Introduction, Incidence and Implications of Noninvasive Follicular Thyroid Neoplasm w/Papillary Like Nuclear Features (NIFTP)

Janice Bone, BS, CTR
Oncology Analytics
Northside Hospital Cancer Institute
Objectives

• Review the reasons for the importance of a new histologic classification for a certain type of thyroid cancer

• Understand the findings of a study that described, supported and defined NIFTP

• Show the implications of NIFTP in regards to reporting, staging and treatment
# Thyroid Cancer – Incidence

### Number of New Cases per 100,000 Persons by Race/Ethnicity & Sex: Thyroid Cancer

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Races</strong></td>
<td>7.3</td>
<td>21.4</td>
</tr>
<tr>
<td><strong>White</strong></td>
<td>7.8</td>
<td>22.8</td>
</tr>
<tr>
<td><strong>Black</strong></td>
<td>3.8</td>
<td>13.4</td>
</tr>
<tr>
<td><strong>Asian / Pacific Islander</strong></td>
<td>7.0</td>
<td>20.2</td>
</tr>
<tr>
<td><strong>American Indian / Alaska Native</strong></td>
<td>4.0</td>
<td>14.3</td>
</tr>
<tr>
<td><strong>Hispanic</strong></td>
<td>5.3</td>
<td>19.6</td>
</tr>
<tr>
<td><strong>Non-Hispanic</strong></td>
<td>7.8</td>
<td>22.1</td>
</tr>
</tbody>
</table>

# Thyroid Cancer: Survival

At a Glance

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated New Cases in 2018</td>
<td>53,990</td>
</tr>
<tr>
<td>% of All New Cancer Cases</td>
<td>3.1%</td>
</tr>
<tr>
<td>Estimated Deaths in 2018</td>
<td>2,060</td>
</tr>
<tr>
<td>% of All Cancer Deaths</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

**Percent Surviving 5 Years**

98.1%

Concerns Regarding the Rising Incidence of Thyroid Cancer

- Incidence of Thyroid cancer per SEER:
  • “Since early 1990s, with incidence in 2013 triple that of 30 years earlier.”

- Rise of incidence of thyroid cancer due to “epidemic of diagnosis” more than “epidemic of disease” causing overdiagnosis and overtreatment.
  • “…intensified surveillance has resulted in an increasing incidence of early cancer with indolent behaviors, a phenomenon commonly described as cancer “overdiagnosis”
  • 2013-Cost of thyroid cancer care of patients estimated 1.6 billion in U.S.

- Overdiagnosis/Overtreatment issues
  • 2009-American Thyroid Association created guidelines discouraging bx of smaller and benign looking nodules.
  • International panel of experts reclassified a subtype of indolent thyroid tumor to prevent overdiagnosis/overtreatment of indolent tumors.

Sources:
It’s Not Cancer: Doctors Reclassify a Thyroid Tumor

A noninvasive follicular thyroid neoplasm with papillary-like nuclear features, or Niftp, a type of tumor that was previously considered a kind of cancer, but has been downgraded by a panel of doctors.

Yuri Nikiforov

• Based on study, a certain type of thyroid tumor that was considered cancer, is not cancer at all.

• Reclassify a type of encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC) to noninvasive follicular thyroid neoplasm w/papillary like nuclear features (NIFTP).

• Downgraded condition will spare removal of total thyroid, tx with radioactive iodine and regular checkups for the rest of patients’ lives.

• Expected to affect 10,000 - 65,000 thyroid cancer patients in the United States.

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; Vanja Nosè, 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

### Summary of Follow-up Information for Patients in Study Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (Noninvasive EFVPTC) (n = 109)</th>
<th>Group 2 (Invasive EFVPTC) (n = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range), y</td>
<td>45.9 (21-81)</td>
<td>42.8 (8-78)</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>91 (83)</td>
<td>71 (70)</td>
</tr>
<tr>
<td>Male</td>
<td>18 (17)</td>
<td>30 (30)</td>
</tr>
<tr>
<td>Tumor size, mean (range), cm</td>
<td>3.1 (1.1-9.0)</td>
<td>2.5 (0.6-5.5)</td>
</tr>
<tr>
<td>Extent of surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobectomy</td>
<td>67</td>
<td>15</td>
</tr>
<tr>
<td>Total thyroidectomy</td>
<td>42</td>
<td>86</td>
</tr>
<tr>
<td>Follow-up, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (range)</td>
<td>14.4 (10-26)</td>
<td>5.6 (1-18)</td>
</tr>
<tr>
<td>Median</td>
<td>13.0</td>
<td>3.5</td>
</tr>
<tr>
<td>Adverse events during follow-up, No. (%)</td>
<td>0</td>
<td>12 (12)</td>
</tr>
</tbody>
</table>

Key Points

**Question**  Do clinical outcomes of noninvasive encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC) warrant reclassification of this tumor as nonmalignant?

**Findings**  This study evaluates cases of encapsulated follicular variant of papillary thyroid carcinoma to establish consensus diagnostic criteria and develop new nomenclature. Among 109 patients with noninvasive EFVPTC, most of whom were treated with lobectomy only and none with radioiodine, all were alive with no evidence of disease at a median follow-up of 13 years.

**Meaning**  Thyroid tumors currently diagnosed as noninvasive EFVPTC have a very low risk of adverse outcome and should be termed “noninvasive follicular thyroid neoplasms with papillary-like nuclear features” (NIFTP).

Box 2. Diagnostic Criteria for NIFTP

1. Encapsulation or clear demarcation\(^a\)
2. Follicular growth pattern\(^b\) with
   <1% Papillae
   No psammoma bodies
   <30% Solid/trabecular/insular growth pattern
3. Nuclear score 2-3
4. No vascular or capsular invasion\(^c\)
5. No tumor necrosis
6. No high mitotic activity\(^d\)

\(^a\) Thick, thin, or partial capsule or well circumscribed with a clear demarcation from adjacent thyroid tissue.

\(^b\) Including microfollicular, normofollicular, or macrofollicular architecture with abundant colloid.

\(^c\) Requires adequate microscopic examination of the tumor capsule interface.

\(^d\) High mitotic activity defined as at least 3 mitoses per 10 high-power fields (400×).

Summary of Results of the Study

• Showed indolent nature of non-invasive EFVPTC (Grp 1 vs. Grp2)

• Creation of the new consensus diagnostic criteria

• Creation of the new nomenclature NIFTP
  – Clear distinction between non-inv EFVPTC and inv EFVPTC
What About Treatment for NIFTP?

- NCCN Guidelines
  - Location: [https://www.nccn.org/professionals/physician_gls/default.aspx](https://www.nccn.org/professionals/physician_gls/default.aspx)
  - Select NCCN Guidelines for Treatment of Cancer by Site
    - Select Thyroid Carcinoma
      - Select NCCN Guidelines PDF

Implications to Treatment for NIFTP per NCCN – Table 1

Implications to Treatment for NIFTP per NCCN – Table 2

FYI- NIFTP (non-invasive follicular thyroid neoplasm with papillary-like nuclear features)

• Why Change Terminology?
• Thyroid cancer is often a low risk tumor
  • Localized disease 5 year regional survival >97%
  • Migrating non-invasive eFVPTC to “NIFTP”
  • Goal: To Identify the subset of patients not requiring total thyroidectomy nor radioactive iodine (nor staging)
• Benefits:
  • Reduced complications/medications/cancer stigma
  • Globally may reduce ‘thyroid cancer’ by 10-20%

Dr. Michelle D. Williams, “Staging Thyroid Cancers”, Associate Professor, Univ of Texas MD Anderson Cancer Center, NCRA Powerpoint at Washington D.C. NCRA Conference
Question (#20160040):

Reportability – Thyroid: Is a final diagnosis of "non-invasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP) reportable when the diagnosis comment states this tumor was historically classified as encapsulated follicular variant of papillary thyroid carcinoma? See Discussion.

Discussion:

The term "non-invasive follicular thyroid neoplasm with papillary-like nuclear features" is now being used, instead of the previous classification of an encapsulated malignant thyroid tumor. Recent evidence supports a very minimal risk of aggressive behavior for these tumors, and pathologists in our area are no longer classifying these as malignant in the final diagnosis.

Answer:

Updated answer for cases diagnosed 1-1-2017 and later

Report NIFTP and assign ICD-O-3 morphology code 8343/2. See NAACCR documents, pg 3.

History:

For cases diagnosed prior to 1-1-2017 We are discussing this terminology change with the other standard setters and with the ICD-O-3 Implementation Workgroup. When a consensus decision is made, it will be reflected in the revised MP/H (to be known as Solid Tumor) rules. For now, you can report noninvasive follicular thyroid neoplasm with papillary-like nuclear features as a synonym for encapsulated follicular variant of papillary thyroid carcinoma and assign 8340/3. Document this in a text field.
• Section 2.2 Reportability of NIFTP as a New Term for EFVPTC

  – Multidisciplinary international expert panel reviewed this issue and described criteria for invasive and noninvasive EFVPTC

  – Noninvasive EFVPC should be reported as NIFTP

  – NIFTP is synonym for noninvasive EFVPTC and standard setters agreed to collect NIFTP with ICD-O-3 code of 8343/2*

  – Standard setters have agreed to collect EFVPTC specified as invasive or NOS to 8343/3*

*Histology codes are effective with cases diagnosed January 1, 2017 and forward

### 9 Appendix B Histology Coding Clarifications for Thyroid Cases

<table>
<thead>
<tr>
<th>Primary Site</th>
<th>Description</th>
<th>Use Histology/Behavior Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid (C73.9)</td>
<td>Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)</td>
<td>8343/2</td>
</tr>
<tr>
<td></td>
<td>Non-invasive encapsulated follicular variant of papillary thyroid carcinoma (non-invasive EFVPTC)</td>
<td>8343/2</td>
</tr>
<tr>
<td></td>
<td>Invasive encapsulated follicular variant of papillary thyroid carcinoma (invasive EFVPTC)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Encapsulated follicular variant of papillary thyroid carcinoma, NOS (EFVPTC, NOS) Synonym: Papillary carcinoma, encapsulated</td>
<td>8343/3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Status</th>
<th>ICD-O-3 Morphology Code</th>
<th>Term</th>
<th>Reportable Y/N</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>New code/term</td>
<td>8339/3</td>
<td>Follicular thyroid carcinoma (FTC), encapsulated angioinvasive (C73.9)</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>New Term</td>
<td>8343/2</td>
<td>Non-invasive EFVPTC (C73.9)</td>
<td>Y</td>
<td>Cases diagnosed 1/1/2017 forward</td>
</tr>
<tr>
<td>New Term</td>
<td>8343/2</td>
<td>Non-invasive encapsulated follicular variant of papillary thyroid carcinoma (non-invasive EFVPTC) (C73.9)</td>
<td>Y</td>
<td>Cases diagnosed 1/1/2017 forward</td>
</tr>
<tr>
<td>New Term</td>
<td>8343/2</td>
<td>Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) (C73.9)</td>
<td>Y</td>
<td>Cases diagnosed 1/1/2017 forward</td>
</tr>
<tr>
<td>New Term</td>
<td>8343/2</td>
<td>Non-invasive FTP (C73.9)</td>
<td>Y</td>
<td>Cases diagnosed 1/1/2017 forward</td>
</tr>
<tr>
<td>New Term</td>
<td>8343/3</td>
<td>Encapsulated follicular variant of papillary thyroid carcinoma, NOS (EFVPTC, NOS) (C73.9)</td>
<td>Y</td>
<td>Cases diagnosed 1/1/2017 forward</td>
</tr>
<tr>
<td>New Term</td>
<td>8343/3</td>
<td>Invasive encapsulated follicular variant of papillary thyroid carcinoma (invasive EFVPTC) (C73.9)</td>
<td>Y</td>
<td>Cases diagnosed 1/1/2017 forward</td>
</tr>
</tbody>
</table>

8-22-18 ICD-0 3 Coding Table on Website

-Link on website:

https://www.naaccr.org/implementation-guidelines/#ICDO3

These documents address the implementation of ICD-O-3 for cases diagnosed on or after January 1, 2018.

- 2018 ICD O 3 Coding Guidelines – 1/10/18
- 2018 ICD O 3 Coding Table .pdf – 8/22/18 (sorted by numeric order)
- 2018 ICD O 3 Coding Table .pdf – 8/22/18 (sorted by alpha order)
- 2018 ICD O 3 Coding Table Excel – 8/22/18

Source: https://www.naaccr.org/implementation-guidelines/#ICDO3
Per 1/2019 COC forum post:
– Discussion: NIFTP should be coded to 8349/1 (per WHO blue book) since the “Physicians have explained that the term non-invasive here is not referring to in-situ, but rather describing the features of the tumor.”

Per SEER:
– Beginning with cases diagnosed 1/1/2017 forward, all standard setters (CoC, AJCC, NAACCR, CDC/NPCR, and SEER) agreed to report NIFTP using 8343/2.
– WHO 4th Edition Tumors of Endocrine organ has proposed 8349/1 however it has not been approved for use by standard setters.
– Do not use information on Cancer Forum for reportability & histology.
– Refer to Standard setter program manual for reportability & histology.

Source: SEER Inquiry System-SEER Data Quality Team email
Review- Reportability and Histology Coding of NIFTP

• Prior to 1/1/2017: For cases diagnosed prior to 1-1-2017. For now, you can report noninvasive follicular thyroid neoplasm with papillary-like nuclear features as a synonym for encapsulated follicular variant of papillary thyroid carcinoma and assign 8340/3. Document this in a text field.

• 1/1/2017 and later: Histology code 8343/2
  – NIFTP is synonym for noninvasive EFVPTC

• What about 8349/1? **DO NOT USE AT THIS TIME.**
  – WHO 4th Ed Tumors of Endocrine organs has proposed a new ICD-O code for NIFTP (8349/1) which has NOT been approved for use by the standard setters at this time.
What About Staging for NIFTP?

<table>
<thead>
<tr>
<th>AJCC TNM Edition 7</th>
<th>AJCC TNM Edition 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Clin Stg: Unstageable (88)</td>
<td>• Clin Stg: Unstageable (88)</td>
</tr>
<tr>
<td>• Path Stg: Unstageable (88)</td>
<td>• Path Stg: Unstageable (88)</td>
</tr>
</tbody>
</table>
Examples of Path Reports with NIFTP at Northside Hospital

• Case 1 Example:
  – Thyroid (Long Suture Left Lobe), Total Thyroidectomy:
    – Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP), 3.5 cm of Left Lobe
    – Background Nodular Thyroid Hyperplasia
    – One Left and One Right Normocellular Parathyroids
    – Two Benign Lymph Nodes

• Case 2 Example
  – Thyroid, Left, Lobectomy:
    • Noninvasive Follicular Thyroid Neoplasm with Papillary Like Nuclear Features, 5.0 CM
EOD and SS2018 for NIFTP

• EOD for 2018
  – Code 000 EOD Primary Tumor
  – Code 000 EOD Regional Nodes
  – Code 00 EOD Mets

• SS2018
  – Code 0 (in situ, noninvasive, intraepithelial)
Incidence of NIFTP in 2017 and 2018

• Northside Hospital Cancer Institute
  – 2017: 0 NIFTP cases/218 total reportable thyroid cancer cases
  – 2018*: 3 NIFTP cases/144 total reportable thyroid cancer cases (2.1 %)

• Stage of Georgia
  – 2017*: 5 NIFTP cases/1057 total reportable thyroid cancer cases (0.47%)
  – 2018: Data not available
    • Data request site
      – https://cfusion.sph.emory.edu/hospitalinfo/DataUpload/datarequest.cfm

• Seattle/Puget Sound SEER Registry – collects for 13 Northwest counties in Washington State
  – 2017*: 43 cases NIFTP/766 total reportable thyroid cancer cases (5.6%)
  – 2018*: 43 cases of NIFTP/746 total reportable thyroid cancer cases (5.76 %)
  – 2019* 22 cases of NIFTP/305 total reportable thyroid cancer cases (7.2 %)

• National SEER data – 2017 and later data not available.

*Incomplete data

Source: Northside Oncology Analytics, Oncolog, Data review/filter 7/1/19
Source: Georgia Comprehensive Cancer Registry, Georgia Dept of Public Health for state case numbers of NIFTP, Data request 1/23/19
Source: Fred Hutchinson Cancer Research Center, Cancer Surveillance System, Data request-6/27/19
Incidence Rates of all Reportable Thyroid Cancers in Georgia State

Source: Georgia Comprehensive Cancer Registry, Georgia Department of Public Health, Data request 1/23/19
Helpful Resource: Ask a SEER Registrar

• Ask a SEER Registrar
  – Location: https://seer.cancer.gov/registars/contact.html
  – Before asking question
    • Check the SEER Inquiry System
    • Direct questions to CoC Canswer Forum
      – SSDI's(Site Specific Data Items)
      – Grade for cases diagnosed 2018+
      – AJCC TNM and CS Stage for Diagnoses 2004 to December 31, 2015
  – Ready to ask a Question –
    • Choose a subject:
      – Solid Tumor Rules(Cases dx’d 2018+)
      – Multiple Primary and Histology Rules (Cases dx’d 2007 – 2017)
      – ICD-O-3 Update(Cases dx’d 2018+)
      – Hematopoietic Rules (Database and Manual)
      – SEER Manual
      – SEER *Rx
      – Staging
        » Extent of Disease 2018, Summary Stage 2018, Collaborative Staging (Cases dx’d 2016+)
    • Other

Source: Ask a SEER Registrar: https://seer.cancer.gov/registars/contact.html
Conclusions – Part I

• Rising incidence thyroid cancer due to overdiagnosis causing overtreatment.

• Per study:
  – Non-invasive EFVPTC showed to have indolent behavior
  – Non-invasive EFVPTC reclassified to NIFTP
  – New diagnostic criteria created for NIFTP

• Reportability and histology coding of NIFTP
  – Yes, NIFTP reportable prior to 2017 – code to 8340/3 histology (for now)
  – Yes, NIFTP reportable 1/1/2017 and later – code to 8343/2 histology
  – Noninvasive EFVPTC is synonym to NIFTP
  – All standard setters agreed on histology code of 8343/2 for NIFTP for 1/1/2017 and later
Conclusions – Part II

- Staging NIFTP
  - TNM staging (nonstageable) – 88
  - EOD and Summary Stage 2018 code 0’s.

- Treatment implications NIFTP
  - NCCN: Lobectomy only, surveillance, horm possible

- Use those resources
  - Ask a SEER Registrar
  - Incidence – Local State and SEER inquiries

- Our work matters!
Resources:

- Dr. Michele D. Williams, "Staging Thyroid Cancers", Associate Professor, Univ of Texas MD Anderson Cancer Center, NCRA Powerpoint at Washington D.C. NCRA Conference.
- Northside Oncology Analytics, Atlanta, GA-Cancer Registry Data, Data request 7/1/19
- Georgia Comprehensive Cancer Registry, Georgia Dept of Public Health for state case numbers of NIFTP, Data request 1/23/19
- Fred Hutchinson Cancer Research Center, Cancer Surveillance System, Seattle, WA, Data request-6/27/19
- All images from Clip Art
Janice Bone, CTR
Oncology Analytics – Tumor Registrar II
Northside Hospital Cancer Institute
Office: 425-753-4074  Fax: 404-845-0035
Website: northside.com/builttobeatcancer
Email: janice.bone@northside.com