Classification of New Thyroid Tumors and Impact on Clinical Management

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Learning Objectives

- At the end of this session, the attendee will be able to:
- 1. Describe newly defined thyroid tumors
- 2. Discuss the history of NIFTP, a reclassified thyroid tumor, and its impact on clinical management
- 3. Differentiate between high grade and poorly differentiated thyroid tumors

FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

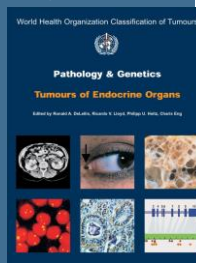
- 1960 described by Dr. Stuart Lindsay
- However, AFIP fascicle (1st and 2nd edition (latter 1969) defined lesions with 50% or more follicle formation as “Follicular carcinoma”
- 1977 Chen and Rosai described 7 cases and called them **FVPTC-because of the nuclei; these were all infiltrative lesions**

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.**

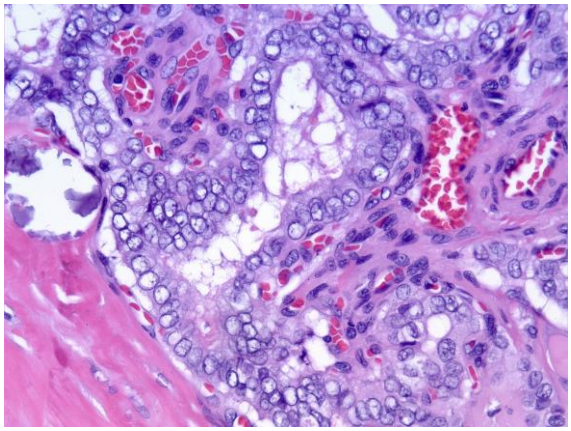
PAPILLARY THYROID CARCINOMA

- **DEFINITION:**
- **A malignant thyroid tumor characterized by a distinctive set of nuclear features**
- **(WHO 2004; 2017; 2023)**



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);
- **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

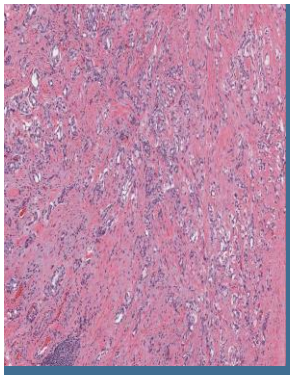
- **The follicular variant was therefore expected to behave as a papillary carcinoma.**
- **And some of them did!**
- **THIS ASSUMED THAT BEHAVIOR WAS RELATED TO NUCLEAR FEATURES.**

FOLLICULAR VARIANT OF PTC: AN HISTORICAL PERSPECTIVE

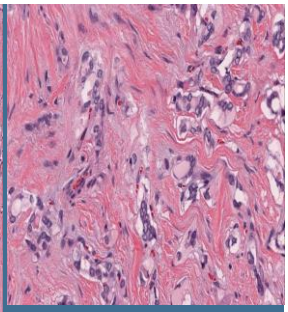
- **BUT,**
- The fly in the ointment landed when pathologists noted some tumors which grew like follicular carcinoma (encapsulated, pushing invasion, vascular invasion) YET had nuclei of papillary carcinoma.

FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

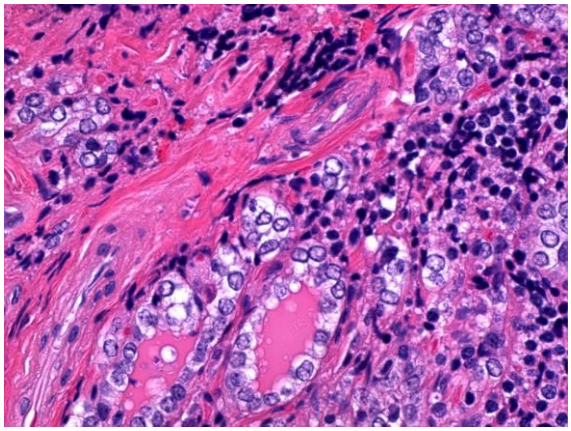
- **THE INFILTRATIVE VARIANT**
  - **Grows as usual PTC**
  - **Excellent nuclei**
  - **Psammoma bodies**
  - **Lymph node metastases (may be papillary pattern)**
  - **Multifocal**
  - **THIS IS TYPE THAT CAN HAVE Braf MUTATIONS and *Ret* TRANSLOCATIONS (SIMILAR TO CLASSIC PTC)**



INFILTRATIVE PORTION OF MAIN TUMOR



HIGHER POWER
NOTE SCLEROSIS,
FOLLICLES,
NUCLEI



FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- **ENCAPSULATED TYPES**

FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

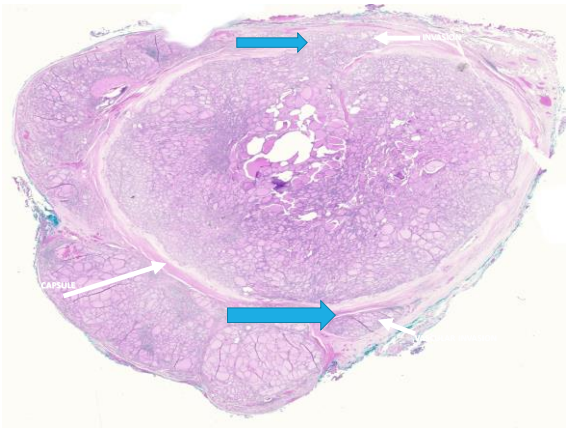
- **ENCAPSULATED VARIANT**
  - a. ***with invasion*** (capsule; vessels)
    - i. diffuse nuclear features
    - ii.multifocal or incomplete nuclear features
  - b. without invasion
    - i. diffuse nuclear features
    - ii.multifocal or incomplete nuclear features

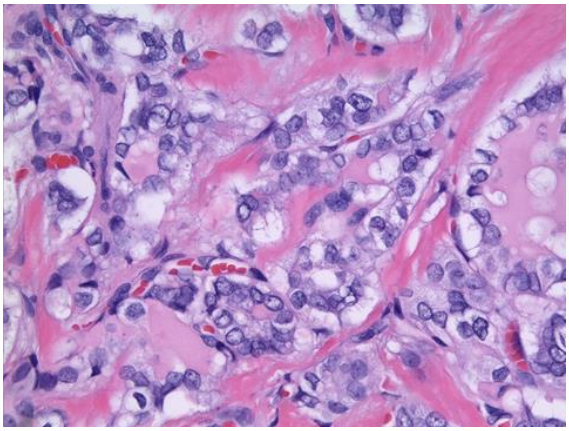
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- **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 **(?Do these have any papillae? Or microPTC in the gland?)**
  - Rarely "multifocal"
  - Hematogenous metastases (bone, lung)
  - Although some show molecular features of PTC that is rare (and some unique molecular changes too). Many show molecular changes of follicular tumors.
  - 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/FA**
- **TCGA CONFIRMS**

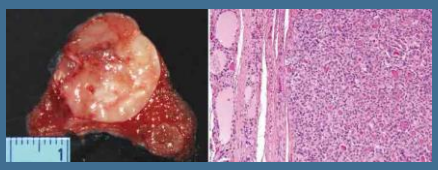
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

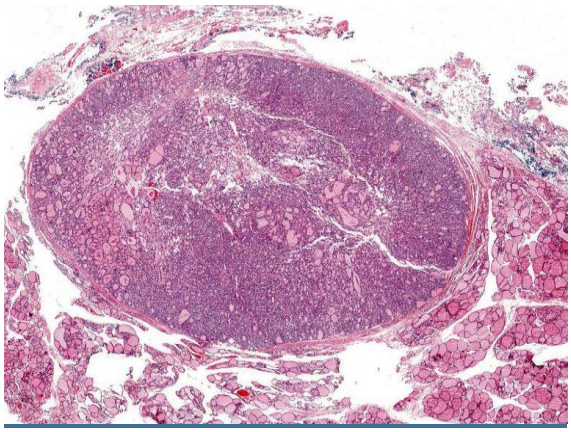
- Encapsulated follicular patterned lesions without venous invasion do not cause death from cancer.
- Data: 1039 consecutive thyroid cancers
- Followup: average-11.9 yrs
- 67 patients DOD
- None of 102 with follicular tumors with PTC nuclei and/or capsular invasion were in DOD group

- (Piana et al AJSP 2010)

FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

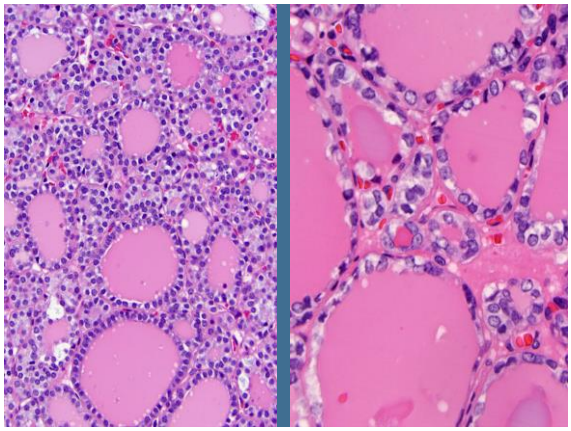
- **ENCAPSULATED *WITHOUT INVASION***
- **These are clonal neoplasms but most do not behave like cancer on longterm followup.**
- **We are overtreating these lesions.**





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

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"?**

NIFT-P

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.

NIFT-P

- **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**

NIFT-P

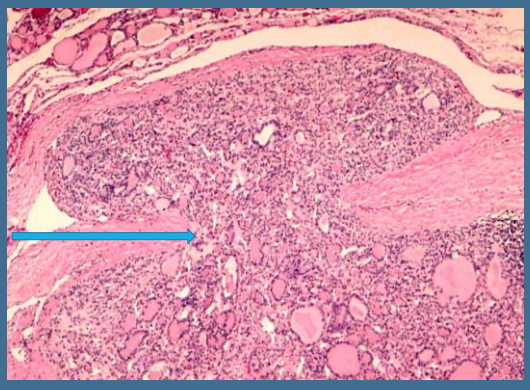
- **Totally encapsulated** or partly encapsulated but **completely circumscribed.**
- Need adequate **sampling** of capsule
- ***NO INVASION***
- **109 cases with median followup 14 years-never heard from again.**

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.**

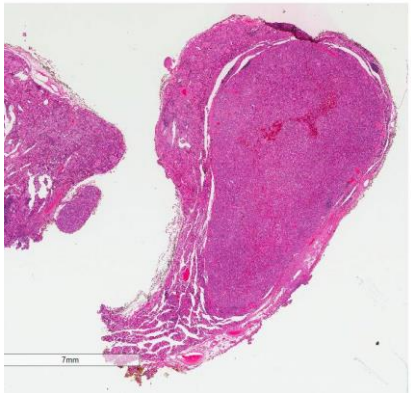


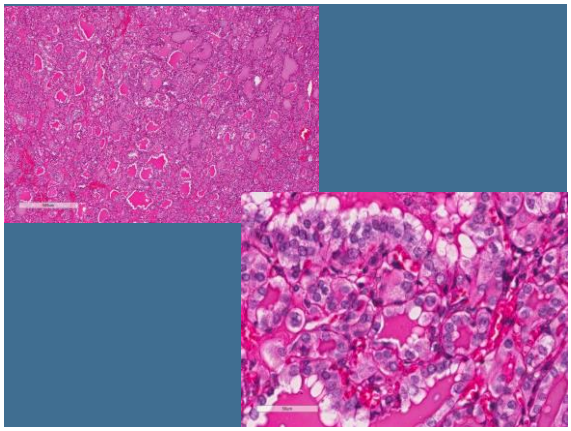
NIFT-P

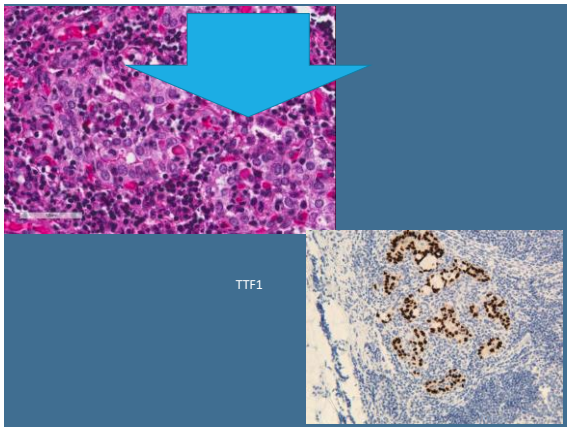
- **Another series (Thompson, L.) Mod Path 2016**
- 77 cases encapsulated with no invasion.
- Size 0.7 to 9.5 cm (average 3.3 cm)
- Some (20 patients) had multiple tumors
- About 75% had surgery alone.
- Followup average 11.8 years—no adverse events.

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!


7mm

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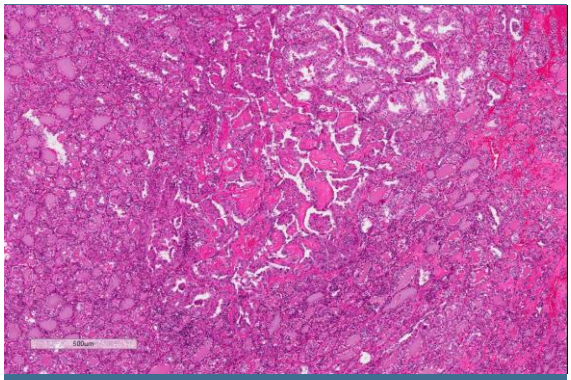


PAPILLARY PATTERN FOCUS

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 mutations usually NRAS; not ***ret*** translocations or Braf V 600E mutations (as PTC).

FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

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

NIFT-P

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

NIFT-P

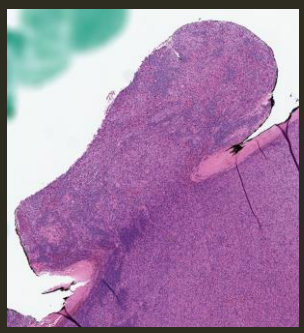
- **ISSUE 2**
- Do we need to go back to old cases and inform patients?
- **MY VIEW IS: *no!!!***
- It is unclear how complete capsule was examined and if focal invasion, may behave less well.
- DIAGNOSIS and TREATMENT RECEIVED AT THE TIME WAS STANDARD OF CARE.

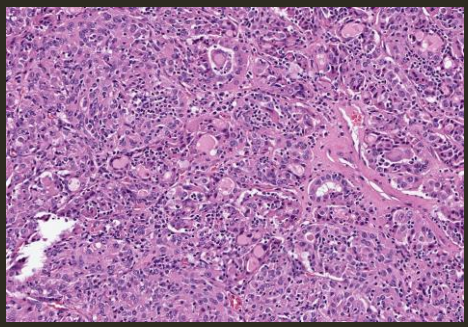
NIFT-P

- **ISSUE 3**
- The problem of cytology.
  - FNA
  - Core biopsies
  - Grading of the nuclear changes.

POORLY-DIFFERENTIATED THYROID CARCINOMA

Pathological Considerations





WHAT ABOUT TUMORS THAT DO NOT EXHIBIT ANAPLASTIC MORPHOLOGY? IS THERE A SPECTRUM OF DE-DIFFERENTIATION?

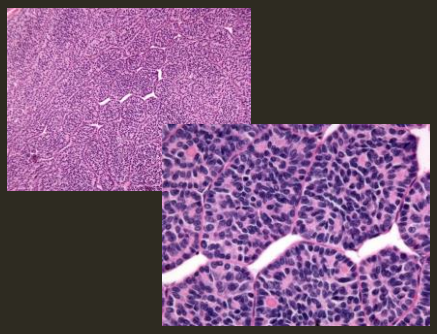
POORLY DIFFERENTIATED THYROID CARCINOMA

HISTORICAL OVERVIEW

- In 2006, a group of endocrine pathologists from around the world met in Turin, Italy and after reviewing a number of cases from North America, Japan and Europe defined "poorly differentiated thyroid carcinoma"
- This became known as the Turin classification.

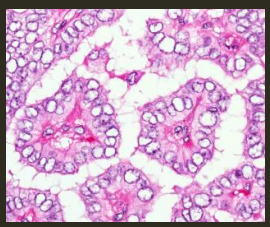
TURIN CRITERIA

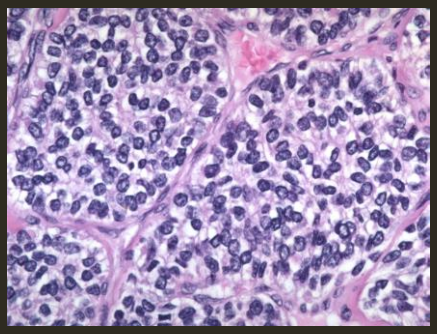
Solid/trabecular/insular growth pattern with invasion



TURIN CRITERIA

Absence of conventional papillary thyroid carcinoma nuclei

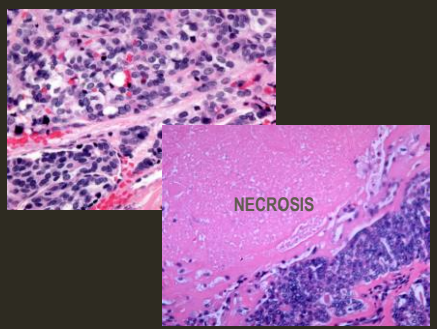




TURIN CRITERIA

Presence of at least one of the following:

- **Convoluted nuclei**
- **Mitotic activity >3/2mm²**
- **Tumor Necrosis**

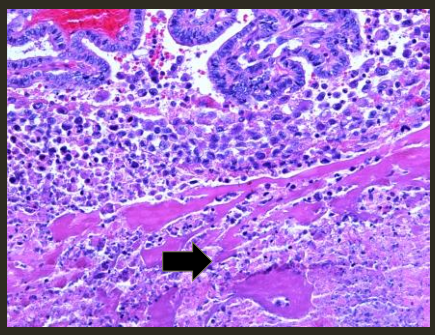


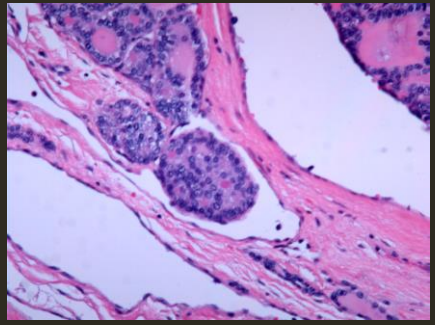
POORLY DIFFERENTIATED THYROID CARCINOMA

CHARACTERISTICS---Can arise de novo or transform from a lower grade precursor

NECROSIS

- Atypical mitoses
- Extrathyroidal
- Vascular invasion





POORLY DIFFERENTIATED CARCINOMA, THYROID

WHAT DOES IT MEAN?

Prognosis intermediate between well-differentiated and anaplastic carcinoma

About 50% survival rate at 5 years

Extrathyroidal most; vascular invasion

Distant metastases common (to lung, bones)

RELATED TOPIC: GRADING OF THYROID CARCINOMA

PAPILLARY:

- Most are grade 1 by pattern and nuclear morphology.

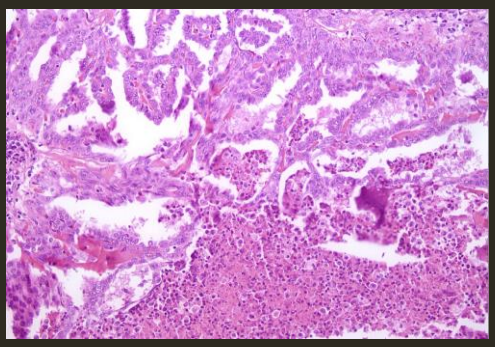
MAINTAIN PAPILLARY GROWTH AND NUCLEI BUT:

- Exhibit necrosis, mitotic activity, nuclear pleomorphism

DIFFERENTIATED HIGH GRADE THYROID CARCINOMA

WHO 2022

- Divides these tumors into two groups:
- Poorly differentiated
- Differentiated high grade carcinoma
  - Maintain architecture (typically a more worrisome subtype of PTC such as hobnail, tall cell etc) but have increased mitotic activity (>5/2 mm^2) and/or necrosis
  - Extrathyroidal extension usually
  - Prognosis worse than well differentiated PTC but not so bad as poorly differentiated thyroid carcinoma.



MOLECULAR ANALYSIS OF POORLY-DIFFERENTIATED AND DIFFERENTIATED HIGH GRADE THYROID CARCINOMA

Some studies have been done and results not uniform.

HOWEVER MOST FALL INTO TWO MAJOR SUBGROUPS: *BRAF* driven or *RAS* driven.

This is probably related to well differentiated tumor from which poorly differentiated tumor arose:

- **Papillary (*BRAF*)**
- **Follicular variant or follicular carcinoma or oncocytic carcinoma (*RAS*)**

LATE MOLECULAR ALTERATIONS

TERT promoter mutation

- High risk of distant metastases

TP53

- Though these can be identified in poorly-differentiated and differentiated high grade carcinoma, they are most often seen in anaplastic carcinoma

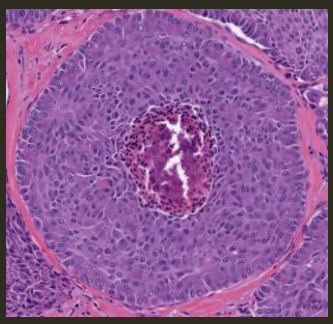
Alterations of PI3K/PTEN/AKT pathway

MEDULLARY THYROID CARCINOMA GRADING

Two major series (one from New York MSK and one from Sydney Australia) studied series of medullary carcinomas and recognized some showed high grade features: i.e. Necrosis and high mitotic rate and/or high Ki67.

Two tiered system: high and low grade based on mitotic (proliferative) index (>5/ 2 mm^2), Ki-67 proliferative index >5%, and/or necrosis.

The high grade lesions are quite rare but do behave in a rapidly aggressive fashion with poorer outcomes in overall survival, recurrence, and distant metastases.



SUMMARY

Xu B, Ghossein RA. Advances in Thyroid Pathology: High Grade Follicular Cell-derived Thyroid Carcinoma and Anaplastic Thyroid Carcinoma. Adv Anat Pathol. 2023 Jan 1;30(1):3-10.

Differentiated high-grade

- Retained architecture of a lower grade tumor with at least one of the following:
  - >5 mitoses/10 high power fields
  - Necrosis
- Higher frequency of BRAF mutation (53-81%)
- Cytokeratin, TTF1, PAX8, Thyroglobulin positive
- 5 year rate of distant metastasis: 48%
- 5 year disease-related mortality: 32%

Poorly-Differentiated

- Solid/trabecular/insular growth pattern
- Lack of usual papillary thyroid carcinoma nuclei
- At least one of the following:
  - Necrosis
  - >3 mitoses/10 high power fields
  - Convoluted nuclei
- Higher frequency of RAS mutation (44-48%)
- Cytokeratin, TTF1, PAX8, Thyroglobulin positive
- 5 year rate of distant metastasis: 60%
- 5 year disease-related mortality: 30%

Anaplastic

- Highly aggressive and undifferentiated histology
- RAS mutation: 27%
- BRAF mutation: 38%
- Usually cytokeratin and PAX8 positive
- Variable TTF1
- Thyroglobulin negative
- Aberrant p53 expression
- 5 year rate of distant metastasis: 75-80%%
- 2 year disease-related mortality: 80%

QUESTIONS?