FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

HISTORICAL PERSPECTIVE

1960 described by Dr. Stuart Lindsay
However, AFIP fascicle (1st and 2nd edition (latter 1969) defined lesions with 50% or more follicle formation as “Follicular carcinoma”
1977 Chen and Rosai described 7 cases and called them FVPTC—because of the nuclei; these were all infiltrative lesions
So in a span of one to two decades, pathologists changed their diagnostic emphasis from \textit{growth pattern} to \textit{nuclear cytology}.

Papillary carcinoma whether it had papillae or how many it had was recognized by its nuclei—and even if the entire tumor was follicular in pattern, if the lesion had \textit{"papillary" nuclei} it was papillary carcinoma.

\textbf{DEFINITION:}
A malignant thyroid tumor characterized by a distinctive set of nuclear features
\begin{itemize}
\item \textbf{NUCLEI}
\begin{itemize}
\item Enlarged
\item Elongated
\item Thick nuclear membrane with small nucleoli
\item Clearing
\item Grooves
\item Inclusions
\end{itemize}
\end{itemize}

\textit{(WHO 2004; 2017)}
This had important clinical relevance—papillary carcinoma tended to show lymphatic spread (both in the gland and into lymph nodes);

Whereas follicular carcinoma was unifocal and hardly ever spread to nodes; if it spread it went hematogenously to distant sites.
FOLLICULAR VARIANT OF PTC: AN HISTORICAL PERSPECTIVE

- This had important clinical relevance—papillary carcinoma tended to show lymphatic spread (both in the gland and into lymph nodes);
- Whereas follicular carcinoma was unifocal and hardly ever spread to nodes; if it spread it went hematogenously to distant sites.
- The follicular variant was therefore expected to behave as a papillary carcinoma.
- And some of them did!
- THIS ASSUMED THAT BEHAVIOR WAS RELATED TO NUCLEAR FEATURES.
FOLLICULAR VARIANT OF PTC: AN HISTORICAL PERSPECTIVE

- BUT,

- The fly in the ointment landed when pathologists noted some tumors which grew like follicular carcinoma (*encapsulated, pushing invasion, vascular invasion*) YET had nuclei of papillary carcinoma.

VARIANTS OF THE VARIANT

- Infiltrative
- Encapsulated
  - Noninvasive
  - Invasive
- Macrofollicular
- Diffuse follicular
- Microcarcinoma in adenoma or nodule

FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- THE INFILTRATIVE VARIANT
  - Grows as usual PTC
  - Excellent nuclei
  - Psammoma bodies
  - Lymph node metastases (may be papillary pattern)
  - Multifocal
  - THIS IS TYPE THAT CAN HAVE Braf MUTATIONS and Ret TRANSLOCATIONS (SIMILAR TO CLASSIC PTC)
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

ENCAPSULATED TYPES

CLASSIC PAPILLARY CARCINOMA CAN BE ENCAPSULATED
Papillae present
May have psammoma bodies
Nuclei perfect

ENCAPSULATED VARIANT
a. *with invasion* (capsule; vessels)
   i. diffuse nuclear features
   ii. multifocal or incomplete nuclear features
b. *without invasion*
   i. diffuse nuclear features
   ii. multifocal or incomplete nuclear features
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

» ENCAPSULATED VARIANT
- If there is invasion and well developed nuclei diffusely throughout the lesion, this would be diagnosed as FVPTC.

» ENCAPSULATED TYPE
- Grows like follicular neoplasm (capsule; pushing invasion)
- Vascular invasion (less any lymphatic invasion)
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- **ENCAPSULATED VARIANT**
- **INVASIVE LESIONS**
  - Rare (<<25%) (if ever) lymph node metastases
  - Rarely "multifocal"
  - Hematogenous metastases (bone, lung)
  - Although some show molecular features of PTC that is rare (and some unique molecular changes too).
  - Often if nodal mets, also mptc in thyroid.

- **MOLECULAR CHANGES**
  - Ras mutations; Pax8/PPAR gamma translocations
  - MOST RESEMBLE FTC
  - TCGA CONFIRMS
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- **ENCAPSULATED WITHOUT INVASION**
- SOME EXAMPLES HAVE DIFFUSE AND WELL DEVELOPED NUCLEAR FEATURES
- SOME WOULD DIAGNOSE THESE AS FVPTC; OTHERS PREFER “ATYPICAL ADENOMA” OR “TUMOR OF UNCERTAIN MALIGNANT POTENTIAL”

Encapsulated follicular patterned lesions without venous invasion do not cause death from cancer.

Data: 1039 consecutive thyroid cancers
Followup: average - 11.9 yrs
67 patients DOD
None of 102 with follicular tumors with PTC nuclei and/or capsular invasion were in DOD group

(Piana et al AJSP 2010)
IS IT PAPILLARY CANCER?

IS IT FOLLICULAR CANCER?

IS IT SOMETHING IN BETWEEN—HYBRID?

IS IT CANCER?

YES

FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- IS IT PAPILLARY CANCER?
- IS IT FOLLICULAR CANCER?
- IS IT SOMETHING IN BETWEEN—HYBRID?
- IS IT CANCER?

ENCAPSULATED VARIANT

With multifocal nuclear features (greater than 2 foci)

**ENTIRE LESION IS CLONAL AND SHOWS SIMILAR MOLECULAR CHANGES IN AREAS WITH AND WITHOUT THE NUCLEI—SO IT IS ALL THE NEOPLASM AND IF INVADES ALL IS CANCER.**
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- **ENCAPSULATED WITHOUT INVASION**
- These are clonal neoplasms but most do not behave like cancer on longterm followup.
- We are overtreating these lesions.

---

FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- Is this merely Follicular adenoma?
- NOT QUITE. WHAT ABOUT THE NUCLEI?
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- WORD **CANCER** is problem

- **ENCAPSULATED NONINVASIVE**
- HISTORICAL SUGGESTIONS:
  - Williams et al 2000------**UMP**
  - Liu et al----------------**behave**
  - benign
  - Kakudo et al----------------**not malignant**
  - SHOULD THESE BE CALLED "BORDERLINE"?
DO NOT USE:

- **Uncertain** WHO IS THIS?—Pathologist, surgeon, patient or the TUMOR?
- **Borderline** “The only thing borderline about a borderline tumor is the pathologist who makes that diagnosis”. Dr. H. Stephen Gallagher (MD ANDERSON CANCER CENTER).
- **Atypical adenoma** This term has been used for a number of unrelated lesions over decades and the term is now meaningless.
- **Carcinoma in situ** Do not use because still has “carcinoma” in the name.

**WHAT'S IN A NAME??**

- DO NOT USE WORD “CARCINOMA” DUE TO PSYCHOLOGICAL IMPLICATIONS
- HENCE AVOID ALSO “CARCINOMA” in SITU.

**WHAT NAME?**

- Must include: “noninvasive” (+/- encapsulated or circumscribed)
- Must include some wording about the nuclei
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

SUGGESTED TERMINOLOGY

NEWER PROPOSAL

NIFTP NonInvasive FollicularThyroid Neoplasm with Papillary Like Nuclear Features

Totally encapsulated or partly encapsulated but completely circumscribed.

Need adequate sampling of capsule

NO INVASION

109 cases with median followup 14 years–never heard from again.

NIFT-P

GRADING OF NUCLEI

- Range 1–9 to 1–3
- PAPILLARY GROWTH <<<1% to NONE
- SOLID AREAS: <30%
- NECROSIS: NONE
- MITOSIS: NONE TO VERY FEW
- INVASION: NONE
NIFT—P

- Encapsulated, and/or circumscribed (complete or partial) but noninvasive (Ni).
- However tumor cells show nuclei with features of ordinary PTC EXCEPT:
  - Often rounder rather than ovoid
  - Less overlap
  - Far fewer intranuclear inclusions
  - Some (occasional) grooves
  - Nuclear change may be multifocal rather than diffuse

NIFT—P

- Noninvasive—
  - How many sections?
  - Total capsule.
  - Is this practical?
  - I think it needs to be done or else you may miss focus of invasion. This changes risk.

NIFT—P

- Noninvasive—
  - How many sections?
  - PERSONAL EXPERIENCE
    - 1. 54 yo woman with 4.5 cm nodule. Originally 8 sections of edge—no invasion (had the nuclei). Went back ~24 more sections of which 5 had capsule and transcapsule invasion. Hence EFVPTC.
    - 2. 49 yo man with 6.9 cm nodule. Original 13 sections of edge—no invasion (had the nuclei). Went back~49 additional sections of which 4 had capsule and transcapsule invasion. EFVPTC.
NIFT-P

- Another series (Thompson, L.) Mod Path 2016)
- 77 cases encapsulated with no invasion.
- Size 0.7 to 9.5 cm (average 3.3 cm)
- Some (20 patients) had multiple tumors
- About 75% had surgery alone.
- Followup average 11.8 years—no adverse events.

NIFTP

- Molecular findings—
  - What data is available for this subgroup of tumors?
  - They are clonal (not hyperplastic nodules) and so NEOPLASMS.
  - They often show mutations similar to FA/FTC.

FOLLICULAR DERIVED NEOPLASMS

<table>
<thead>
<tr>
<th>PATTERN</th>
<th>GENE</th>
<th>NUCLEI</th>
<th>RELATIONSHIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary</td>
<td>Braf</td>
<td>PTC</td>
<td>mptc</td>
</tr>
<tr>
<td>Follicular</td>
<td>Ras</td>
<td>PTC</td>
<td>NIFTP</td>
</tr>
<tr>
<td>Follicular</td>
<td>Ras</td>
<td>Norm</td>
<td>FA</td>
</tr>
</tbody>
</table>
PAPILLARY THYROID CARCINOMA

- **PATTERN F vs P**  
  Pre 1960

- **NUCLEAR CYTOLOGY**  
  1960-2000+

- **INVASIVENESS +/-**  
  2015-----

FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- **ENCAPSULATED WITHOUT INVASION NIFTP**
- **TREATMENT SHOULD BE CONSERVATIVE:**
  - Lobectomy
  - No RAI

NIFT-P WHAT IT IS NOT

- Not encapsulated PTC (should not have papillae nor psammoma bodies)
- Should not have 30% or more solid areas
- Should not have necrosis or mitoses
- Not microcarcinoma (Not yet studied for subcentimeter nodules).
- Not oncocytic tumor (Not yet studied).
NIFT-P  WHAT IT IS NOT

- Not encapsulated PTC  (should not have papillae nor psammoma bodies).

- PERSONAL EXPERIENCE:
  - 32 yo woman with 2.7 cm nodule.  Totally encapsulated noninvasive follicular pattern with nuclear features. One of 21 sections showed a 1.3 mm focus of papillary growth.
  - Delphian node micrometastasis!

NIFT-P

- Issue 1
  - A. Is followup long enough? METHUSALAH
  - B. Well developed vs questionable nuclei—does it matter?
  - C. Are they "cancer" or are they Benign?

NIFT-P

- PROBLEMATIC ISSUE
- ANOTHER VIEW
  (Kossai M et al Institut Gustave Roussay Paris: ATA Abstract 2016)
  - Examined all cases of thyroid cancer with distant mets. Reviewed primary cancer in 96 cases.
  - 10 cases were FVPTC and of these 3 were encapsulated BUT invasive.
  - No cases of NIFTP were found on review of the primary tumors in patients with distant mets.
NIFT-P

- **PROBLEMATIC ISSUE**
  - (Valdezarbas P et al Moffitt cancer Center ATA abstract 2016.)
  - 1998 – 2015
  - Of 141 FVPTC, 66% were NIFTP
  - Node mets (NIFTP 2.2%; IFVPTC 25 %)
  - Distant Mets (NIFTP 2.2%; IFVPTC 6.3%)
  - We do not know how well sectioned cases were as this was retrospective study. Need to wait for the paper.

- **FOLLICULAR VARIANT OF PAPILLARY CARCINOMA: ENCAPSULATED NONINVASIVE**
  - Only a few patients will have adverse clinical course (2 in the literature)
  - So conservative approach may be appropriate
  - Barlotta et al; Baloch et al
  - (Positive margin; incomplete sectioning)

- **NIFT-P**
  - **ISSUE 2**
  - Do we need to go back to old cases and inform patients?
  - **MY VIEW IS: no!!!**
  - It is unclear how complete capsule was examined and if focal invasion, may behave less well.
  - DIAGNOSIS and TREATMENT RECEIVED AT THE TIME WAS STANDARD OF CARE.
ISSUE 3
The problem of cytology.
- FNA
- Core biopsies
- Grading of the nuclear changes.

ISSUE 4
Future issues
- Subcentimeter nodules
- Oncocytic cytology allowed
- Multifocal nodules
- Will longer followup show some will be aggressive?
- Will molecular differences show some are truly precursors to invasive lesions and others not??