THE DIAGNOSIS OF PAPILLARY THYROID CARCINOMA:

How much (or how little) is enough?

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PAPILLARY THYROID CARCINOMA

- Most common type of thyroid malignancy - 85% of thyroid cancers
- Most common endocrine malignancy
PAPILLARY THYROID CARCINOMA

- Clinical
  - Any age
  - Microscopic to large
  - Female: Male = 2-4:1
  - Radiation history
  - Lymph nodes
  - Prognosis 95% at 25 years
PAPILLARY THYROID CARCINOMA

- Gross
  - Any size
  - Confined or extrathyroidal
  - May show capsule (especially follicular variant)
  - May be cystic
  - May note gross calcification or even bone
PAPILLARY THYROID CARCINOMA

- Pathology
  - Papillae and/or follicles
  - Can be totally follicular
  - Sclerosis
  - Calcification (psammoma bodies)
  - NUCLEI
PAPILLARY THYROID CARCINOMA

- Psammoma bodies
  - GHOSTS of dead Papillae
  - In stroma or lymphatics
  - Importance in lymph nodes
PAPILLARY THYROID CARCINOMA

PATHOLOGY

- Lymphatic invasion early on
- May show vascular invasion also
- Lymph nodes positive over 50% at diagnosis
- May present as nodal metastasis in neck especially cystic (confused with branchial cleft cyst)
PAPILLARY THYROID CARCINOMA

- The characteristic morphologic feature was historically: **PAPILLLAEE**
- In older literature, if greater than 50% of a tumor was follicular in pattern, it was classified as either:
  - MIXED PAPILLARY-FOLLICULAR CA
  - FOLLICULAR CA
In 1960s, some authors (notably Stuart Lindsay) began to pay attention to the nuclear features. Hence over time, the nuclear morphology became the most overriding diagnostic consideration. It no longer mattered how much of the tumor was papillary or even if all of it was follicular in pattern.
In 1977, Chen and Rosai described the follicular variant of papillary carcinoma.

Over 30 years we have witnessed debate and dispute about this tumor; panels of experts have been shown to have wide diagnostic variations ranging from adenoma to carcinoma.
PAPILLARY THYROID CARCINOMA

- WHAT ARE THE QUESTIONS TODAY?
- MORE IMPORTANTLY WHAT ARE THE ANSWERS?
PAPILLARY THYROID CARCINOMA

- If we rely solely on nuclear criteria, then many lesions would be considered FVPTC

- SUCH AS: Chronic sialadenitis, chronic endometritis, etc.
PAPILLARY THYROID CARCINOMA

- THE NUCLEI
  - Elongated
  - Enlarged
  - Cleared out center
  - Thick nuclear membrane
  - Grooves
  - Inclusions
  - Tiny nucleoli
PAPILLARY THYROID CARCINOMA

- In the thyroid the nuclei that are excellent mimics of the PTC nuclei include those in:
  - Hashimoto thyroiditis
  - Graves’ disease
  - Some nodular goiters
PAPILLARY THYROID CARCINOMA

- So perhaps the nuclei alone are not enough.
- I personally require the nuclei be present in a “mass” lesion.
- This is especially true in Hashimoto disease.
I do not believe that one can have a diffuse papillary cancer of the thyroid.

In some Hashimoto or Graves’ glands, every follicular epithelial cell had a nucleus with features of PTC.

THIS IS NOT CANCER.
From molecular analysis it has been shown that in Hashimoto disease:

1. Areas of epithelium with abnormal nuclei show LOH and
2. Low levels of ret/PTC translocation
3. But almost no cases of Braf mutations.
PAPILLARY THYROID CARCINOMA

- So the question raised is
- Is the epithelium in Hashimoto disease “DYSPLASTIC”, “PRENEOPLASTIC”?
From an epidemiologic and clinical viewpoint, the incidence of clinical papillary carcinoma in Hashimoto disease appears slightly increased over background BUT

The frequency of microptc is really elevated.
The problems with these data are myriad but a few are:

- The definition (clinically, serologically and histopathologically) of Hashimoto thyroiditis.
- The definition of the background population.
- Most patients with thyroiditis do not have surgery (if there is no nodule) so it impossible to know the true incidence of cancer (microptc).
PAPILLARY THYROID CARCINOMA

- Data for Graves’ disease are even sparser, since it is unusual to have surgery for this disorder.
- Clinical cancer in Graves’ disease is unusual.
NOW Let us turn attention to nodules (mass lesions).

We consider mass lesions as any size nodule that appears at low power magnification as a lesion and different from whatever is going on in the diffuse background disease.
PAPILLARY THYROID CARCINOMA

- If such a nodule has a papillary architecture and nuclei as previously defined, it is papillary cancer no matter what its size.
- If such a nodule has a totally follicular architecture and nuclei as previously defined, is it papillary cancer?
- MY ANSWER IS YES.
We need to recognize that there are different patterns of the FOLLICULAR VARIANT OF PAPILLARY CARCINOMA.
PAPILLARY THYROID CARCINOMA

- FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- The easiest to recognize is the infiltrative pattern.
## PAPILLARY THYROID CARCINOMA, FOLLICULAR VARIANT

<table>
<thead>
<tr>
<th>TYPE</th>
<th>Dx: CANCER</th>
<th>Dx: OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infiltrative</td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>Encapsulated; invasive; nuclei diffuse or multifocal</td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>Encapsulated; diffuse nuclei</td>
<td>Most YES</td>
<td>Atypical adenoma; UMP</td>
</tr>
<tr>
<td>Encapsulated; multifocal nuclei or equivocal nuclei</td>
<td>Few YES</td>
<td>Many atypical adenoma; few UMP</td>
</tr>
<tr>
<td>Encapsulated; one focus nuclei</td>
<td>Many microPTC in adenoma</td>
<td>Many just adenoma</td>
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<tr>
<td>WHY?</td>
<td></td>
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ENCAPSULATED FVPTC

(Per Baloch ZW)

FVPTC

FVPTC WITH CAP & VAS INV

PTC MCA IN ADENOMA
PAPILLARY THYROID CARCINOMA

THE NUCLEI
- Elongated
- Enlarged
- Cleared out center
- Thick nuclear membrane
- Grooves
- Inclusions
- Tiny nucleoli
PAPILLARY THYROID CARCINOMA

- BACK TO THE NUCLEI
- My reasoning for considering encapsulated follicular tumors with multifocal nuclei as FVPTC
- Sometimes in node and/or bone metastases, the nuclei look normal and not like PTC nuclei, yet these are metastases.
- Thus, if can happen in mets, why not in the primary site?
PAPILLARY THYROID CARCINOMA, FOLLICULAR VARIANT

- A little Molecular data.
- The follicular variant (the encapsulated varieties) tend to fall somewhere in between classic papillary carcinoma and classic follicular carcinoma
- Thus they have less ret/PTC rearrangements, rarely Braf mutations (as does classic PTC) and more ras mutations (similar to follicular carcinoma).
PAPILLARY THYROID CARCINOMA, FOLLICULAR VARIANT

- A little Clinicopathologic data.
- The follicular variant (the encapsulated varieties) tend to show fewer nodal metastases (about 20-25%) than classical PTC.
- They show more bony metastases and often have vascular invasion in the primary.
PAPILLARY THYROID CARCINOMA

- BACK TO THE NUCLEI
- NOW FOR THE CYTOPATHOLOGIST

- WHY IS IT SO DIFFICULT TO DIAGNOSE FOLLICULAR VARIANT PTC ON FNA?
PAPILLARY THYROID CARCINOMA

NOW FOR THE CYTOPATHOLOGIST

WHY IS IT SO DIFFICULT TO DIAGNOSE FOLLICULAR VARIANT PTC ON FNA?

I think it is because although the nuclei are enlarged oval and have grooves, they rarely show intranuclear inclusions and so the FNA diagnosis is often suspicious but not definitive.
PAPILLARY THYROID CARCINOMA

- FOLLICULAR VARIANT
- Sometimes there are undercalls
- Best nuclei tend to be under capsule of lesion, not usually sampled by the FNA (tends to sample center where nuclei may not be well developed).
NOW BACK TO THE CYTOPATHOLOGIST

- Sometimes there are “overcalls” although these are rare.
- Grooves can be seen in other nuclei in the thyroid.
- One can get squamous metaplasia (spontaneous) in **benign** conditions and this can be overdiagnosed.
PAPILLARY THYROID CARCINOMA

NOW FOR THE CYTOPATHOLOGIST

- There is a possible marker that may be useful—EMERIN

- As shown by Bussolati’s group, this marker shows nuclear irregularities in histological and cytological preps of papillary carcinoma but not in nonptc lesions.

- HISTOPATH April 2009
PAPILLARY THYROID CARCINOMA

NOW FOR THE CYTOPATHOLOGIST

Sometimes there are “overcalls” although these are rare.

Beware of oncocytic cells which can be large and have nuclear grooves, especially in hyperfunctioning glands and nodules. If the nucleus has a nucleolus and/or is round, do not make a diagnosis of PTC.
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SALIENT POINTS

At the conclusion of this lecture, the members of the audience should:

1. Understand the subtypes of follicular variant of papillary carcinoma (currently a controversial diagnosis).
2. Recognize that certain benign reactive conditions can demonstrate nuclear changes that simulate papillary cancer nuclei.
3. Learn the diagnostic clues that are helpful in dividing these lesions into clinically relevant entities.
4. Appreciate the applications of the diagnostic criteria to the cytological diagnosis of papillary thyroid carcinoma.

Keywords: Papillary thyroid carcinoma, follicular variant, nuclear features, diagnostic criteria
The entity of follicular variant of papillary thyroid carcinoma (FVPC) which had been recognized in the 1960s by Lindsay\(^1\) was elegantly defined in 1977 by Chen and Rosai. Until that time, most textbooks and review articles on the pathology of papillary thyroid carcinoma (PTC) classified follicular patterned thyroid tumors as “follicular carcinoma” without reference to nuclear features or growth pattern.\(^3\)

In a short time, the pathology community noticed the importance of nuclear characteristics in the classification of, and biological behavior of well differentiated thyroid carcinoma. The AFIP fascicle and the WHO defined lesions as papillary carcinoma solely on the basis of “peculiar nuclear morphology without regard to architectural growth, i.e. whether or not papillary structures were present.

Over the past 30 years, many follicular patterned tumors of the thyroid were diagnosed as papillary carcinoma based on these nuclear features (enlargement, elongation (oval rather than rounded shape), nuclear clearing, intranuclear grooves and inclusions, and small nucleoli with thickened nuclear membranes). Lesions which were infiltrative and those which were partially or completely encapsulated were included in this category.

Problems arose in the diagnosis of completely en capsulated tumors since even so-called “experts” in endocrine pathology showed very poor agreement among themselves in defining the nuclei of papillary carcinoma. Lloyd et al evaluated inter-observer variability in the diagnosis of FVPC; 87 cases were reviewed by 10 experienced endocrine pathologists.

The cohort included cases with one or more diagnostic nuclear features of papillary carcinoma and some with capsular (67%) and vascular invasion (5.7%). A concordant diagnosis of FVPCA was made by all 10 reviewers with a cumulative frequency of 39%. In this series, 24.1% of the patients had metastatic disease, in this group a diagnosis of FVCA was made by all 10 reviewers with a cumulative frequency of 66.7%, and 7 of the reviewers made a diagnosis of FVPCA with a cumulative frequency of 100%.

Hirokawa et al submitted 21 encapsulated follicular patterned thyroid lesions to four American and four Japanese pathologists for expert review. There was unanimous agreement among all pathologists in 2 (10%) cases, 7 of 8 pathologists agreed in 29% and 6 of 8 pathologists in 76% of cases. All pathologists, however, agreed on the diagnosis of benign vs. malignant lesion in 13(62%) of 21 cases. Interestingly, the American pathologists frequently made the diagnosis FVPC as compared to Japanese pathologists (25% vs. 4%).\(^9\) Elsheikh et al assessed inter and intra-observer agreement among 6 thyroid experts by using 15 cases in which the original pathologists considered the differential diagnosis of FVPC vs. follicular adenoma (FA). There was complete agreement in the diagnosis of FVPC in 2 (13%), complete agreement on benign and malignant diagnoses in 4 (27%) and majority agreement in 8 (53%) cases.

Several authors agree that this variability in the diagnosis of FVPC is due to the lack of agreement on the minimal diagnostic criteria. The diagnosis of papillary cancer is established by examining the nucleus. Most often the cytopathologists will not render the diagnosis of papillary carcinoma in thyroid fine needle aspiration specimens until all
major diagnostic features are evident. Any specimens which fell short of this are
diagnosed as suspicious for papillary carcinoma. Numerous studies have shown that that
rate of malignancy in cases diagnosed as such is 60-75% and interestingly most cases on
histologic examination are found to FVPC. Verhulst et al employed a scoring system for
the diagnosis of PTC. In this study the 132 thyroid tumors (66 PTC and 66 follicular
adenoma) were used as a training set to establish the scoring system which was tested on
a validation set of 58 thyroid tumors (29 PTC and 29 FNA) to assess its efficacy in the
diagnosis of PTC. Theses authors found that the microscopic criteria for PTC were highly
variable among cases and ranged from 0% to 75%, nuclear enlargement was the only
feature that was present in 75% of the tumor cells in 94% of cases. Interestingly, in the
validation part of the study eight cases of PTC majority of which were follicular
patterned were in gray zone i.e. at or below the threshold score for the diagnosis of PTC.

The hope for a marker that may help define the nuclei of papillary carcinoma
remains to be fulfilled. At least one marker may show some promise but more work
needs to be done to confirm it. The group from the University of Turino has studied
Emerin a nuclear membrane component and found that immunohistochemical staining
shows differences between papillary carcinomas and benign mimics, normal thyroid and
nonmalignant lesions. The staining is applicable to both cytologic and histologic
preparations.

The considerable inter and intra-observer variability in the diagnosis of FVPC
which often creates treatment dilemmas among clinicians i.e. whether to treat or not i.e.
completion thyroidectomy (in cases where lobectomy is done as the initial procedure)
and/or radioiodine ablation. The result of this confusion is that many cases of FVPC
(especially encapsulated lesions) are sent to thyroid pathology experts for second opinion

Due to this controversy the Chernobyl Pathologist group have proposed the term
“well-differentiated thyroid tumor of uncertain malignant potential” for encapsulated
follicular patterned tumor that only shows some or unconvincing features of PTC.
We recognize that the follicular variant of papillary carcinoma represents a
heterogeneous group of tumors due to its variable growth patterns (architectural) and
distribution of nuclear features of papillary carcinoma.

**The un-encapsulated invasive tumor** is a lesion which grows in an infiltrative
pattern and is without question therefore a carcinoma. In its growth pattern resembles
classical papillary carcinoma. However, the lesion demonstrates no papillae and is
composed exclusively of follicles. The nuclei throughout the lesion are the characteristic
nuclei of papillary carcinoma. These lesions may show lymphatic invasion, multifocal
growth within the thyroid, and on occasion psammoma bodies; lymph node metastases
are not unusual and may even demonstrate papillary growth. These cases do not usually
produce difficulties in diagnosis.

**The encapsulated tumor** represents the group that may cause diagnostic
disagreements. In encapsulated tumors which show invasion of the tumor capsule or
capsular blood vessels, most pathologists will consider these cancers; the diagnostic issue
is whether these should be classified as follicular or papillary carcinoma. We consider
these papillary carcinomas if the nuclear features are present, whether these are diffuse
throughout the tumor or are present in multiple locations within the neoplasm. The
encapsulated FVPC without invasion and showing diffuse nuclear changes of PTC will
be classified by many experienced pathologists as FVPTC; however, problems exist in those encapsulated noninvasive lesions with multifocal nuclear change but in which the nuclei do not show all of the characteristic features listed above of papillary cancer i.e. unconvincing. Most often, there are few if any nuclear inclusions. Finally there are lesions that contain a sub-centimeter area of follicles with papillary nuclei that if present in the normal thyroid would be diagnosed as a papillary microcarcinoma; such rare lesions should be diagnosed as papillary microcarcinoma arising in and confined within a follicular adenoma. These have the biologic characteristics and probably better clinical outlook than identical lesions of intra-glandular incidentally found microcarcinoma; i.e., very small to almost nonexistent risk of metastatic potential.
REFERENCES

1. Lindsay S. Carcinoma of the thyroid gland: a clinical and pathologic study of 239 patients at the University of California Hospital. Springfield, IL; 1960.


36. LiVolsi VA and Baloch ZW. The many faces of follicular variant of papillary thyroid carcinoma. *Path Case Rev* 2010 (in press).