP only

China (n=11):
- 46% Use NIFTP only
- 27% Both
- 27% Use only noninvasive eFV-PTC

India (n=6):
- 33% Use NIFTP only
- 33% Both
- 33% Use only noninvasive eFV-PTC

Japan (n=20):
- 25% Use NIFTP only
- 20% Both
- 55% Use only noninvasive eFV-PTC

Korea (n=23):
- 1% Use NIFTP only
- 61% Both
- 35% Use only noninvasive eFV-PTC

Q2. What is opinion of your clinicians about NIFTP?

- adopted NIFTP
- mixed reception
- not familiar with NIFTP

Overall (n=56):
- 13% adopted NIFTP
- 43% mixed reception
- 45% not familiar with NIFTP

China (n=10):
- 30% adopted NIFTP
- 60% mixed reception
- 10% not familiar with NIFTP

India (n=6):
- 17% adopted NIFTP
- 83% mixed reception
- 0% not familiar with NIFTP

Thailand (n=8):
- 13% adopted NIFTP
- 50% mixed reception
- 38% not familiar with NIFTP

Korea (n=13):
- 8% adopted NIFTP
- 48% mixed reception
- 46% not familiar with NIFTP

Japan (n=19):
- 5% adopted NIFTP
- 16% mixed reception
- 79% not familiar with NIFTP

Q3. Did you change a sampling technique of the capsule of encapsulated thyroid lesions after NIFTP implementation?

- Yes, now submit in toto
- No, used to submit in toto
- No

Overall (n=58):
- 26% Yes, now submit in toto
- 52% No, used to submit in toto
- 22% No

India (n=6):
- 50% Yes, now submit in toto
- 17% No, used to submit in toto
- 33% No

Korea (n=13):
- 31% Yes, now submit in toto
- 69% No, used to submit in toto
- 0% No

China (n=11):
- 27% Yes, now submit in toto
- 45% No, used to submit in toto
- 27% No

Japan (n=20):
- 15% Yes, now submit in toto
- 65% No, used to submit in toto
- 20% No

Thailand (n=8):
- 13% Yes, now submit in toto
- 38% No, used to submit in toto
- 50% No

Q4. Do you use papillary thyroid carcinoma nuclear score proposed by the NIFTP working group?

- Yes, a part of report
- Yes, but rarely mentioned
- No

Overall (n=58):
- 5% Yes, a part of report
- 40% Yes, but rarely mentioned
- 55% No

Thailand (n=8):
- 13% Yes, a part of report
- 38% Yes, but rarely mentioned
- 50% No

Korea (n=13):
- 8% Yes, a part of report
- 54% Yes, but rarely mentioned
- 38% No

Japan (n=20):
- 5% Yes, a part of report
- 15% Yes, but rarely mentioned
- 80% No

China (n=11):
- 15% Yes, a part of report
- 55% Yes, but rarely mentioned
- 45% No

India (n=6):
- 50% Yes, a part of report
- 50% Yes, but rarely mentioned
- 0% No
The impact of NIFTP on the relative decrease in ROM for the Bethesda diagnostic categories

Pathology 2018 in press
Limitations and challenges

NIFTP is not a ‘finished product’
it is still evolving and the concepts outlined here require validation and if needed, modification
1. Encapsulation or clear demarcation
2. Follicular growth pattern with
   - <1% Papillae
   - No psammoma bodies
   - <30% solid/trabecular/insular growth pattern
3. **Nuclear score 2 - 3**
4. No vascular or capsular invasion
5. No tumor necrosis
6. No high mitotic activity (<3 mitoses per 10 HPF)

**Florid nuclear features of PTC is not an exclusion criterion, but is rarely seen without true papillae.** If such nuclear features are seen, examination of the entire tumor, not just the capsule, with optional, but recommended analyses for *BRAF* V600E using either IHC or molecular techniques may be necessary.
Modifications of Diagnostic Criteria for NIFTP

• Misclassification of invasive infiltrative FVPTC with \textit{BRAF}V600E mutation as NIFTP should be avoided.

• With detailed histological examination of the entire tumor, most NIFTPs with suggested metastasis and/or \textit{BRAF} V600E mutation can be eliminated.

• If genotyping is available, \textit{BRAF} V600E mutation, \textit{RET}/\textit{PTC} rearrangements, and \textit{TERT} mutations should be used to exclude NIFTP.

• Needless to say, any tumors with histologically confirmed metastasis should not be classified in the borderline tumor category.
**Exclusion criteria:**

*BRAF V600E*, *RET/PTC*, *TERT* promoter mutations

**BRAF** V600E EFVPTC

**RAS (+) or BRAF K601E NIFTP**
### RAS mutations in thyroid cancer

<table>
<thead>
<tr>
<th></th>
<th>FA</th>
<th>FTC / EFVPTC</th>
<th>PDTC</th>
<th>ATC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20-25%</td>
<td>30-45%</td>
<td>20-40%</td>
<td>10-20%</td>
</tr>
</tbody>
</table>

Putative progression of RAS-driven follicular-patterned thyroid tumors

- **FA**
- **NIFTP**: Minimally invasive FTC / PTC
- Widely invasive FTC / PTC
- PDTC
- ATC

Accumulation of secondary mutations as a result of chronic RAS activation

*BMC Medicine (2016) 14:12*
Case 6

2013. 1.
F/74
24 x 36 x 51 mm
FNA: Benign

2014. 9.
40 x 32 x 50 mm
CNB: Follicular neoplasm
Poorly differentiated thyroid ca.

- NRAS mutation
- TERT promoter mutation
Papillary thyroid carcinoma

- Malignant epithelial tumor showing evidence of follicular cell differentiation and a set of distinctive nuclear features.
- PTC is usually invasive.
- Papillae, invasion or cytological features of papillary thyroid carcinoma are required.

ICD-O codes
1) Papillary carcinoma 8260/3
2) Follicular variant of PTC 8340/3
3) Encapsulated variant of PTC 8343/3
4) Papillary microcarcinoma 8341/3
5) Columnar cell variant of PTC 8344/3
6) Oncocytic variant of PTC 8342/3
### Variants of papillary thyroid carcinoma

1) Papillary microcarcinoma  
2) Encapsulated variant  
3) Follicular variant  
4) Diffuse sclerosing variant  
5) Tall cell variant  
6) Columnar cell variant  
7) Cribriform-morular variant  
8) Hobnail variant  
9) Papillary thyroid carcinoma with fibromatosis/fasciitis-like stroma  
10) Solid/trabecular variant  
11) Oncocytic variant  
12) Spindle cell variant  
13) Warthin-like variant
Encapsulated variant of PTC

- about 10% of all cases of PTC
- Blood borne metastases are rare
- Survival rate is nearly 100%
Main DDx: Follicular adenoma with papillary hyperplasia
Follicular variant of PTC

Exclusively or almost exclusively follicular growth pattern

1) Infiltrative subtype

2) Encapsulated subtype with invasion

3) Macrofollicular variant

4) Diffuse or multinodular follicular variant
Tall cell variant of PTC

- Two to three times taller
- Eosinophilic (oncocytic-like) cytoplasm, Distinct cell borders
- ≥ 30% of all tumor cells
Elongated “tram track” follicles
Tall cells: Height to width ratio

two to three times taller

Variation depending on the plane of section
## Historical evolution of the diagnostic criteria for TCV

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>H:W ratio</th>
<th>Tall cells %</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017</td>
<td>WHO</td>
<td>2~3:1</td>
<td>&gt;30%</td>
</tr>
<tr>
<td>2015</td>
<td>ATA</td>
<td>3:1</td>
<td>&gt;50%</td>
</tr>
<tr>
<td>2014</td>
<td>Jung CK et al.</td>
<td>3:1</td>
<td>&gt;50% TCV, 10-50% TCF</td>
</tr>
<tr>
<td>2014</td>
<td>Ganly et al.</td>
<td>2:1</td>
<td>&gt;50% TCV, 30-49% TCF</td>
</tr>
<tr>
<td>2008</td>
<td>Ito et al</td>
<td>3:1</td>
<td>&gt;50%</td>
</tr>
<tr>
<td>2007</td>
<td>Ghossein &amp; LiVolsi</td>
<td>2:1</td>
<td>&gt;50%</td>
</tr>
<tr>
<td>2004</td>
<td>WHO</td>
<td>3:1</td>
<td>No %</td>
</tr>
<tr>
<td>1996</td>
<td>Ostrowski &amp; Merino</td>
<td>2:1</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>1988</td>
<td>Johnson et al.</td>
<td>2:1</td>
<td>&gt;30%</td>
</tr>
<tr>
<td>1976</td>
<td>Hawk &amp; Hazard</td>
<td>2:1</td>
<td>No %</td>
</tr>
</tbody>
</table>
Columnar cell variant of PTC

- lack the conventional nuclear features of PTC
- pseudostratified epithelium,
- subnuclear vacuolization or clear cytoplasm
- CDX2(+)
Columnar cell variant of PTC

CDX2
Hobnail variant

- Apically located nuclei with prominent nucleoli
- Eosinophilic cytoplasm
- > 30% of cells with hobnail features
- Loss of cellular cohesion
Diffuse sclerosing variant

- Second or third decade of life
- Dense sclerosis
- Numerous psammoma bodies
- Chronic lymphocytic thyroiditis
- Squamous metaplasia
- Lymphatic invasion
Cribriform-morular variant
Hereditary Thyroid cancer

- Medullary thyroid cancer
- Familial non-medullary thyroid cancer
- Familial adenomatous polyposis, Cowden's disease, Werner's syndrome and Carney complex

Cribriform-Morular Variant of PTC

- Young women
- FAP: ~40%
- APC, CTNNB1 mutations
- no BRAF mutation
Risk of structural disease recurrence in patients without structurally identifiable disease after initial therapy

**High Risk**
- Gross extrathyroidal extension, incomplete tumor resection, distant metastases, or lymph node >3 cm

**Intermediate Risk**
- Aggressive histology, minor extrathyroidal extension, vascular invasion, or >5 involved lymph nodes (0.2-3 cm)

**Low Risk**
- Intrathyroidal DTC, ≤5 LN micrometastases (<0.2 cm)

- FTC, extensive vascular invasion (≈30-55%)
- pT4a gross ETE (≈30-40%)
- pN1 with extranodal extension, >3 LN involved (≈40%)
- PTC, >1 cm, TERT mutated ± BRAF mutated* (≈40%)
- pN1, any LN >3 cm (≈30%)
- PTC, extrathyroidal, BRAF mutated*(≈10-40%)
- PTC, vascular invasion (≈15-30%)
- Clinical N1 (≈20%)
- pN1, >5 LN involved (≈20%)
- Intrathyroidal PTC, <4 cm, BRAF mutated* (≈10%)
- pT3 minor ETE (≈3-8%)
- pN1, all LN <0.2 cm (≈5%)
- pN1, ≤5 LN involved (≈5%)
- Intrathyroidal PTC, 2-4 cm (≈5%)
- Multifocal PTMC (≈4-6%)
- pN1 without extranodal extension, ≤3 LN involved (2%)
- Minimally invasive FTC (≈2-3%)
- Intrathyroidal, <4 cm, BRAF wild type* (≈1-2%)
- Intrathyroidal unifocal PTMC, BRAF mutated*, (≈1-2%)
- Intrathyroidal, encapsulated, FV-PTC (≈1-2%)
- Unifocal PTMC (≈1-2%)

Thyroid. 2016;26:1-133
Follicular thyroid carcinoma

ICD-O codes

- Follicular thyroid carcinoma 8330/3
- Minimally invasive 8335/3
- Encapsulated angioinvasive 8339/3
- Widely invasive 8338/3
### Classification follicular thyroid carcinoma

<table>
<thead>
<tr>
<th>Traditional</th>
<th>AFIP 2014</th>
<th>WHO 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimally invasive</td>
<td>Minimally invasive</td>
<td>With capsular invasion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>With limited vascular invasion (&lt; 4 vessels)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>With extensive vascular invasion (≥4 vessels)</td>
</tr>
<tr>
<td>Widely invasive</td>
<td>Widely invasive</td>
<td></td>
</tr>
</tbody>
</table>

**AFIP, Armed Forces Institute of Pathology**
Cancer 2006;106:1669–76
Extensive vascular invasion (≥4 foci)

- Tumors with limited invasion of vessels (< 4) have a better prognosis than do those with extensive vascular invasion.

Risk of structural disease recurrence

Thyroid. 2016;26:1-133
Histopathology of FTC

- Capsular and/or vascular invasion
- Microfollicular, normofollicular, macrofollicular, and other patterns (e.g. cribriform)
- No nuclear features of PTC

Intravascular tumor cells should be adherent to the vessel walls, either covered by endothelium or in a context of thrombus or fibrin
Endothelial Cell Markers

CD31/CD34

ERG/Fli-1
Encapsulated angioinvasive FTC

• Tumors with limited invasion of vessels (< 4) have a better prognosis than do those with extensive vascular invasion

Vascular invasion
• Armed Forces Institute of Pathology fascicle, 1992
  : focal (<4 invasive foci) and extensive (≥4 foci)

• WHO
  : vascular invasion is often prominent in widely invasive FTC, but alone, does not categorize an FTC as “widely invasive”
Widely invasive FTC

• Extensive invasion of the thyroid and extrathyroidal soft tissues.
• Vascular invasion is often prominent, but alone, does not categorize an FTC as “widely invasive”
• More important than the extent of thyroid or soft tissue invasion is the identification of extensive angioinvasion
Multinodular invasive growth
1) Clear cell variant: >50% clear cells
2) Signet-ring cell type
3) FTC with a glomeruloid pattern: round to oval epithelial tufts growing within them, mimicking a renal glomerulus
4) Spindle cell FTC
Hűrthle (oncocytic) cell tumors

>75% of the tumor is composed of Hűrthle cells

Hűrthle cell adenoma 8290/0
Hűrthle cell carcinoma 8290/3

Different from non-Hűrthle cell thyroid carcinomas
- HCC can spread to cervical nodes
- HCC had larger tumors, higher-stage disease, and lower survival rates
- More common in men
- Older age
### The revised Bethesda System

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Risk of malignancy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Nondiagnostic or Unsatisfactory</td>
<td>5-10</td>
</tr>
<tr>
<td>II. Benign</td>
<td>0-3</td>
</tr>
<tr>
<td>III. AUS/FLUS</td>
<td>~5-15 (\rightarrow) ~10-30</td>
</tr>
<tr>
<td>IV. FN/SFN</td>
<td>15-30 (\rightarrow) 25-40</td>
</tr>
<tr>
<td>V. Suspicious for malignancy</td>
<td>50-75</td>
</tr>
<tr>
<td>VI. Malignant</td>
<td>97-99</td>
</tr>
</tbody>
</table>
## The revised Bethesda System

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Risk of malignancy (%)</th>
<th>Risk of malignancy if NIFTP is not CA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Nondiagnostic or Unsatisfactory</td>
<td>5-10</td>
<td>No change</td>
</tr>
<tr>
<td>II. Benign</td>
<td>0-3</td>
<td>No change</td>
</tr>
<tr>
<td>III. AUS/FLUS</td>
<td>~10-30</td>
<td>6-18</td>
</tr>
<tr>
<td>IV. FN/SFN</td>
<td>25-40</td>
<td>10-40</td>
</tr>
<tr>
<td>V. Suspicious for malignancy</td>
<td>50-75</td>
<td>45-60</td>
</tr>
<tr>
<td>VI. Malignant</td>
<td>97-99</td>
<td>94-96</td>
</tr>
</tbody>
</table>
### Anticipated changes in the implied risk of malignancy of TBSRTC diagnostic categories and recommendations for comments due to the surgical pathology diagnosis of NIFTP

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Risk of malignancy with NIFTP (%)</th>
<th>Optional note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondiagnostic or Unsatisfactory</td>
<td>No significant change</td>
<td>None</td>
</tr>
<tr>
<td>Benign</td>
<td>No significant change</td>
<td>None</td>
</tr>
<tr>
<td>AUS or FLUS</td>
<td>6-18</td>
<td>None</td>
</tr>
<tr>
<td>Follicular neoplasm or Suspicious for a FN</td>
<td>10-40</td>
<td>The histopathologic follow-up of cases diagnosed as such includes follicular adenoma, follicular carcinoma, and follicular variant of papillary thyroid carcinoma, including its recently described indolent counterpart NIFTP.</td>
</tr>
<tr>
<td>Suspicious for malignancy</td>
<td>45-60</td>
<td>The cytomorphologic features are suspicious for a follicular variant of papillary thyroid carcinoma and its recently described indolent counterpart NIFTP.</td>
</tr>
<tr>
<td>Malignant</td>
<td>94-96</td>
<td>A small proportion of cases (~3–4%) diagnosed as malignant – compatible with papillary thyroid carcinoma – may prove to be NIFTP on histopathologic examination.</td>
</tr>
</tbody>
</table>
AUS/FLUS, FN/SFN, or suspicious for PTC?
• It is desirable to eliminate from the malignant category tumors likely to harbor a NIFTP.
• A suspected PTC with an exclusively follicular architecture, especially one that lacks intranuclear cytoplasmic pseudoinclusions and psammoma bodies (e.g., many follicular variants of PTC), is best interpreted as “suspicious for malignancy” rather than malignant.
Updated AJCC/TNM system

downstages a significant number of patients by

1) raising the age cutoff from 45 to 55 years of age at diagnosis

2) removing microscopic extrathyroidal extension from the definition of T3 disease
Extrathyroidal extension (ETE)

Minor extrathyroid extension was removed from the definition of T3 disease

Minor ETE: not clinically appreciated
- Involvement of perithyroidal adipose tissue, strap muscles, nerves, or small vascular structures detected only by microscopy
- Lack of prognostic significance
- T1 or T2 disease

Gross ETE: grossly evident
- Identified by imaging or intraoperative findings
- T3b disease
- T4a disease
- T4b disease
Gross extrathyroidal extension

a clinical finding based on radiologic and/or clinical evidence of macroscopic tumor extending outside the thyroid gland
Tumor size: 1.5 x 1.4 cm

OP record: presence of strap muscle invasion

T1 or T3?

Microscopic ETE

Strap muscle
Gross extrathyroidal extension

Identified by imaging or intraoperative findings

• T3b disease – gross ETE involving only strap muscles
• T4a disease – gross ETE involving the subcutaneous soft tissues, larynx, trachea, esophagus, muscle, or recurrent laryngeal nerve
• T4b disease – gross ETE involving prevertebral fascia or encasing the carotid artery or mediastinal vessels

Pathological staging requires the use of all information obtained during clinical staging, as well as histologic study of the surgically resected specimen.
Primary tumor (T) for papillary, follicular, poorly differentiated, Hurthle cell and anaplastic thyroid carcinomas

TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
T1: Tumor ≤ 2 cm in greatest dimension limited to the thyroid
   - T1a: Tumor ≤ 1 cm in greatest dimension limited to the thyroid
   - T1b: Tumor > 1 cm but ≤ 2 cm in greatest dimension limited to the thyroid
T2: Tumor > 2 cm but ≤ 4 cm in greatest dimension limited to the thyroid
T3*: Tumor > 4 cm limited to the thyroid or gross extrathyroidal extension invading only strap muscles
   - T3a*: Tumor > 4 cm limited to the thyroid
   - T3b*: Gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, thyrohyoid or omohyoid muscles) from a tumor of any size
T4: Includes gross extrathyroidal extension into major neck structures
   - T4a: Gross extrathyroidal extension invading subcutaneous soft tissues, larynx, trachea, esophagus or recurrent laryngeal nerve from a tumor of any size
   - T4b: Gross extrathyroidal extension invading prevertebral fascia or encasing carotid artery or mediastinal vessels from a tumor of any size
### Regional lymph node (N)

**NX:** Regional lymph nodes cannot be assessed

**N0:** No evidence of regional lymph node metastasis
- **N0a**: One or more cytologic or histologically confirmed benign lymph nodes
- **N0b**: No radiologic or clinical evidence of locoregional lymph node metastasis

**N1:** Metastasis to regional nodes
- **N1a**: Metastasis to level VI or VII (pretracheal, paratracheal, prelaryngeal / Delphian or upper mediastinal) lymph nodes; this can be unilateral or bilateral disease
- **N1b**: Metastasis to unilateral, bilateral or contralateral lateral neck lymph nodes (levels I, II, III, IV or V) or retropharyngeal lymph nodes

**Pathologic confirmation of lymph node status is not required**, and patients can be classified as having N0 disease, as long as there is no evidence of lymph node metastasis on routine preoperative and intraoperative evaluations (clinical examination, imaging, and intraoperative findings).
### Differentiated thyroid cancer

<table>
<thead>
<tr>
<th>When age at diagnosis is...</th>
<th>And T is...</th>
<th>And N is...</th>
<th>And M is...</th>
<th>Then the stage group is...</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 55 yrs</td>
<td>Any T</td>
<td>Any N</td>
<td>M0</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td>II</td>
</tr>
<tr>
<td>≥ 55 yrs</td>
<td>T1</td>
<td>N0/NX</td>
<td>M0</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N0/NX</td>
<td>M0</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>T3a/T3b</td>
<td>Any N</td>
<td>M0</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>T4a</td>
<td>Any N</td>
<td>M0</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>T4b</td>
<td>Any N</td>
<td>M0</td>
<td>IVA</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td>IVB</td>
</tr>
</tbody>
</table>

### Anaplastic thyroid cancer

<table>
<thead>
<tr>
<th>T is...</th>
<th>And N is...</th>
<th>And M is...</th>
<th>Then the stage group is...</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1-T3a</td>
<td>N0/NX</td>
<td>M0</td>
<td>IVA</td>
</tr>
<tr>
<td>T1-T3a</td>
<td>N1</td>
<td>M0</td>
<td>IVB</td>
</tr>
<tr>
<td>T3b</td>
<td>Any N</td>
<td>M0</td>
<td>IVB</td>
</tr>
<tr>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
<td>IVB</td>
</tr>
<tr>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td>IVC</td>
</tr>
</tbody>
</table>
### Differentiated thyroid cancer

**Age at diagnosis < 55 years**
- **Stage I:** any T any N M0
- **Stage II:** any T any N M1

**Age at diagnosis ≥ 55 years**
- **Stage I:**
  - T1 N0 / NX M0
  - T2 N0 / NX M0
- **Stage II:**
  - T1 N1 M0
  - T2 N1 M0
- **Stage III:**
  - T1 - 3 N1a M0
- **Stage IVA:**
  - T4a any N M0
  - T1 - 3 N1b M0
- **Stage IVB:** any T any N M0
- **Stage IVC:**
  - any T any N M1

### Medullary thyroid carcinoma
- **Stage I:** T1 N0 M0
- **Stage II:**
  - T2 N0 M0
  - T3 N0 M0
- **Stage III:**
  - T1 - 3 N1a M0
- **Stage IVA:**
  - T4a any N M0
  - T1 - 3 N1b M0
- **Stage IVB:**
  - T4b any N M0
- **Stage IVC:**
  - any T any N M1

### Anaplastic thyroid carcinoma
- **Stage IVA:**
  - T1 - T3a N0 / NX M0
- **Stage IVB:**
  - T1 - T3a N1 M0
  - T3b any N M0
  - T4 any N M0
- **Stage IVC:**
  - any T any N M1
Thank you