THE FOLLICULAR VARIANT OF PAPILLARY THYROID CARCINOMA AND NIFTP
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

● HISTORICAL PERSPECTIVE
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

● 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
FOLLICULAR VARIANT OF PTC: HISTORICAL PERSPECTIVE

- So in a span of one to two decades, pathologists changed their diagnostic emphasis from *growth pattern* to *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 “papillary” nuclei” it was papillary carcinoma.
PAPILLARY THYROID CARCINOMA

DEFINITION:

A malignant thyroid tumor characterized by a distinctive set of nuclear features

(WHO 2004; 2017)
PAPILLARY CARCINOMA THYROID

- NUCLEI
  - Enlarged
  - Elongated
  - Thick nuclear membrane with small nucleoli
  - Clearing
  - Grooves
  - Inclusions
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)
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.
In metastatic sites especially in bone, the nuclei of papillary carcinoma in follicular variant subtype may be absent or have incomplete features.
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.
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

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)
INFILTRATIVE FVPTC
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- ENCAPSULATED TYPES
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

REMEMBER

- CLASSIC PAPILLARY CARCINOMA CAN BE ENCAPSULATED
- Papillae present
- May have psammoma bodies
- Nuclei perfect
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

● 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.
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- 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.
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- ENCAPSULATED VARIANT
- INVASIVE LESIONS

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”
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- 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)
Tumours with a small number of PTC nuclei and/or questionable PTC nuclei often display high observer variation. Tumours are divided into WITH INVASION and WITHOUT INVASION. The WITH INVASION category includes EFV-PTC and FTC, which are malignant. The WITHOUT INVASION category includes WDT-IMP, a well-differentiated tumour of indeterminate malignant potential. This tumour should be treated as BENIGN.
DIAGNOSIS OF FOLLICULAR VARIANT OF PAPILLARY THYROID CARCINOMA

CLASSICAL TYPE

NON-ENCAPSULATED TYPE

ENCAPSULATED TYPE

PROBLEMATIC ISSUE

FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

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

YES
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- 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 long-term 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
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- 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.
NEW 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
SUGGESTED TERMINOLOGY

NIFTP  NonInvasive Follicular Thyroid Neoplasm with Papillary Like Nuclear Features

IS IT GOOD?  NO! IT IS LONG AND ARDUOUS AND CAN BE COMEDIC
NIFT-P

THE NAME IS TOO LONG SO IT IS SHORTENED TO NIFT-P

BUT SOME CALL IT “NIFTY”
NIFT-P

- 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. (ORIGINAL SERIES 2016)
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

- ORIGINAL SERIES 2016
Criteria and examples for scoring nuclear features (June 27, 2015)

Nuclear score: Sum of three nuclear features (each 0 or 1)
So, total score will vary between 0 and 3

Nuclear features:

1. Size and Shape
   - Enlargement
   - Elongation
   - Overlapping

2. Membrane Irregularities
   - Irregular contours
   - Grooves
   - Pseudoinclusions

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

Absent/insufficiently expressed (0)  Present/Sufficient (1)

Slight changes not sufficient to call “yes”!
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

- Similar to invasive EFVPTC
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.
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-RAS (usually NRAS Mutations).
FOLLICULAR DERIVED NEOPLASMS

PATTERN
NUCLEI

- Papillary
- Follicular PTC
- Follicular Normal

GENE

- Braf
- Ras
- Ras

RELATIONSHIP

- mptc---- Classic PTC
- NIFTP-- Inv EVFVPTC
- FA FTC
PAPILLARY THYROID CARCINOMA

PATTERN  F vs P  Pre 1960

NUCLEAR CYTOLOGY  1960-2000+

INVASIVENESS  +/  2015------
NIFTP

- ENCAPSULATED WITHOUT INVASION

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
● ??Oncocytic variant. (Not enough studies)
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!
PAPILLARY PATTERN FOCUS
Several studies with followup data suggest that NIFTP under 1 cm exist and have an excellent prognosis. Although these are retrospective reviews, since lesions are small they appear to be totally sectioned and examined; followups of up to 12 years indicate they do not have any clinical danger.

Xu et al  Endocrine 2018

Shafique et al Endo Pathol 2018.
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**?
Examine 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**
  - (Valderabarro 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.
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA: ENCAPSULATED NONINVASIVE

LONG-TERM FOLLOWUP; LITTLE DATA

- 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)
SEVERAL PUBLISHED STUDIES INDICATE NIFT-P CAN METASTASIZE TO NODES.

SOME OF THE CASES HAVE HAD Braf V 600 E MUTATIONS TOO.

THE COMPLETE SECTIONING OF SUCH LESIONS IS OFTEN NOT STATED SO EITHER FOCAL INVASION OR PAPILLAE MAY HAVE BEEN MISSED.

IN SOME REPORTS, TOTAL THYROIDECTOMY NOT DONE OR mPTC FOCUS OR FOCI ALSO PRESENT IN THE GLAND.
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 WERE STANDARD OF CARE.
The problem of cytology.

○ FNA
○ Core biopsies
○ Grading of the nuclear changes

Most diagnosed as AUS/FLUS, followed by FN. Some diagnosed as suspicious for PTC and a few as outright PTC.
EVEN AT THE MOLECULAR LEVEL, THERE IS OVERLAP WITH MOST NIFTP AND EVFVPTC SHOWING RAS MUTATIONS.

MANY CYTOLOGY LABS AND EVEN MOLECULAR PATHOLOGY REPORTS HAVE A DISCLAIMER ABOUT LESION BEING NIFTP. ENCOURAGE AN INITIAL CONSERVATIVE APPROACH.
NIFT-P

FROZEN SECTION

DO NOT DO IT!!

In order to diagnose NIFTP total sampling needs to be done and this cannot be done at frozen.

If final diagnosis is NIFT-P, lobetomy is enough.

If final diagnosis is PTC, lobetomy may also be enough.
Future issues
  - 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??
THE FOLLICULAR VARIANT OF PAPILLARY THYROID CARCINOMA AND NIFTP