NIFTP: Histopathology of a Cytological Monkey Wrench

B. Wehrli
Non-Invasive Encapsulated Follicular Variant of Papillary Thyroid Carcinoma
Non-Invasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP)
Objectives

- Review development of NIFTP
- Review histological criteria of NIFTP
- Review implications of NIFTP
Incidence of Thyroid Cancer (1973-2002)
NCI Surveillance, Epidemiology & End Reporting

2.4 x Increase

JAMA. 2006;295:2164-2167
Thyroid Cancer Incidence & Mortality (1973-2002)

JAMA. 2006;295:2164-2167
Papillary Thyroid Cancer & Size (1988-2002)

87% of Increase

JAMA. 2006;295:2164-2167
Papillary Thyroid Carcinoma – Follicular Variant
## Prevalence of FVPTC at Different Time Intervals

<table>
<thead>
<tr>
<th>Source</th>
<th>Setting/ Location</th>
<th>Time interval</th>
<th>Total number of PTC</th>
<th>FVPTC (% of all PTC)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2009</td>
<td>230</td>
<td>25.2%</td>
</tr>
<tr>
<td>Lupi et al., <em>J Clin Endocrinol Metab</em> 92:4085-4090, 2007</td>
<td>University of Pisa, Pisa, Italy</td>
<td>2006</td>
<td>500</td>
<td>22.8%</td>
</tr>
<tr>
<td>R. Ghossein, unpublished</td>
<td>MSKCC, New York, USA</td>
<td>1977-1999</td>
<td>615</td>
<td>20.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2000-2003</td>
<td>303</td>
<td>27.7%</td>
</tr>
</tbody>
</table>
Follicular Variant PTC - Subtypes

- Infiltrative/Non-encapsulated
- Encapsulated/Well-circumscribed with Capsular and/or Vascular Invasion
- Encapsulated/Well-circumscribed without Capsular and Vascular Invasion
Recurrence-Free & Survival Probability of Patients with FVPTC, CPTC, TCPTC

n=6282
Addressing overdiagnosis and overtreatment in cancer: a prescription for change

Laura J Esserman, Ian M Thompson, Brian Reid, Peter Nelson, David F Ransohoff, H Gilbert Welch, Shelley Hwang, Donald A Berry, Kenneth W Kinzler, William C Black, Mina Bissell, Howard Parnes, Sudhir Srivastava

Panel: Consensus of the working group recommendations regarding overdiagnosis and overtreatment presented to the National Cancer Institute

- Recognize the complexity of overdiagnosis
- Embrace the development of new terminology to replace the word cancer when appropriate, when data or companion diagnostics support the classification of low-risk lesions as indolent lesions of epithelial origin (IDLEs)
- Create observational registries for IDLEs and disorders with low or uncertain risk of progression to cancer
- Mitigate overdiagnosis by testing strategies that lower the chance of detecting unimportant lesions
- Embrace new concepts for how to approach cancer progression and prevention
Question: Do clinical outcomes of noninvasive encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC) warrant reclassification of this tumor as nonmalignant?

DESIGN, SETTING, AND PARTICIPANTS: International, multidisciplinary, retrospective study of patients with thyroid nodules diagnosed as EFVPTC, including 109 patients with noninvasive EFVPTC observed for 10 to 26 years and 101 patients with invasive EFVPTC observed for 1 to 18 years. Review of digitized histologic slides collected at 13 sites in 5 countries by 24 thyroid pathologists from 7 countries. A series of teleconferences and a face-to-face conference were used to establish consensus diagnostic criteria and develop new nomenclature.

OBJECTIVE: To evaluate clinical outcomes, refine diagnostic criteria, and develop a nomenclature that appropriately reflects the biological and clinical characteristics of EFVPTC.
**Selection Criteria for Study Cohorts and Case Contribution**

**Encapsulated or well-circumscribed nodule**

**Follicular growth pattern with no papillae**

**Nuclear features of PTC**

- **Non-Invasive EFVPTC**
  - >1 cm
  - No vascular invasion
  - No capsular invasion
  - Adequate capsule sampling
  - No other invasive tumours in gland except single microcarcinoma
  - No RAI therapy
  - 10 yr F/U minimum

- **EFVPTC with Invasion**
  - Vascular invasion and/or capsular invasion
  - 1 yr F/U minimum
EFVPTC
N = 268

Noninvasive
N = 138

Invasive
N = 130
Consensus Diagnostic Criteria for EFVPTC

**Major Features**

- Encapsulation
- Clear Demarcation

JAMA Oncol 2016 Aug 1;2(8):1023-9
Consensus Diagnostic Criteria for **Invasive** EFVPTC

**Major Features**

- Vascular invasion
- Capsular invasion

*JAMA Oncol 2016 Aug 1;2(8):1023-9*
Consensus Diagnostic Criteria for EFVPTC

Major Features

- Nuclear Features of PTC
  - Enlargement
  - Crowding/overlapping
  - Elongation
  - Irregular contours
  - Grooves
  - Pseudoinclusions
  - Chromatin clearing

JAMA Oncol 2016 Aug 1;2(8):1023-9
True papillae <1%
Consensus Exclusion Criteria for EFVPTC
Consensus Exclusion Criteria for EFVPTC

- Psammoma bodies
- Tumour necrosis
- High mitotic activity \( \geq 3/10 \) hpf
- Cell/morphologic characteristics of other PTC variants (tall cell, solid, etc)
EFVPTC
N = 268

Noninvasive
N = 138

Excluded
N = 29

Consensus
N = 109

Lack nuclear = 14
Invasion = 6
Papillae = 4
Solid = 4

Invasive
N = 130

Excluded
N = 29

Consensus
N = 101

Papillae = 17
Infiltrative = 8
Lack nuclear = 3
No invasion = 2
## Clinical Information & Outcomes

<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>

- Distant mets: 5
  - 2 capsular
  - 1 vascular
  - 2 caps + vascular
- LN recurrence: 1
- Local persistence: 1
- Biochemical failure: 5

JAMA Oncol 2016 Aug 1;2(3):1023-9
Thyroid tumours classified as noninvasive EFVPTC, using strict criteria, have a very low risk of adverse outcome and should be renamed
Noninvasive

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

Name to reflect: main morphological features, neoplastic nature, indolent behaviour

JAMA Oncol 2016 Aug 1;2(8):1023-9
Non-Invasive Follicular Thyroid Neoplasm With Papillary-Like Nuclear Features

(NIFTP)
What are the implications of NIFTP?
A Thyroid Carcinomas

- Papillary thyroid carcinoma, 84%
- Medullary thyroid carcinoma, 4%
- Follicular thyroid carcinoma, 2%
- Poorly differentiated thyroid carcinoma, 6%
- Hürthle-cell carcinoma, 2%
- Anaplastic thyroid carcinoma, 1%
- Other, 1%

B Papillary Thyroid Carcinoma

- Microcarcinoma (all variants), 33%
- Classical variant (BRAF>RTK fusions), 32%
- Follicular variant, infiltrative (BRAF>RAS), 6%
- Follicular variant, encapsulated with invasion (RAS or PAX8-PPARG), 4%
- Follicular variant, encapsulated without invasion (RAS), 17%
- Tall cell (BRAF), 7%

C NIFT-P — An Indolent Neoplasm

Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFT-P)

Box 2. Diagnostic Criteria for NIFTP

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

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×).
# Estimation of Worldwide Incidence of NIFTP

<table>
<thead>
<tr>
<th>Source</th>
<th>Parameter</th>
<th>Value</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferlay J. et al (2012)(^1)</td>
<td>Total number of new cases of thyroid cancer worldwide</td>
<td>298,000</td>
<td>298,000</td>
</tr>
<tr>
<td>Aschebrook-Kilfoy B. et al. (2011)(^2)</td>
<td>Percentage of papillary thyroid carcinoma (PTC) among all thyroid carcinomas</td>
<td>84%</td>
<td>250,320</td>
</tr>
<tr>
<td>Estimation based on unpublished data(^3)</td>
<td>Percentage of encapsulate follicular variant of PTC with no invasion among all PTC</td>
<td>18.6%</td>
<td>46,560</td>
</tr>
</tbody>
</table>
NIFTP Implications - Clinicians

• Estimated 46,000 cases worldwide
• Recurrence rate is likely <1% in the first 15 years
  – De-escalate clinical management
    • No completion thyroidectomy, no RAI therapy
  – Staging not necessary
  – Reduced need for long-term surveillance
  – Reduce risk of secondary disease following RAI
NIFTP Implications – Surgical Pathologist

• As detection of vascular and/or capsular invasion critical to diagnosis, complete capsule sampling important

• Awareness of and application of diagnostic criteria – need to sample entire lesion due to exclusion criteria – psammoma body

• No need to use synoptic report?

• Calculate and compare institutional rates to published rates
Implications - Patients

- Reduce psychological impact – not cancer
- Reduced need for surgery
- Reduced need for RAI therapy
- Reduced need for follow-up surveillance

**Table 1. Thyroid Cancer Surveillance Direct and Indirect Costs for the Year After Treatment**

<table>
<thead>
<tr>
<th></th>
<th>Cost per patient</th>
<th>Cost for all incident patients in 2015 (15,363)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct costs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrasound (× 1)</td>
<td>$123</td>
<td>$1,889,649</td>
</tr>
<tr>
<td>Tg test (× 2)</td>
<td>$60</td>
<td>$921,780</td>
</tr>
<tr>
<td>Tg Ab test (× 2)</td>
<td>$58</td>
<td>$891,054</td>
</tr>
<tr>
<td>Office visit (× 2)</td>
<td>$146</td>
<td>$2,242,998</td>
</tr>
<tr>
<td>Total direct costs</td>
<td>$387</td>
<td>$5,945,481</td>
</tr>
<tr>
<td>Indirect costs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Out-of-pocket expenses</td>
<td>$2,400</td>
<td>$36,871,200</td>
</tr>
<tr>
<td>Productivity loss</td>
<td>$1,601</td>
<td>$24,596,163</td>
</tr>
<tr>
<td>Psychosocial distress</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Total indirect costs</td>
<td>$4,001</td>
<td>$61,467,363</td>
</tr>
<tr>
<td>Total direct and indirect costs</td>
<td>$4,388</td>
<td>$67,412,844</td>
</tr>
</tbody>
</table>

**Table 2. Thyroid Cancer Surveillance Direct and Indirect Costs for Each Subsequent Year After the First Posttreatment Year**

<table>
<thead>
<tr>
<th>Test</th>
<th>Cost per patient</th>
<th>Cost for all prevalent patients in 2015 minus incident cases (132,677)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct costs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrasound</td>
<td>$123</td>
<td>$16,319,271</td>
</tr>
<tr>
<td>Tg test</td>
<td>$30</td>
<td>$3,980,310</td>
</tr>
<tr>
<td>Tg Ab test</td>
<td>$29</td>
<td>$3,847,633</td>
</tr>
<tr>
<td>Office visit</td>
<td>$73</td>
<td>$9,685,421</td>
</tr>
<tr>
<td>Total direct costs</td>
<td>$255</td>
<td>$33,832,635</td>
</tr>
<tr>
<td>Indirect costs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Out-of-pocket expenses</td>
<td>$2,028</td>
<td>$269,068,956</td>
</tr>
<tr>
<td>Productivity loss</td>
<td>$1,601</td>
<td>$212,415,877</td>
</tr>
<tr>
<td>Psychosocial distress</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Total indirect costs</td>
<td>$3,629</td>
<td>$481,484,833</td>
</tr>
<tr>
<td>Total direct and indirect costs</td>
<td>$3,884</td>
<td>$515,317,468</td>
</tr>
</tbody>
</table>

All costs are in US dollars.
Tg, thyroglobulin; Tg Ab, thyroglobulin antibody; TSH, thyrotropin.
Clinical Safety of Renaming Encapsulated Follicular Variant of Papillary Thyroid Carcinoma: Is NIFTP Truly Benign?

David N. Parente¹ · Wouter P. Kluijfhout¹ · Pim J. Bongers¹ · Raoul Verzijl¹ · Karen M. Devon¹,² · Lorne E. Rotstein¹ · David P. Goldstein³ · Sylvia L. Asa⁴ · Ozgur Mete⁴ · Jesse D. Pasternak¹

- Lower incidence – 2.1%
- Adverse outcomes
  - 5 lymph node mets
  - 1 lung mets
- Support de-escalation of treatment
- NIFTP is low-risk cancer, not benign

Fig. 1 Study flow diagram with incidence

World J Surg Published online: 21 August 2017
Conclusions

• NIFTP has a very indolent behaviour when strict histologic criteria are met
• Reclassification will affect a large population
• De-escalation of treatment for NIFTP will reduce consequences associated with a diagnosis of cancer