THYROID PATHOLOGY UPDATE

FOLLICULAR LESIONS
FOLLICULAR THYROID LESIONS

■ NODULES
  - Adenomatous (Hyperplastic) nodule
  - Adenoma
  - Follicular carcinoma
  - Follicular variant of Papillary carcinoma
FOLLICULAR THYROID LESIONS

- Adenomatous (Hyperplastic) Nodule

- Definition
  - +/- Capsule
  - Multiple
  - Variegated
<table>
<thead>
<tr>
<th>Adenoma</th>
<th>Definition</th>
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<tbody>
<tr>
<td></td>
<td>- Capsule</td>
</tr>
<tr>
<td></td>
<td>- Solitary</td>
</tr>
<tr>
<td></td>
<td>- Uniform</td>
</tr>
<tr>
<td></td>
<td>- Background normal</td>
</tr>
<tr>
<td></td>
<td>- NO INVASION</td>
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FOLLICULAR THYROID LESIONS

- Follicular carcinoma
  - Definition
    - Capsule (thick, often calcified)
    - Solitary
    - Uniform
    - INVASION
Interior of tumor

MUSHROOM LIKE INVASION

CAPSULE

Surrounding thyroid
FOLLICULAR THYROID LESIONS

- Follicular variant papillary carcinoma
  - Definition
  - +/- capsule
  - +/- Uniform
  - Follicular pattern
  - +/- invasion
  - NUCLEI
FOLLICULAR THYROID LESIONS

WHAT HAVE MODERN TECHNIQUES SHOWN US?
FOLLICULAR THYROID LESIONS

- TOPIC 1
  - Adenomatous nodule VS. Adenoma
  - Are multiple nodules needed? Can one have a solitary adenomatous nodule?
  - If defined histologically, yes!
FOLLICULAR THYROID LESIONS

- Adenomatous nodule VS Adenoma
- Clonality—70% are clonal and the same clone! So they are neoplasms?
FOLLICULAR THYROID LESIONS

- **BUT**

- **PRACTICAL:**

- So long as benign, OKAY for patient!
- (However, our cytology colleagues really do not like this!!)
FOLLICULAR THYROID LESIONS

- TOPIC 2
- FOLLICULAR CARCINOMA
- Invasion of capsule ONLY—Is it enough?
- INTO—Atypical adenoma, Carcinoma, Uncertain (UMP)
- THROUGH, BEYOND ??
- UNCLEAR
<table>
<thead>
<tr>
<th><strong>CURRENT CLASSIFICATION</strong></th>
<th><strong>PROPOSED CLASSIFICATION</strong></th>
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<tbody>
<tr>
<td>Minimally invasive</td>
<td>Minimally invasive</td>
</tr>
<tr>
<td>(gross encapsulation)</td>
<td>(capsule only)</td>
</tr>
<tr>
<td>Widely invasive</td>
<td>Angioinvasive grossly</td>
</tr>
<tr>
<td></td>
<td>encapsulated</td>
</tr>
<tr>
<td></td>
<td>Widely invasive</td>
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</tbody>
</table>
Poorly differentiated carcinoma

Necrosis
FOLLICULAR THYROID LESIONS

- TOPIC 2
- FOLLICULAR CARCINOMA
- Capsule invasion only
- Very rare if only capsule invasion to recur or metastasize
CLINICAL CASE

- 66 year old man with lytic lesion C6 vertebra.
- Follicular thyroid tissue Tg and TTF1 +
- Thyroid: 3.4 cm encapsulated follicular tumor with only capsule invasion.
SIMILAR TO 3 OF 44 CASES OF EVANS
IN THESE CASES,

- IS IT APPROPRIATE TO EXTRAPOLATE TO PREDICT PROGNOSIS IN THE THYROID TUMOR THAT DOES NOT PRESENT AS METASTASIS?
FOLLICULAR THYROID LESIONS

FOLLICULAR CARCINOMA
- CAPSULE INVASION ONLY
- Data lacking:
- Retrospective
  - Incomplete sectioning
  - Confusion with papillary cancer
FOLLICULAR THYROID LESIONS

FOLLICULAR CARCINOMA
- CAPSULE INVASION ONLY
- Data lacking:
- Prospective
  - Rare lesions
  - Very long follow-up needed
FOLLICULAR THYROID LESIONS

- CONTROVERSY 2
- FOLLICULAR CARCINOMA
- CAPSULE INVASION ONLY

- MIMIC: WHAFFT
Worrisome Histologic Alterations Following FNA Thyroid
FOLLICULAR THYROID LESIONS

- "UNCERTAIN MALIGNANT POTENTIAL"
- Meaning??
- Problem: Followup; clinical relevance; Clinician and patient confusion.
FOLLICULAR THYROID LESIONS

- UNCERTAIN MALIGNANT POTENTIAL TUMORS
  - There are two varieties:
  - **FTUMP** (follicular tumor of UMP)
    - DDx: FTC
  - **WDTUMP** (well differentiated tumor of UMP)
    - DDx: FVPTC
## FOLLICULAR THYROID LESIONS

<table>
<thead>
<tr>
<th></th>
<th>NUCLEI</th>
<th>CAPSULE</th>
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<tbody>
<tr>
<td>Adenoma</td>
<td>--</td>
<td>intact</td>
</tr>
<tr>
<td>FTC</td>
<td>--</td>
<td>invaded</td>
</tr>
<tr>
<td>PTC</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>FTUMP</td>
<td>--</td>
<td>+/-</td>
</tr>
<tr>
<td>WDTUMP</td>
<td>+/-</td>
<td>+/-</td>
</tr>
</tbody>
</table>
FOLLICULAR THYROID LESIONS

- TOPIC 3
- FOLLICULAR CARCINOMA
- VASCULAR INVASION
- Less controversial; most call cancer
- Problem is agreed on criteria for vessel invasion
FOLLICULAR THYROID LESIONS

- WIDELY INVASIVE FOLLICULAR CARCINOMA
- Here no controversy—tumor invades in thyroid and extrathyroidal.
- Surgical and clinical diagnosis
- Pathologist tells type of cancer
FOLLICULAR THYROID LESIONS

- WIDELY INVASIVE FOLLICULAR CARCINOMA
  - Rare lesion
  - Most have large areas of poorly differentiated carcinoma
  - Prognosis poor; hematogenous spread
  - If poorly differentiated, may not take up iodine for therapy.
POORLY DIFFERENTIATED CARCINOMA
FOLLICULAR THYROID LESIONS

- TOPIC 4
- FOLLICULAR VARIANT PAPILLARY CARCINOMA
  - Subset of papillary carcinoma entirely composed of follicles lined by cells having the nuclear features of papillary carcinoma.
“NUCLEAR FEATURES ARE EVERYTHING”

- Clear nuclei, grooves, pseudoinclusions

- ARE NUCLEAR FEATURES ALONE DIAGNOSTIC OF PAPILLARY CARCINOMA FOLLICULAR VARIANT EVEN IN THE TOTAL ABSENCE OF INVASION ??
THE MANY FACES OF FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

IS SUBDIVIDING ONLY VALID IN REAL ESTATE??
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

**DEFINITION:**

- One of the follicular patterned lesions of the thyroid
- Based on nuclear features which are those of papillary carcinoma
PAPILLARY CARCINOMA
THYROID

- NUCLEI
- Enlarged
- Elongated
- Thick nuclear membrane with small nucleoli
- Clearing
- Grooves
- Inclusions
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- IS IT PAPILLARY CANCER?
- IS IT FOLLICULAR CANCER?
- IS IT SOMETHING IN BETWEEN-HYBRID?
- IS IT CANCER?
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- There are variants.
- Six subtypes:
  1. Infiltrating
  2. Microcarcinoma within adenoma
  3. Encapsulated
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- INFILTRATING
  - This tumor is unencapsulated and invades the normal thyroid at its edges.
  - This tumor behaves as usual papillary carcinoma—"multifocal"; nodal mets.
  - Invade lymphatics
  - Often extrathyroidal
THE INFILTRATIVE VARIANT

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

- INFILTRATIVE TYPE
- Acts like PTC
- Multifocal
- ETE
- Nodal metastases

Liu et al 2006
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- THERE ARE VARIANTS.
- SIX SUBTYPES:
  1. Infiltrating
  2. Microcarcinoma within adenoma
  3. Encapsulated
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- FOLLICULAR ADENOMA CONTAINING ONE FOCUS OF MICROPAPILLARY CARCINOMA
- Should be considered as microcarcinoma in normal thyroid.
- May do even better since it is confined within adenoma as well as within gland.
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

SUBVARIANTS

Two are easy to diagnose:

a. Infiltrative type
b. Microcarcinoma in adenoma or adenomatous nodule.
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- CLASSIC PAPILLARY CARCINOMA CAN BE ENCAPSULATED
  - Papillae present
  - Nuclei perfect
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- ENCAPSULATED TYPE
- This is the problem
- Growth like follicular neoplasm (capsule; pushing invasion)
- Vascular invasion (less lymphatic invasion)
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
ENCAPSULATED FVPTC

FVPTC

FVPTC WITH CAP & VAS INV

PTC MCA IN ADENOMA
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- ENCAPSULATED VARIANT
- INVASIVE LESIONS
  - Rare (<25% lymph node metastases)
  - Rarely “multifocal”
  - Hematogenous metastases (bone, lung)
  - Although some show molecular features of PTC that is rare
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- ENCAPSULATED VARIANT
- INVASIVE LESIONS

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

- ENCAPSULATED INVASIVE VARIANT
- REFLECTING HISTOLOGY, MOLECULAR BIOLOGY AND CLINICAL FEATURES, SOME PREFER ANOTHER NAME—HYBRID, WDCNOS
- HOWEVER ALL WILL CALL IT CANCER
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- **HYBRID** (Asa & LiVolsi; Sobrinho-Simoes)
- **WDCNOS** (Chernobyl Path Panel)
  - Well differentiated carcinoma not otherwise specified.
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- HYBRID or WDCNOS:
- Growth pattern of FTC (capsule with invasion) but
- Atypical nuclei (incomplete for PTC)
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- ENCAPSULATED WITHOUT INVASION
- SOME EXAMPLES HAVE DIFFUSE AND WELL DEVELOPED NUCLEAR FEATURES
- MANY WOULD DIAGNOSE THESE AS FVPTC; OTHERS PREFER ATYPICAL ADENOMA OR WDTUMP
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- LONGTERM FOLLOWUP; LITTLE DATA
- Only a few patients will have adverse clinical course.
- So conservative approach may be appropriate

- Liu et al
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- ENCAPSULATED WITHOUT INVASION
- SOME EXAMPLES HAVE MULTIFOCAL AND/OR POORLY DEVELOPED NUCLEAR FEATURES
- MANY WOULD DIAGNOSE THESE AS ATYPICAL ADENOMA OR WDTUMP; OTHERS WOULD CALL THESE FVPTC
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- ENCAPSULATED WITHOUT INVASION AND MULTIFOCAL NUCLEI:
- LITTLE FOLLOWUP DATA ON THIS GROUP
- LITTLE IF ANY MOLECULAR DATA
- SHORTTERM THESE TUMORS SEEM TO BEHAVE LIKE ADENOMAS: NEED MORE DATA ON THIS GROUP.
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)
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- Is this merely Follicular adenoma?

- NOT QUITE. EVERY NOW AND THEN ON LONGTERM FOLLOWUP, THEY WILL RECUR AND METASTASIZE.

- FOR LEGAL ISSUES, USE SOME OTHER TERMINOLOGY
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- Compared to STUMP (Smooth muscle tumor of uncertain malignant potential)
  - In uterus, shows mitotic activity in tumor cells but fewer than sarcoma criteria

- WHEN THIS DIAGNOSIS IS MADE, VIRTUALLY ALL GET TAH
- MAY RECUR IN PELVIS OR METASTASIZE AFTER MANY YEARS (BEYOND 10 years)
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- ENCAPSULATED WITHOUT INVASION AND MULTIFOCAL NUCLEI:

- TREATMENT SHOULD BE CONSERVATIVE IN THESE ACCORDING TO WHAT DATA IS AVAILABLE ON FOLLOWUP.
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- **FOOD FOR THOUGHT**
- **WHAT ABOUT THOSE LESIONS THAT ARE ENCAPSULATED AND HAVE MULTIFOCAL NOT DIFFUSE NUCLEAR FEATURES?**
- **HOW DO WE DETERMINE SIZE?**
- **IS WHOLE NODULE CANCER?**
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- FOOD FOR THOUGHT

- FACT: In lymph node mets, sometimes follicles have “normal nuclei”—yet this is cancer

- PROPOSITION: Why if in some mets nuclei are not classic, can this not be true in parts of the primary??
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- FOOD FOR THOUGHT
- Some microdissection studies have shown translocations in *ret* in both areas with and without nuclear features.
- Tumors which stain for HBME-1 stain in both areas as well.
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- ALL ANSWERS CERTAINLY NOT IN!!
FOLLICULAR THYROID LESIONS

- PRACTICAL MATTERS:
  - Adenomatous nodule and Adenoma-BENIGN—lobectomy enough
  - Follicular carcinoma capsule invasion only—Is lobectomy enough—not known (PROBABLY)
  - Follicular carcinoma vasculoinvasive—treat as carcinoma with total thyroidectomy and RaI; no need for node dissection
FOLLICULAR THYROID LESIONS

- **PRACTICAL MATTERS:**
- **Follicular variant papillary carcinoma**
  - If invasive and nuclei classic—treat as papillary carcinoma; local customs apply. Thyroidectomy +/- nodes; RaI.
  - If encapsulated or nuclei equivocal—equivalent to UMP—controversial but lobectomy may be enough. (Tumor size and patient age may come into play)
THYROID PATHOLOGY UPDATE

FOLLICULAR LESIONS