Oncocytic and high grade non-anaplastic thyroid carcinoma

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JUAN ROSAI MD

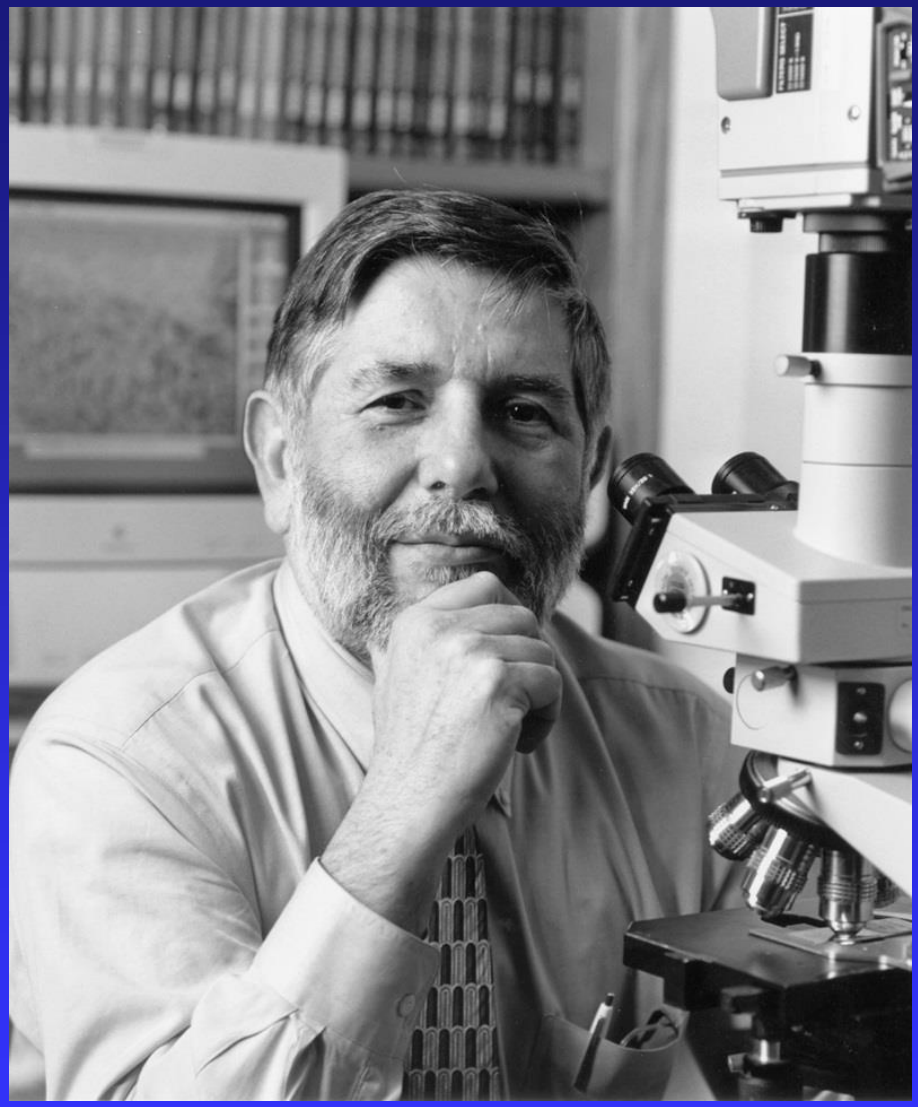
-M.D. at 21 yrs old

-Description of 75 entities: Sinus Histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease), desmoplastic small round cell tumor, poorly differentiated thyroid carcinoma, papillary thyroid carcinoma follicular variant….

-Director of Pathology, Yale

-Chairman of Pathology, Memorial Sloan-Kettering Cancer Center

-Chairman of Pathology, National cancer institute (tumori), Milan



1940-2020

The Lamentation of Pierre Masson

"*No classification is more difficult to establish than that of thyroid [carcinomas]. Their pleomorphism is almost the rule; very few are adapted to a precise classification*

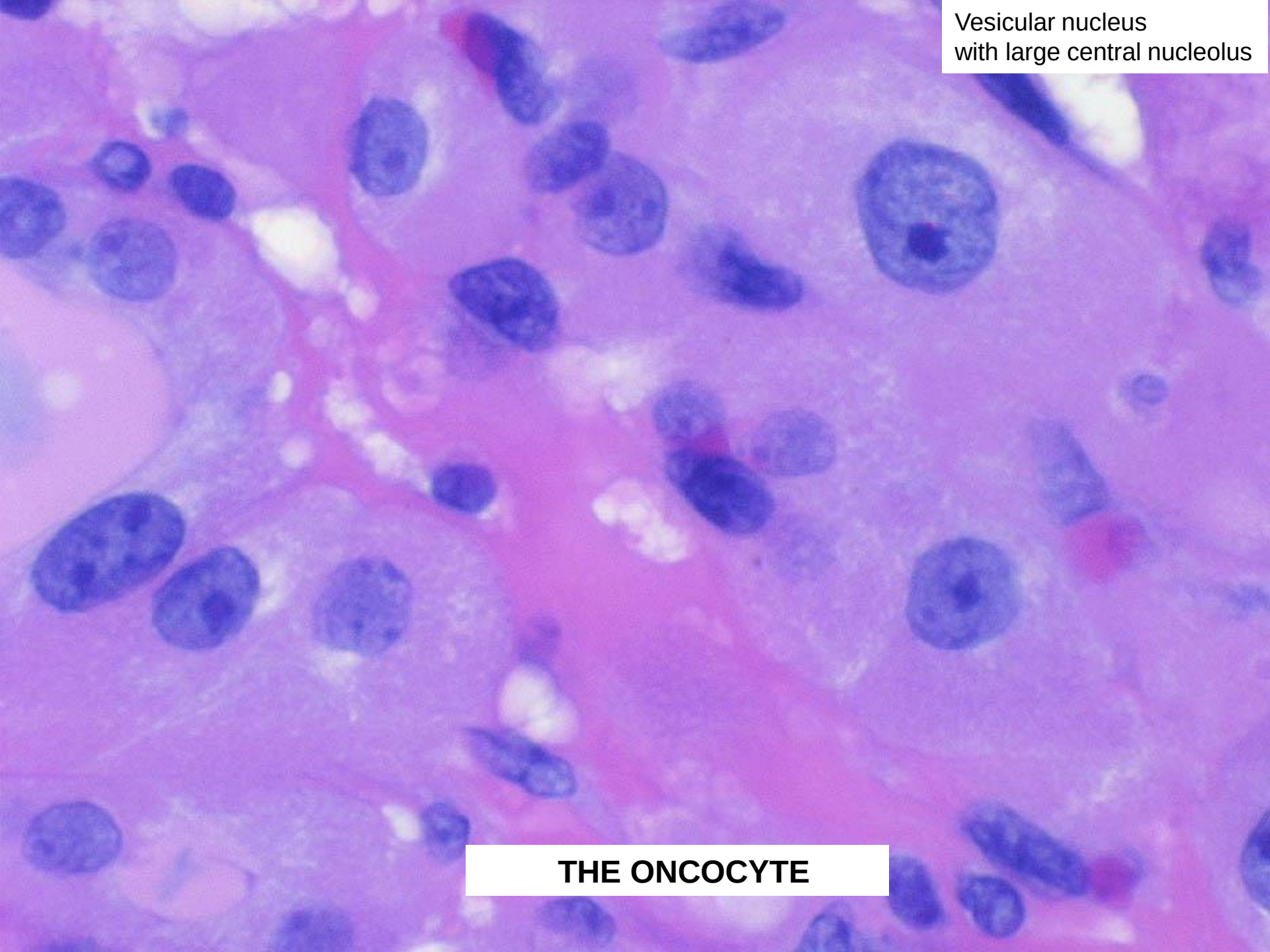
….. Of all cancers, they teach, perhaps, the greatest lessons of humility to histopathologists"

1880-1959

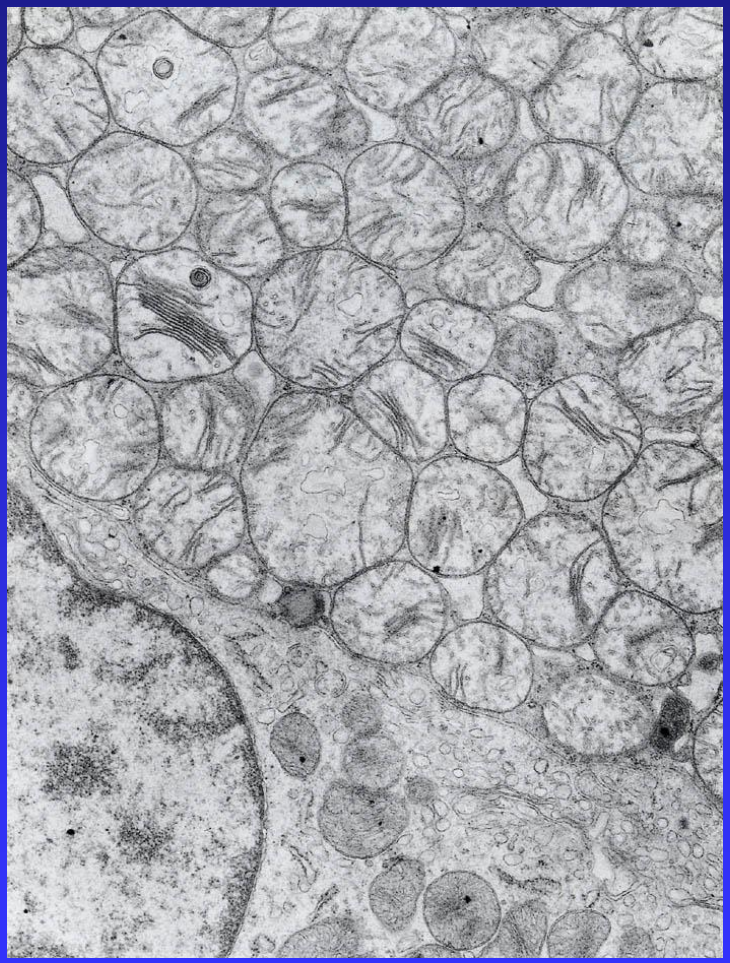
ONCOCYTIC LESIONS OF THE THYROID GLAND

Oncocytic Change

- Cellular enlargement characterized by an abundant eosinophilic **granular** cytoplasm (as a result of the accumulation of **mitochondria** in the vast majority of cases).


Vesicular nucleus
with large central nucleolus
THE ONCOCYTE

ELECTRON MICROSCOPY OF HURTHLE CELL



Mitochondria

Terminology of Oncocytic Cells of the Thyroid

- "HURTHLE" (Most commonly used term and a misnomer). The cells Karl Hurthle described in dogs were probably C cells. 1894.
- "ASKENAZY" cells (Germany): Initial description by Askenazy in 1898.
- Oxyphilic cells.
- Oncocyte.

Classification of Oncocytic Lesions of the Thyroid Gland

TUMORS

- Oncocytic (ex-Hurthle cell) adenoma .
- Oncocytic (ex-Hurthle cell) carcinoma

Classification of Oncocytic Lesions of the Thyroid Gland

TUMORS

- Oncocytic (NIFTP)
- Papillary carcinoma, oncocytic variant.
- Poorly differentiated carcinoma with predominant oncocytic features.
- Medullary carcinoma, oncocytic variant.

Classification of Oncocytic Lesions of the Thyroid Gland

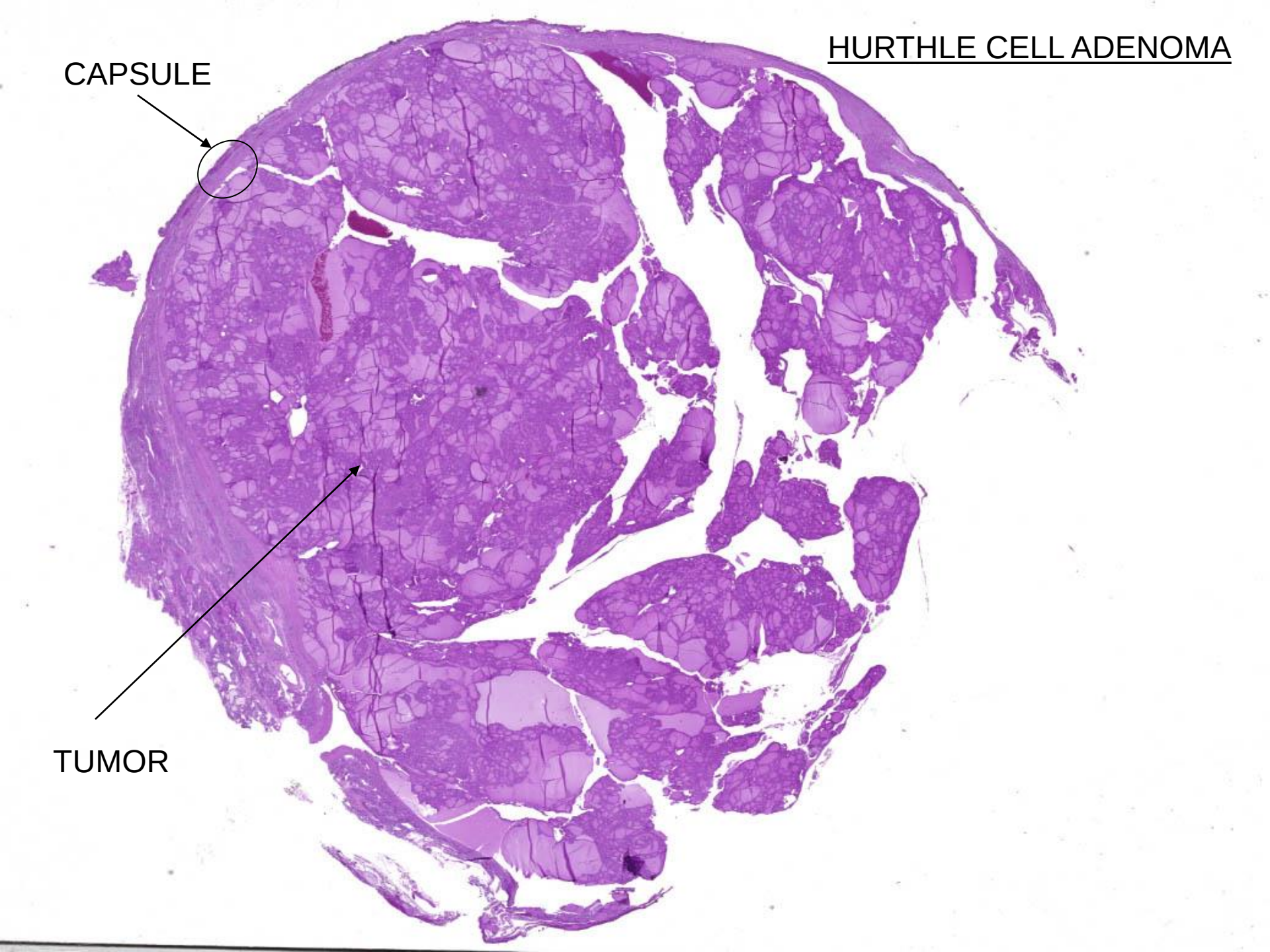
NON-NEOPLASTIC

- "Hyperplastic" nodule composed of Hurthle cells

Oncocytic (ex-Hurthle cell) adenoma

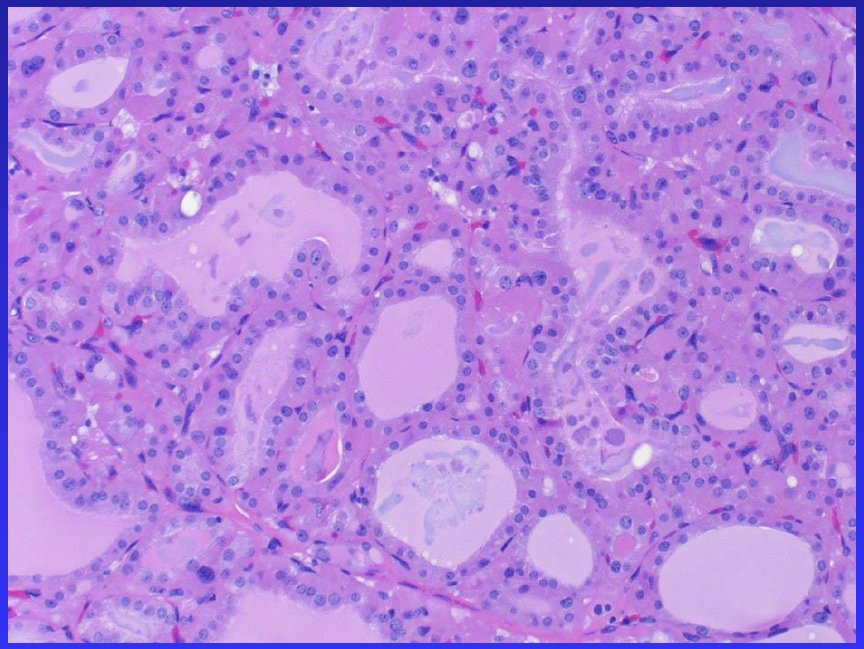
- Definition: A benign encapsulated thyroid tumor, composed predominantly (>75%) of follicular cells with oncocytic features.
- These cells DO NOT display the nuclear features of papillary thyroid carcinomas.
- THERE IS NO CAPSULAR OR VASCULAR INVASION.

HURTHLE CELL ADENOMA

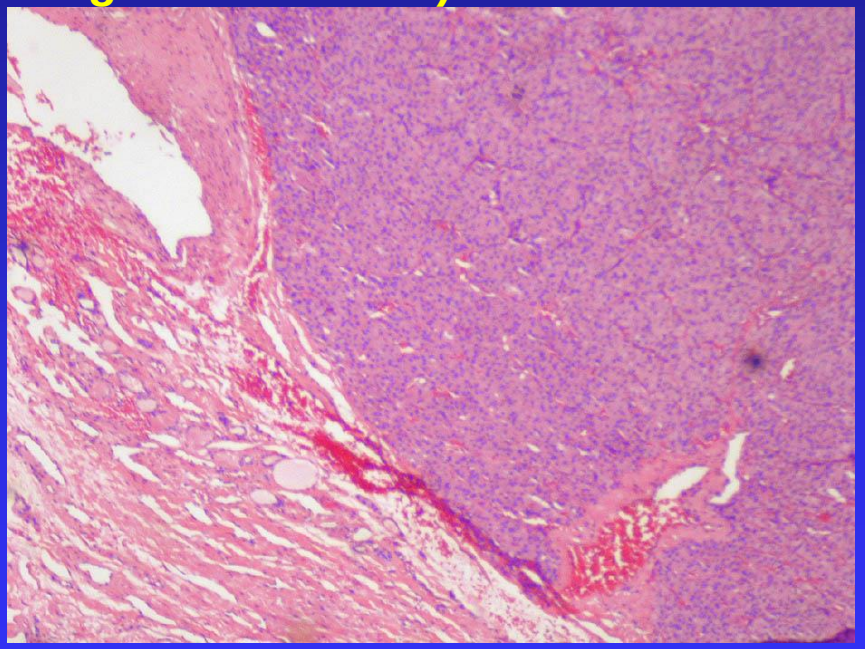


Follicular adenoma growth patterns

Follicular pattern



Solid/trabecular pattern (previously known as Unknown Malignant Behavior)



ONCOCYTIC (ex-HURTHLE CELL) ADENOMA

- THE LACK OF CAPSULAR

  INVASION AND VASCULAR INVASION

  DEFINE THE BENIGN PHENOTYPE.

  but this definition did not come easily.

First Controversy: Criteria To Define Malignancy

- 1907: Langhans: First description of Hurthle cell tumor: no microscopic evidence of malignancy in 5 cases, 2 of which died.
- 1926: Wegelin: Majority of Hurthle cell tumors are benign
- 1941: Harry: All Hurthle cell tumors are adenocarcinomas of moderate malignancy.
- 1941: Warren: Hurthle cell tumors are "benign tumors with malignant potential".

First Controversy: Criteria To Define Malignancy

- 1951: American Cancer Society: "All Hurthle cell neoplasms should be treated aggressively during the initial operation because of their malignant potential".

- 1951: Frazell and Duffy: **Vascular invasion crucial.**

- 1954: Horn:" The mere observation of tumor cells within vascular lumina may well be artifact and the source of diagnostic error…"

- 1974: Thompson NW, Dunn EL, Batsakis JG et al.: "any (Hurthle cell) lesion over 2 cm, regardless of what the pathologist says should be treated definitively at the time of original operation".
- 1988: McLeod et al: The therapy of Hurthle cell tumors is controversial because of the "unreliable correlation between their histopathologic features and clinical behavior."

- *After 80 long years……..*

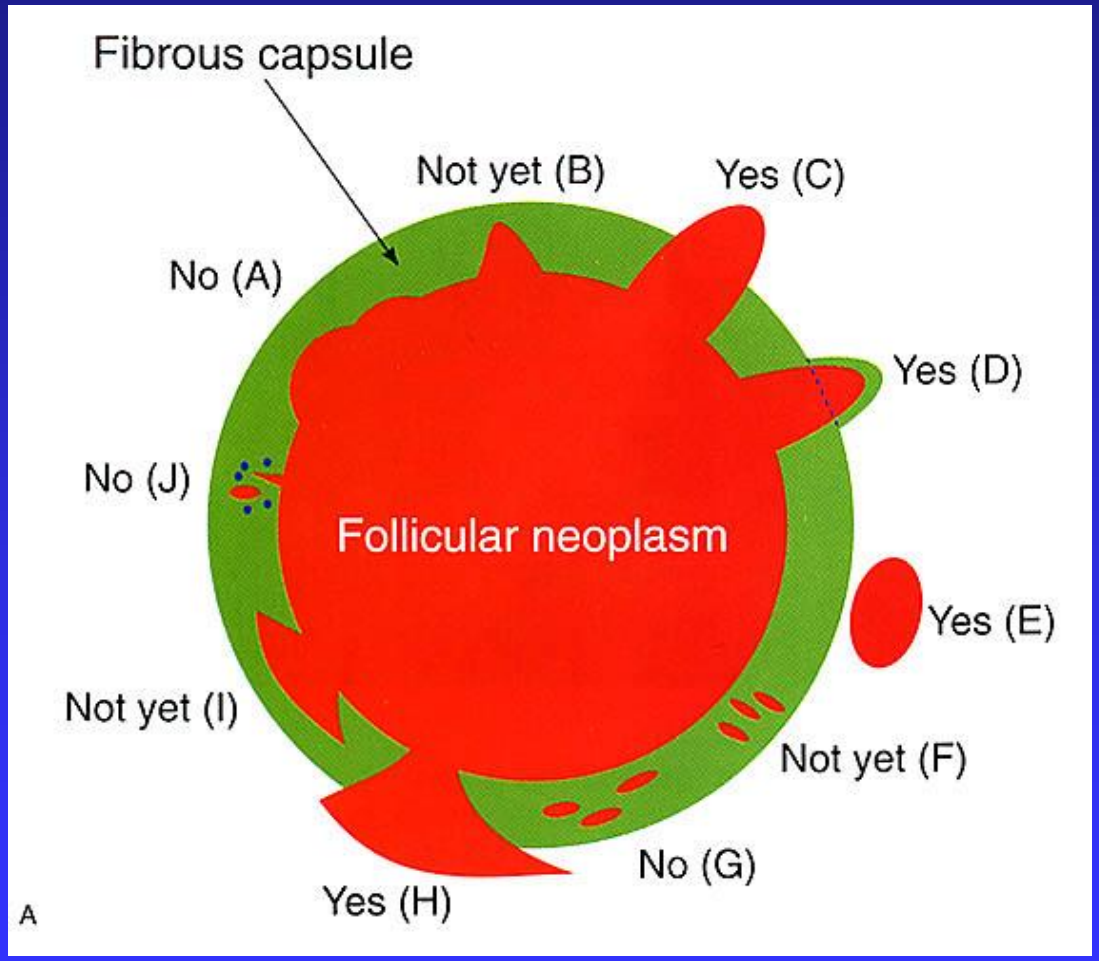
Traditional Microscopic Criteria of Capsular and Vascular Invasion Define Malignancy

- Bronner MP, Livolsi VA. Oxyphilic tumors of the thyroid: microscopic features predict biologic behavior. *Surg Pathol 1:137-150, 1988.*

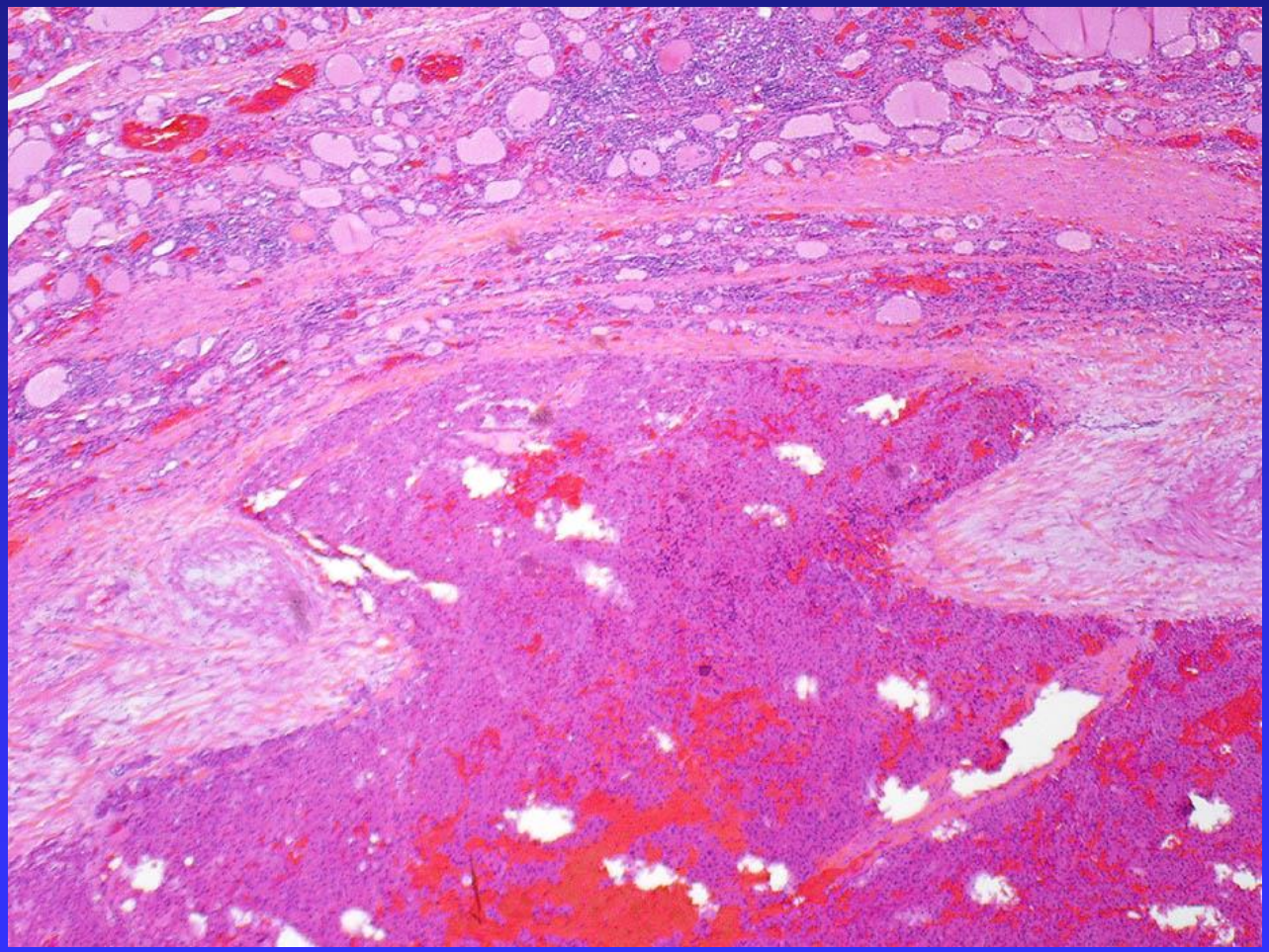
- Carcangiu ML, et al. Follicular Hurthle cell tumors of the thyroid gland. *Cancer 68:1994-1953,1991.*

Stojadinovic A, Ghossein RA, Hoos A, Urist MJ, Spiro RH, Shah JP, Brennan MF, Shaha A, Singh B. Hurthle Cell Carcinoma: a critical histopathologic appraisal. *J Clin Oncol 15:2616-25, 2001.*

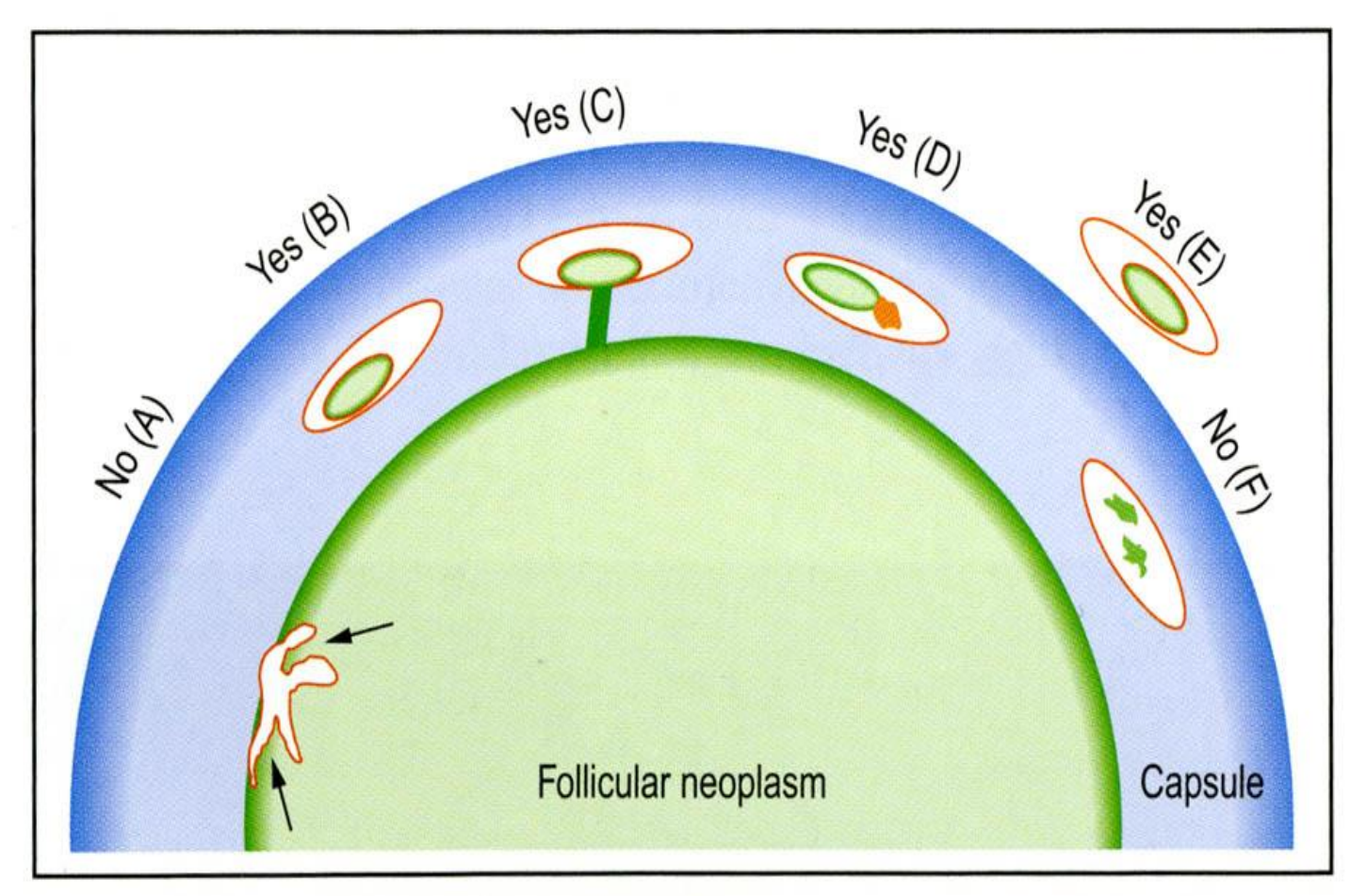
Assessment of capsular invasion in thyroid tumors



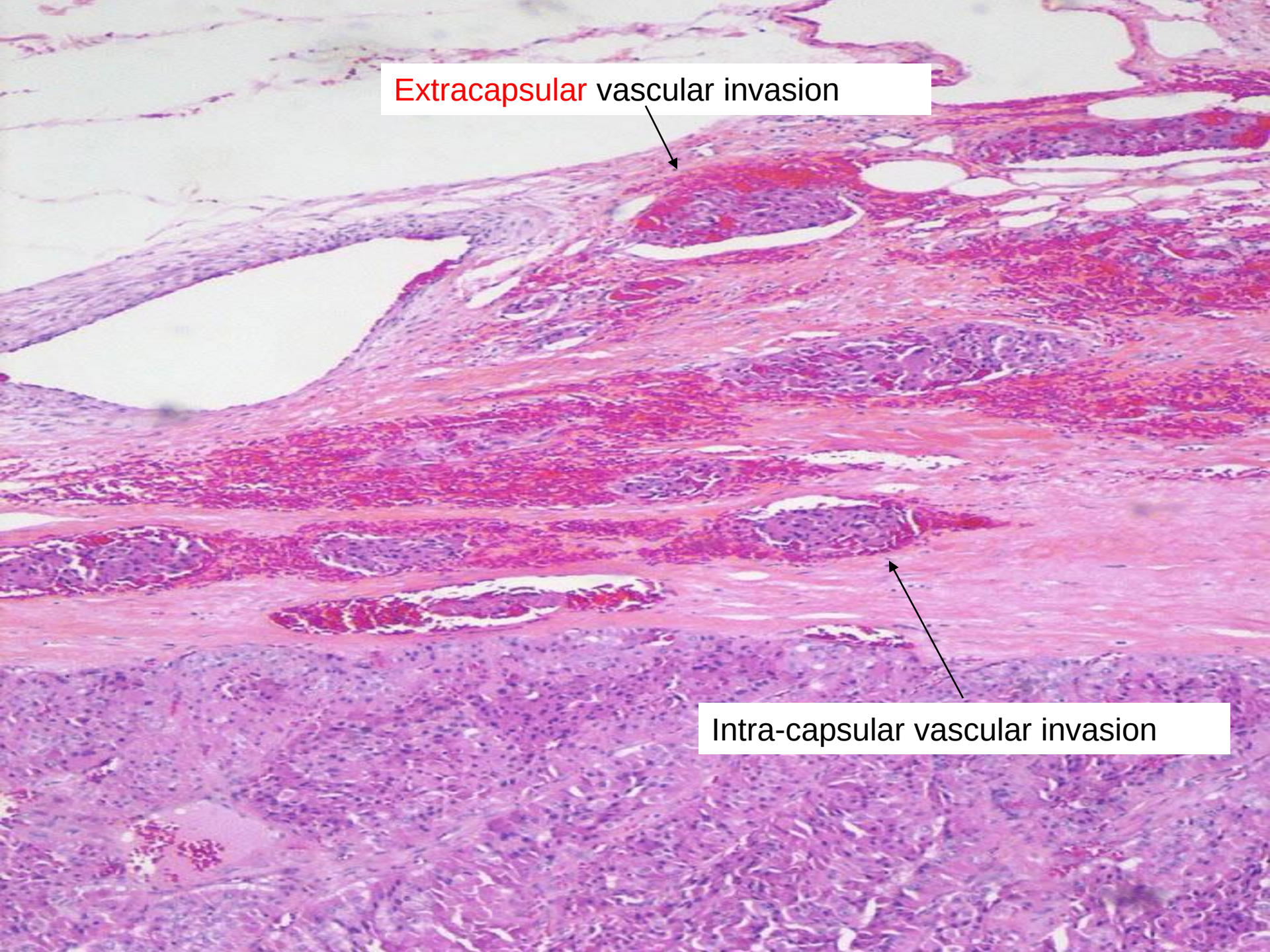
CAPSULAR INVASION



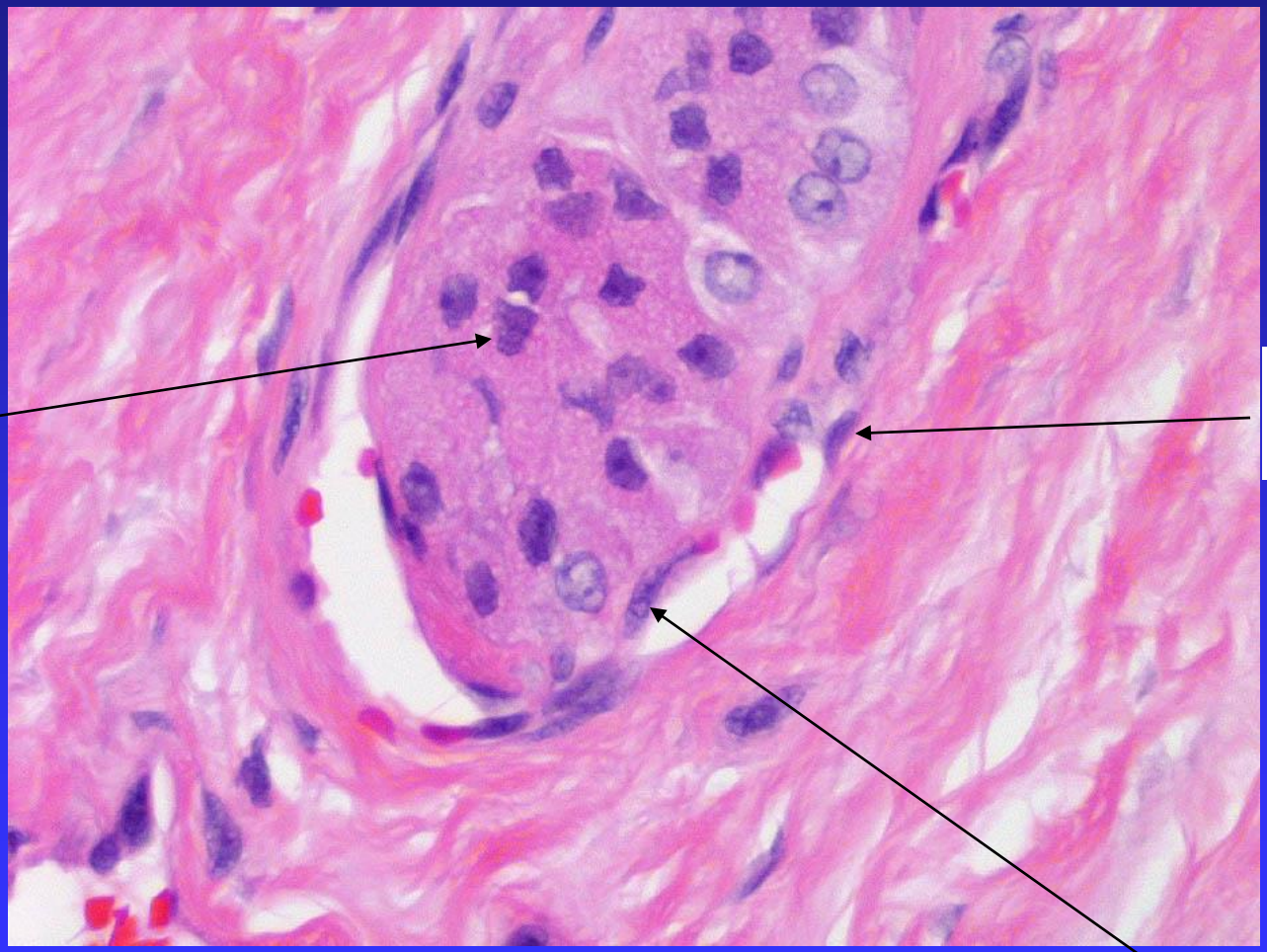
Vascular invasion



Chan JK


Extracapsular vascular invasion
Intra-capsular vascular invasion

VASCULAR INVASION



Hurthle cell in tumor thrombus

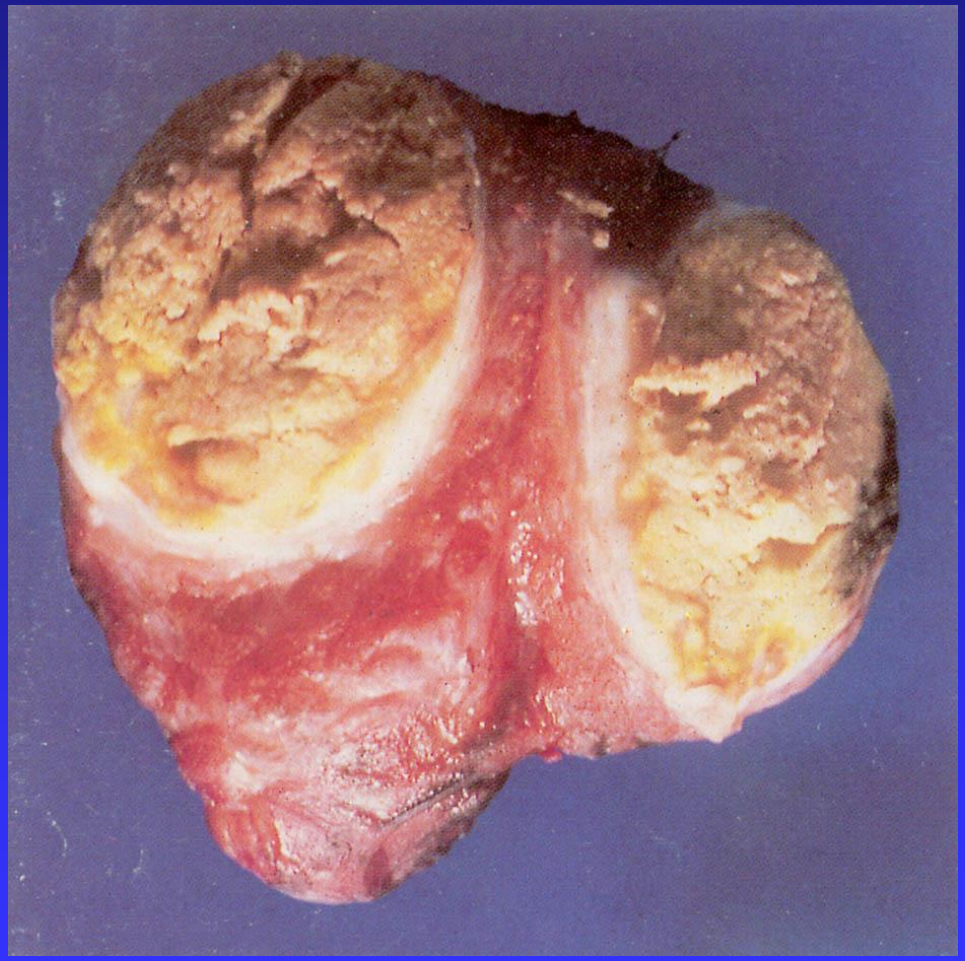
Endothelial cell of vessel

Endothelial cell on tumor thrombus

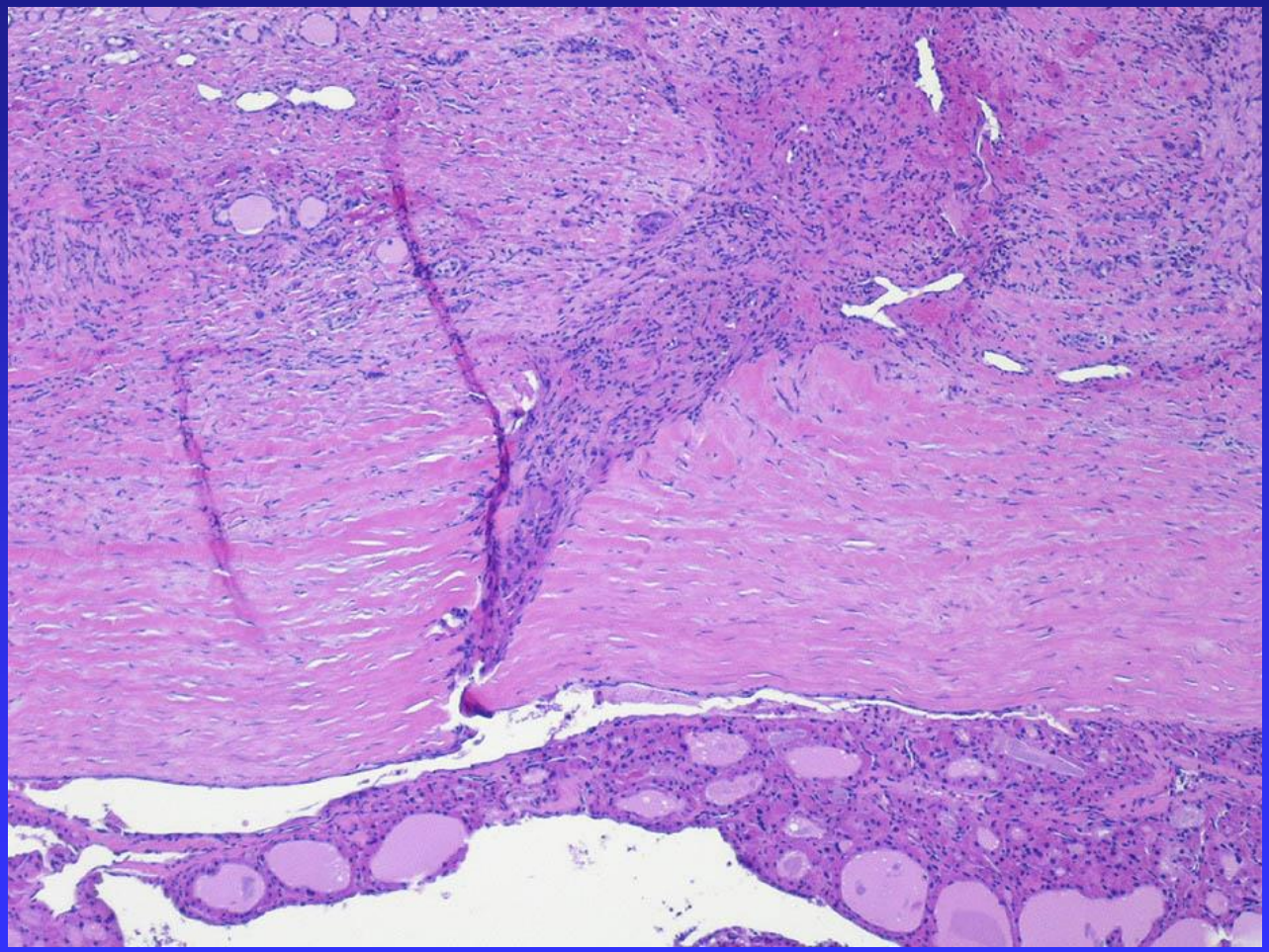
Pitfalls in the Diagnosis of Hurthle Cell Adenoma

1. FNA induced necrosis
2. Misplaced follicles through the capsule along the FNA track. (Mistaken for capsular invasion).
3. Incomplete capsular invasion (old criteria)
4. Artifactual dislodgment of tumor cells in vessels due to sectioning.
5. Psammoma body-like structures within follicular lumen.

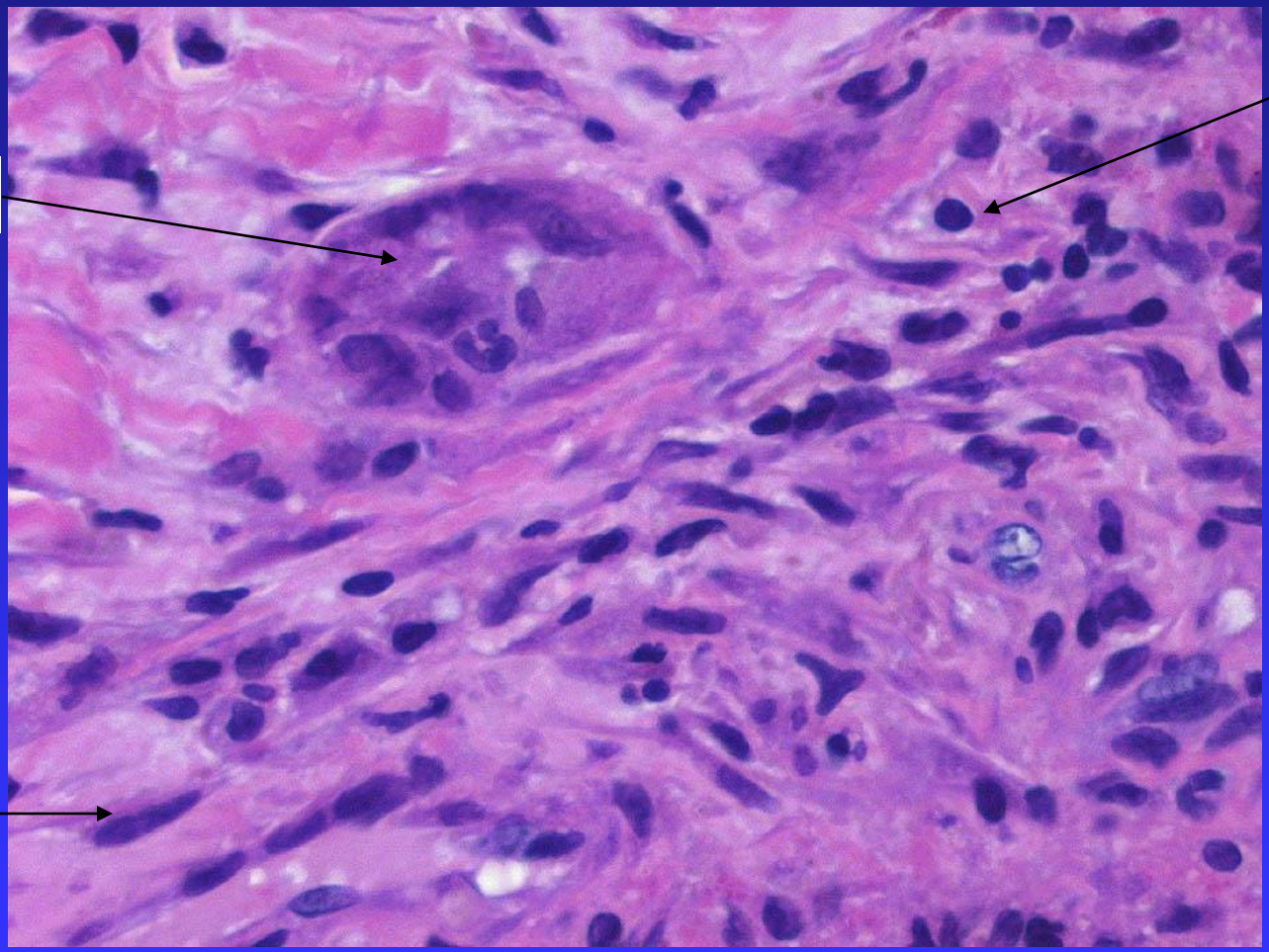
HURTHLE CELL ADENOMA TOTALLY INFARCTED BY FNA



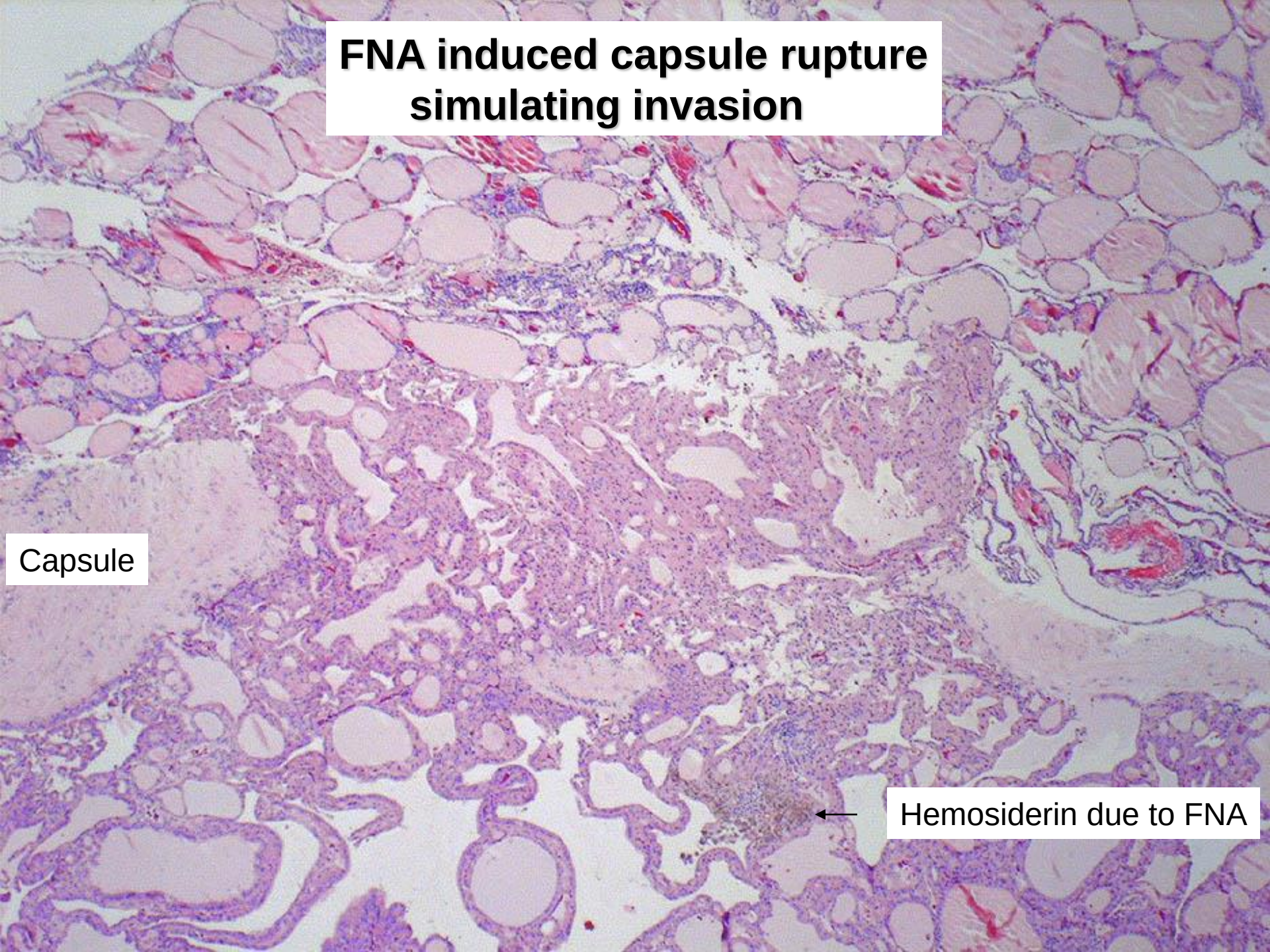
FNA ARTEFACT SIMULATING INVASION



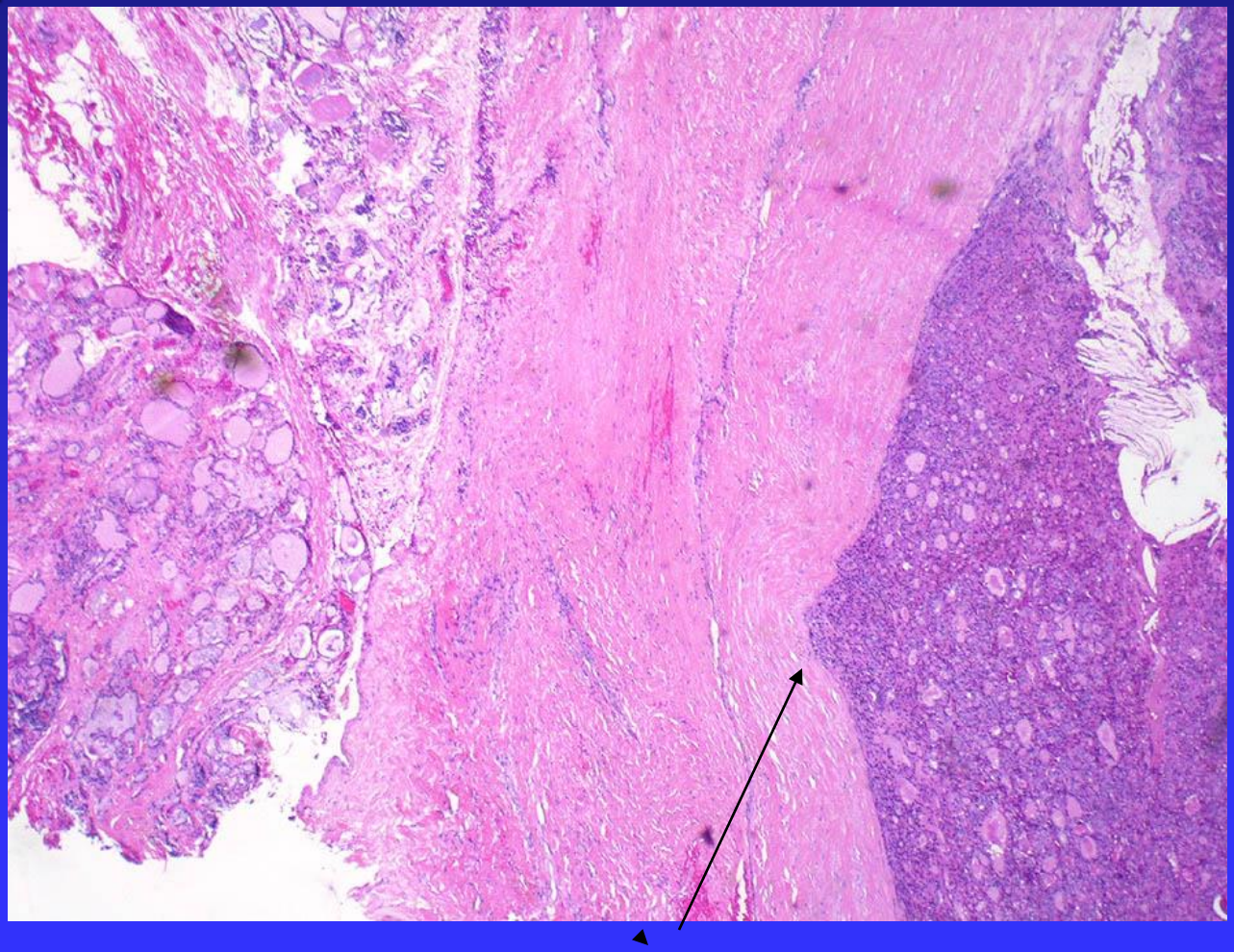
FNA ARTEFACT SIMULATING INVASION



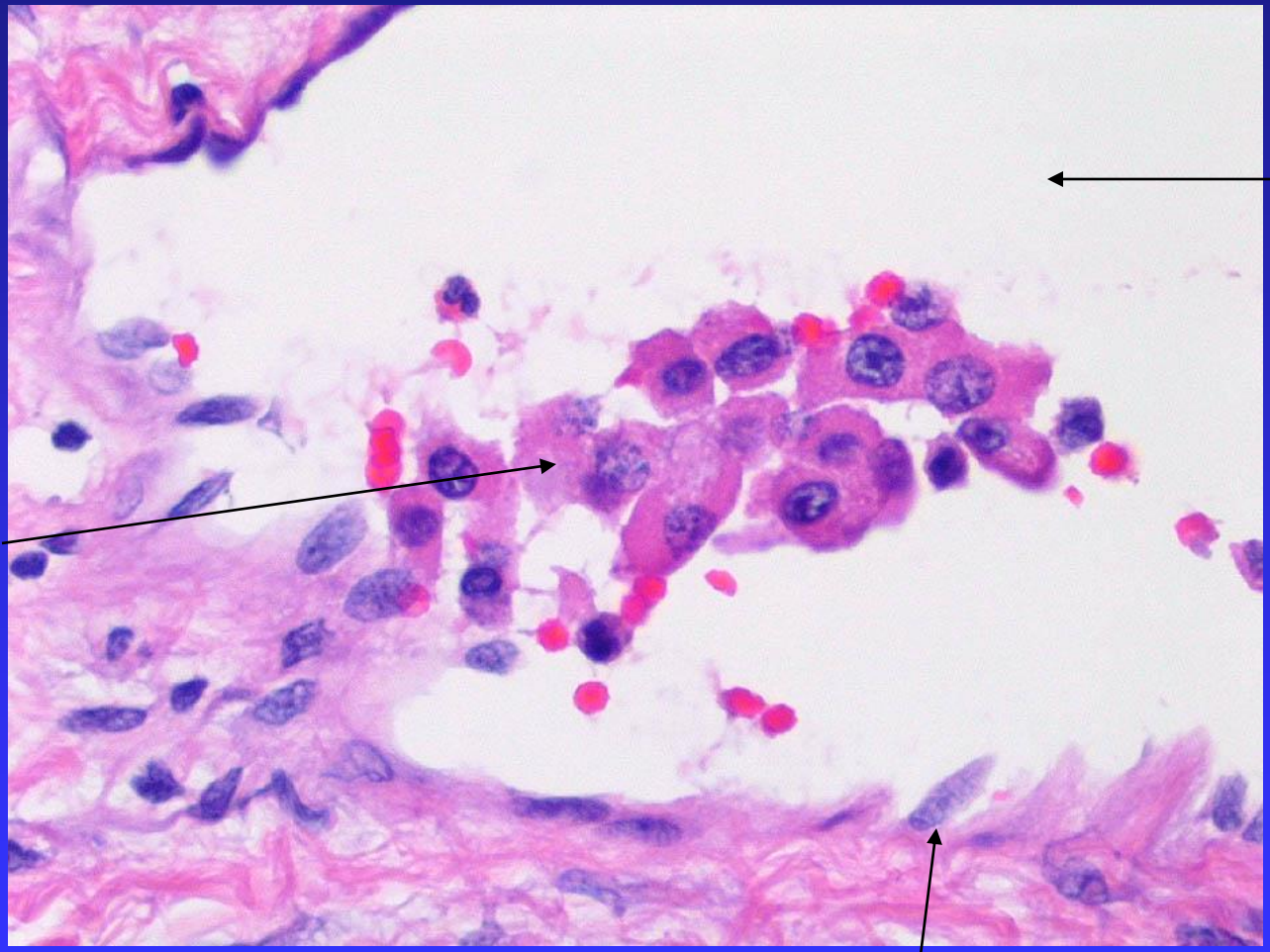
FNA induced capsule rupture simulating invasion



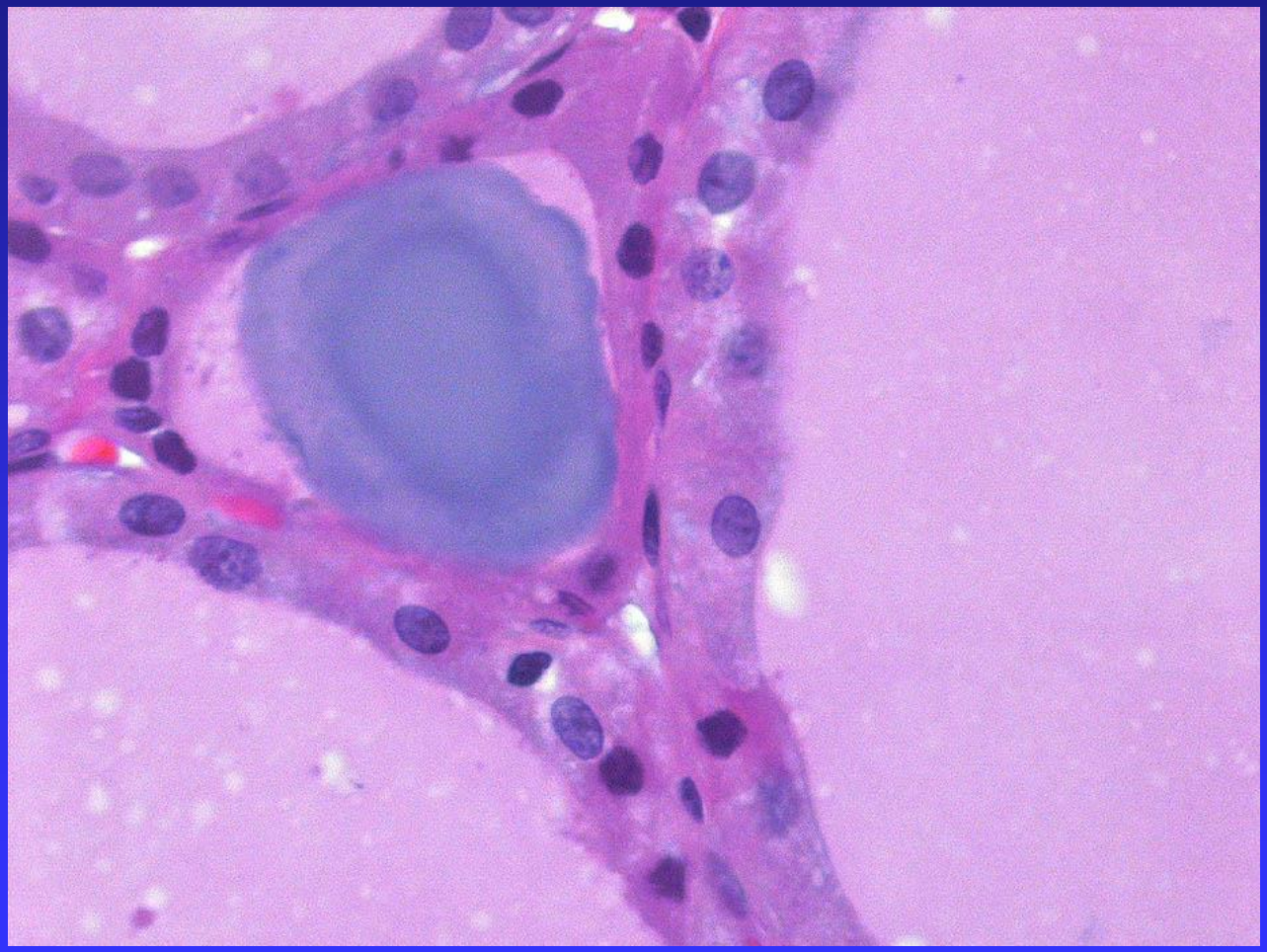
CAPSULAR IRREGULARITY MIMICKING CAPSULAR INVASION (OLD CRITERIA FOR INVASION)



ARTIFACTUAL DISLODGEMENT OF TUMOR CELLS IN VESSELS SIMULATING VASCULAR INVASION



PSEUDOPSAMMOMA BODY IN HURTHLE CELL ADENOMA



SECOND CONTROVERSY:
STRATIFICATION OF PATIENTS WITH HURTHLE CELL CARCINOMA.

FOLLICULAR and HURTHLE CELL CARCINOMA.

- Diagnosis of follicular carcinoma depends on capsular and vascular invasion.
- Criteria for capsular and lymphovascular invasion controversial.
- **Definition of minimally invasive carcinoma controversial.**

FOLLICULAR and HURTHLE CELL CARCINOMA.

- Diagnosis of follicular carcinoma depends on capsular and vascular invasion.
- Criteria for capsular and lymphovascular invasion controversial.
- **Definition of minimally invasive carcinoma controversial.**

Why is it clinically important?

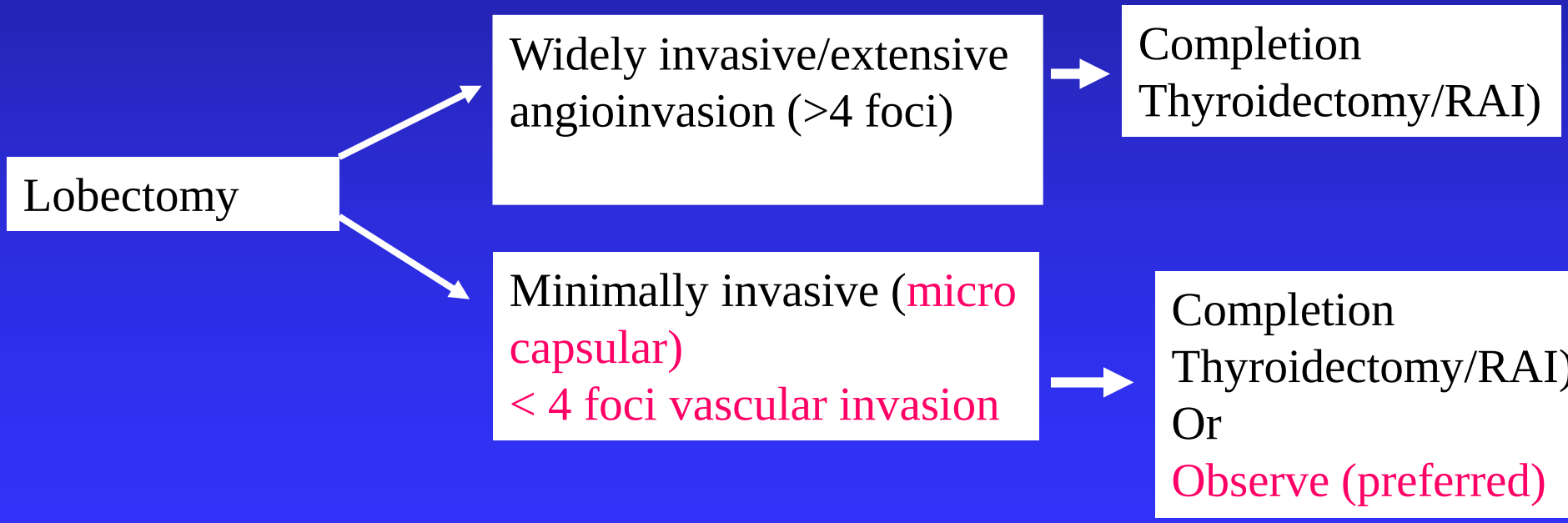
- Not all surgeons treat minimally invasive carcinoma with total thyroidectomy and RAI.

- Intrathyroidal, well differentiated follicular thyroid cancer with capsular invasion and no or minimal (<4 foci) vascular invasion do not routinely require adjuvant RAI.

  American Thyroid Association Guidelines Task Force 2015 update

Why is it clinically important?

National Comprehensive Cancer Network guidelines 2021 follicular/Hurthle cell ca

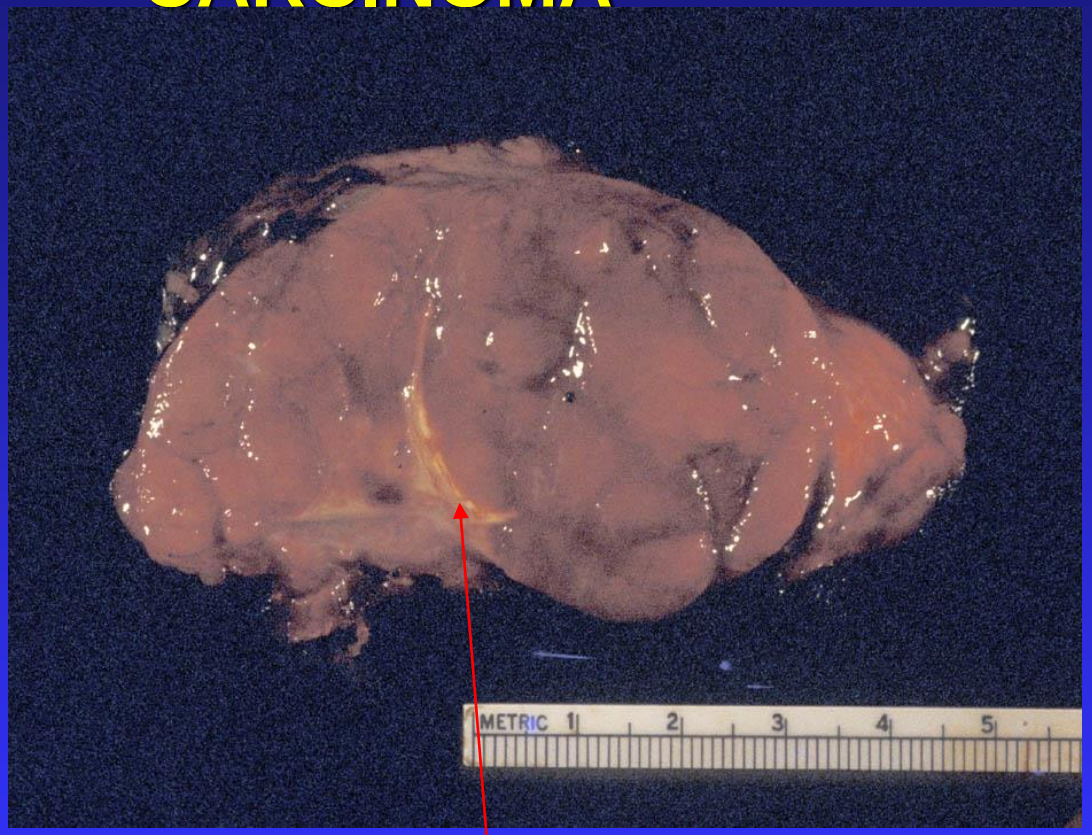


WIDELY INVASIVE FOLLICULAR/HURTHLE CELL CARCINOMA

-Grossly apparent invasion of thyroid and/or soft tissue.

-Poor prognosis: 25-50% mortality at 10 years.

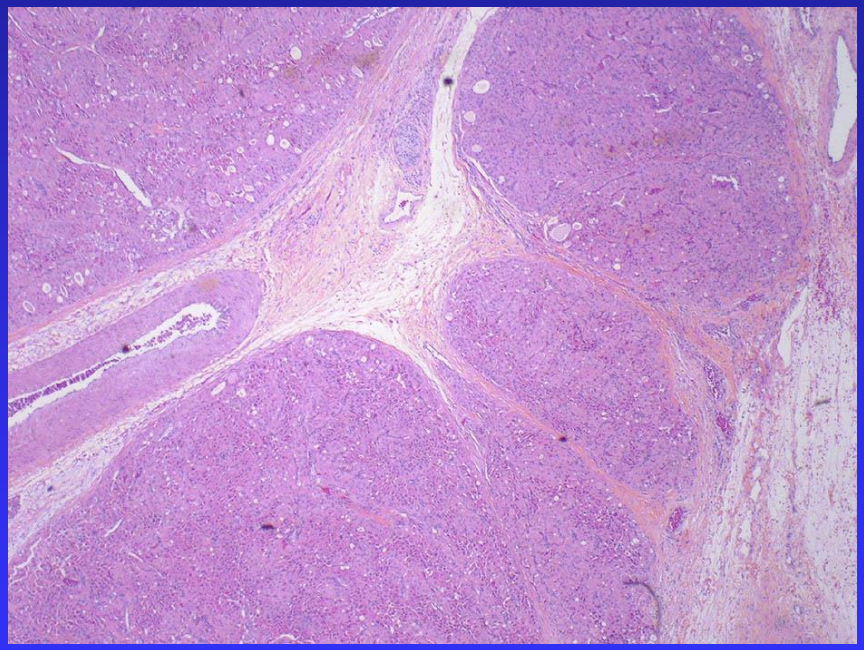
-Unanimous agreement.



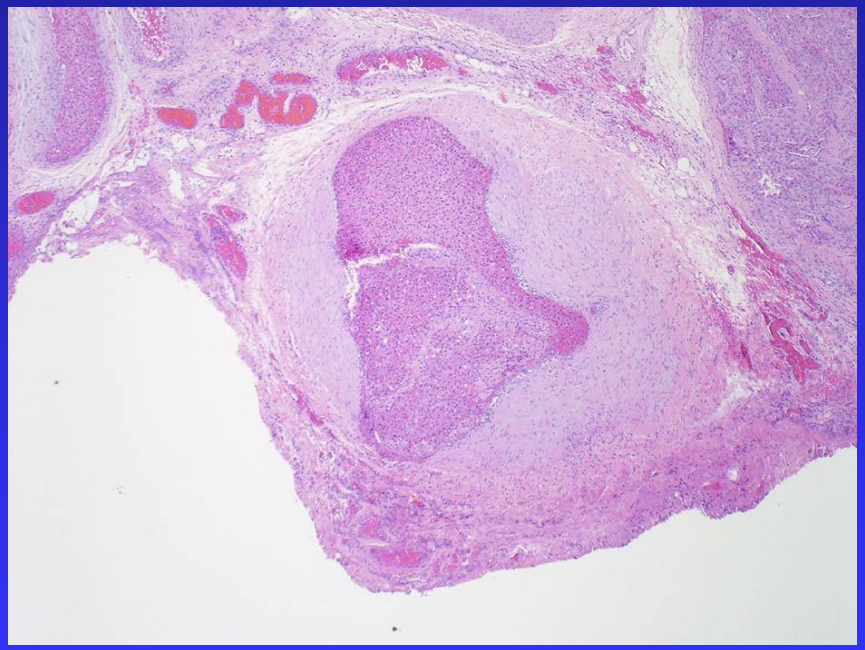
Remnant of tumor capsule

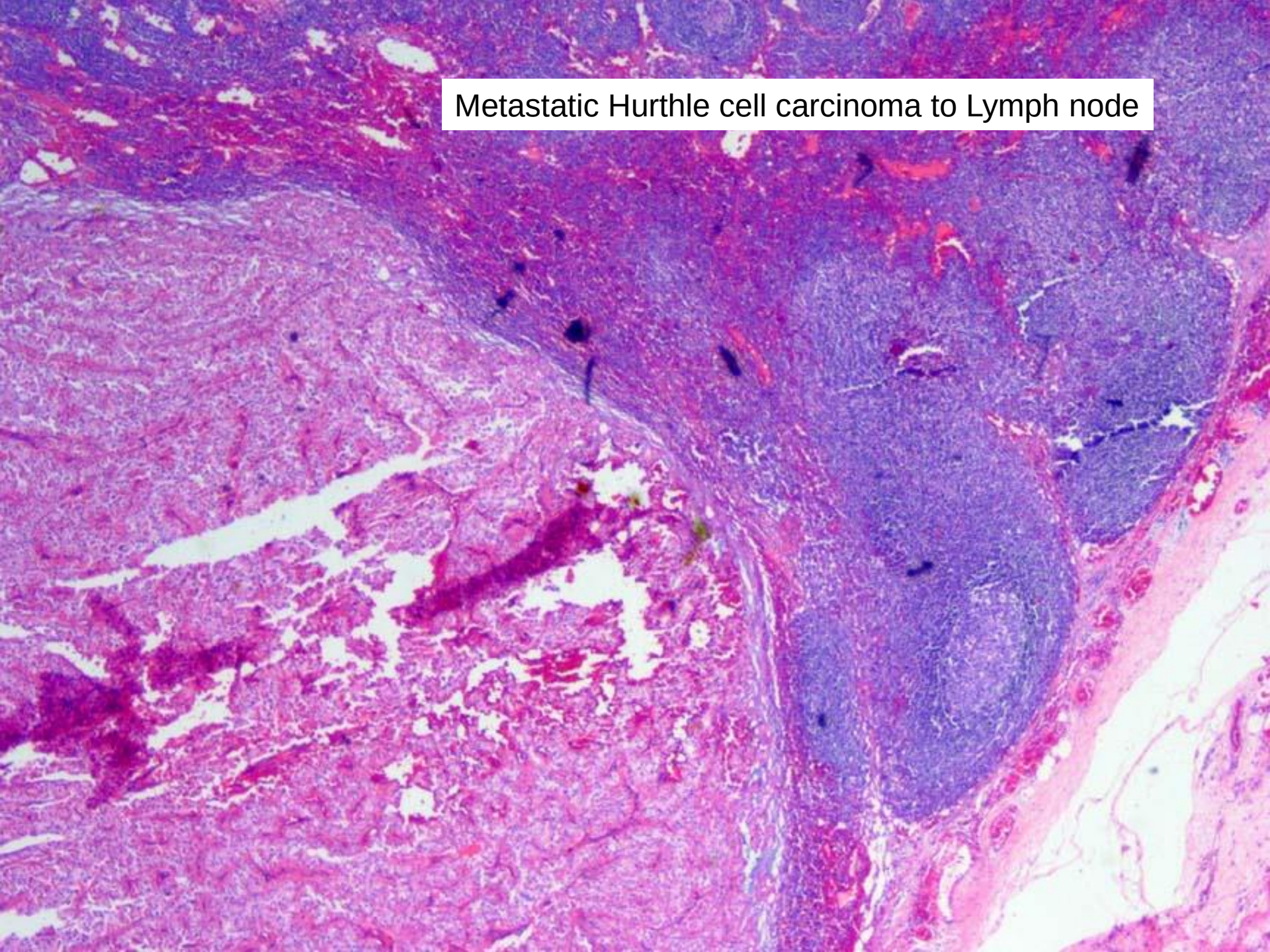
Widely invasive Hurthle cell carcinoma

Multinodular invasive growth pattern



Extra-thyroid vascular invasion




Metastatic Hurthle cell carcinoma to Lymph node

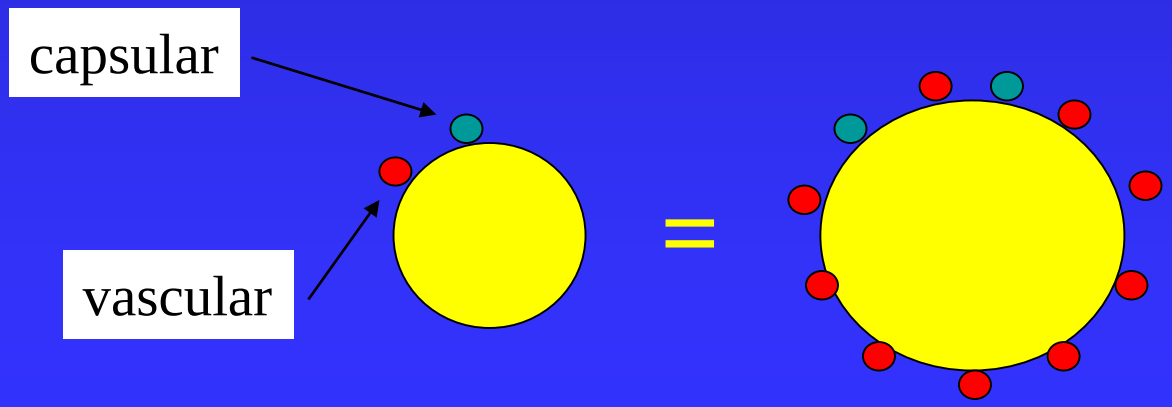
MINIMALLY INVASIVE FOLLICULAR/HURTHLE CELL CARCINOMA

VARIOUS DEFINTIONS

All Well defined grossly encapsulated follicular/Hurthle cell carcinomas= Minimally Invasive

- Grossly well defined and encapsulated tumor with capsular and/or vascular invasion that is usually microscopic. (Overall low risk)

-AFIP fascicle on thyroid tumors, 1992, 2014.



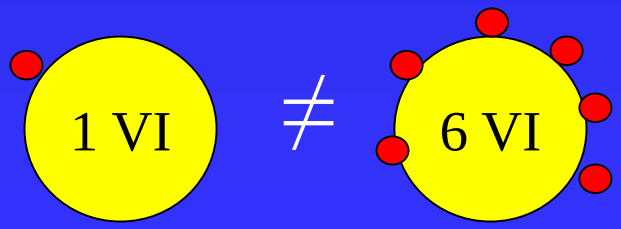
Alternative terminology for encapsulated follicular/Hurthle carcinoma (Dr Livolsi)

- Encapsulated follicular carcinoma with capsular invasion only: Minimally invasive (Extremely low risk)
- Encapsulated follicular carcinoma with vascular invasion: Angioinvasive follicular carcinoma. (High risk)

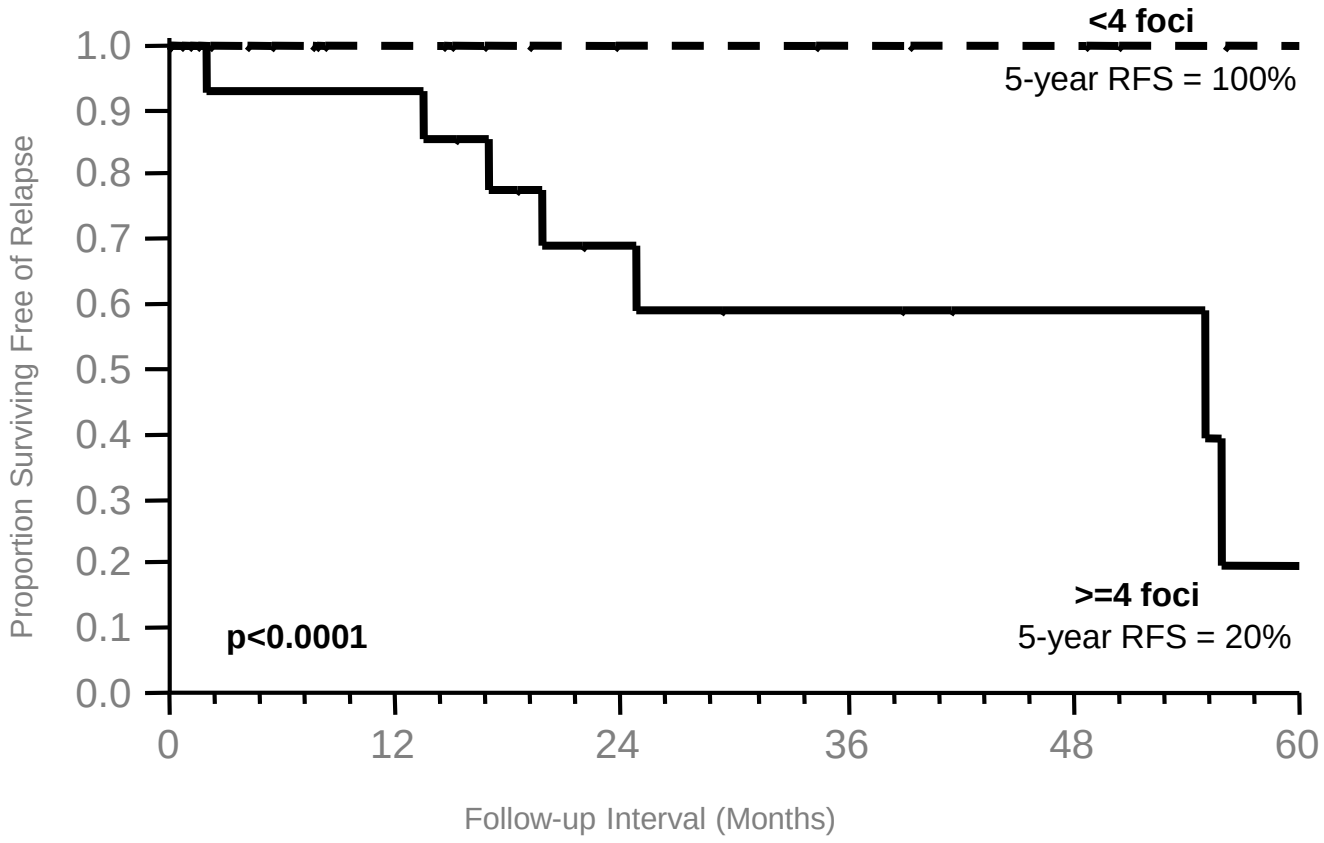
Vascular invasion ≠ Capsular invasion

Another terminology based on the number of invasive foci (Memorial Sloan-Kettering)

- capsular invasion: Minimally invasive (extremely low risk)
- ≥ 4 foci of vascular invasion: Encapsulated follicular carcinoma with extensive vascular invasion (High risk)
- In between (<4 foci of vascular): Encapsulated follicular carcinoma with focal vascular invasion (lower risk)



Relapse free survival (RFS) according to number of foci of vascular invasion in encapsulated follicular carcinoma, oncocytic variant



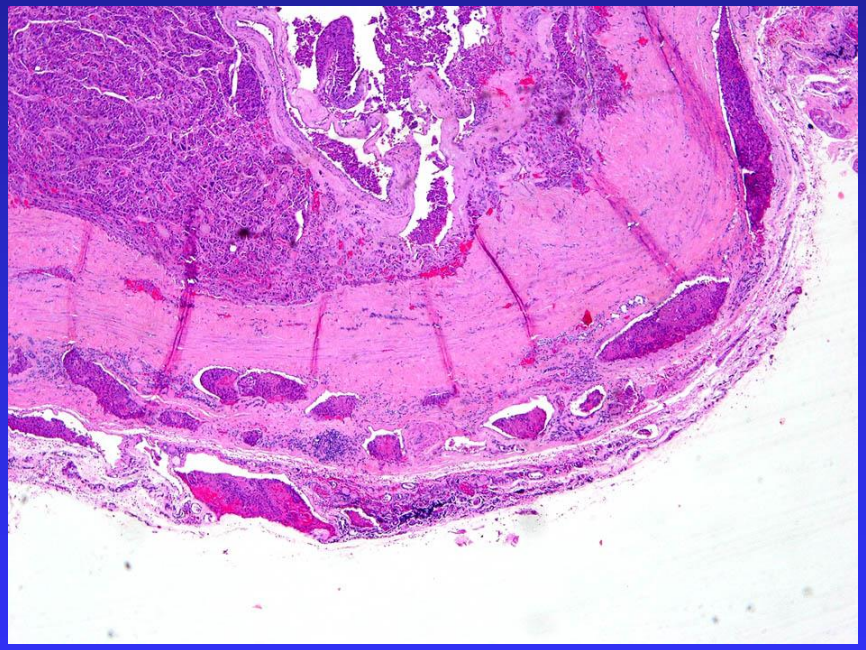
Median FU: 35.9 months

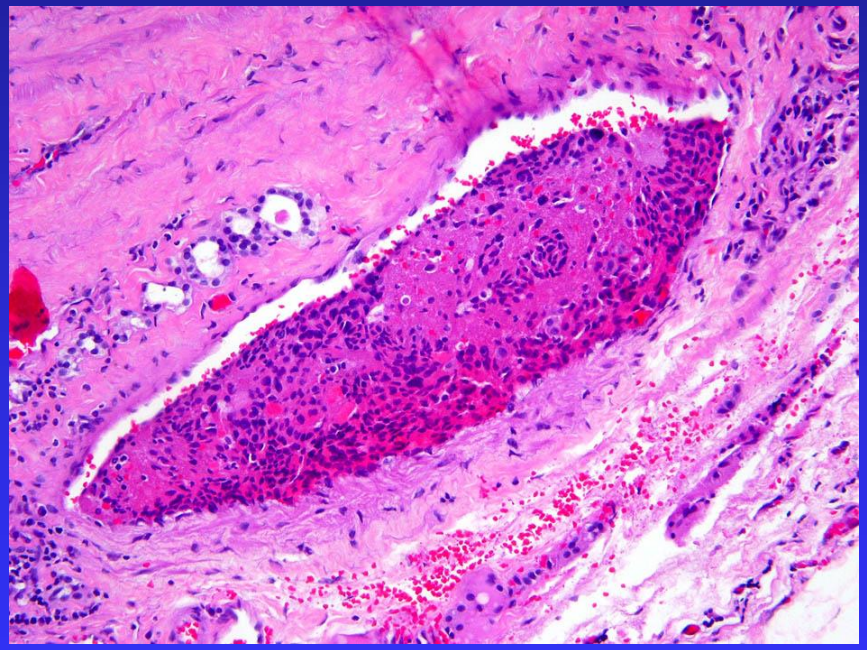
Ghossein et al. *Cancer 106:1669. 2006*

- In 1986, Dr Lang stated that >=5 foci of vascular invasion defines widely invasive follicular carcinoma *but his article was dismissed (arbitrary).*

Lang W et al. Risk factors in follicular thyroid carcinomas. A retrospective follow-up study covering a 14-year period with emphasis on morphological findings. *Am J Surg Pathol.* 1986; **10**: 246-255.

50 yr old with grossly encapsulated Hurthle cell carcinoma with extensive microscopic angioinvasion





Bone metastases 10 years later

Impact of vascular invasion on nomenclature of follicular/Hurthle cell carcinomas (WHO 2017-2022)

- Minimally invasive: Capsular invasion only
- Angioinvasive: Any vascular invasion (VI) in encapsulated tumors. Focal (<4 foci of VI). Extensive (≥ 4 foci of VI)
- Widely invasive: Gross and extensive invasion of thyroid gland.

Integrated Genomic Analysis of Hürthle Cell Cancer

Ganly I, Makarov V, Deraje S, Dong Y, Reznik E, Seshan V, Nanjangud G, Eng S, Bose P, Kuo F, Morris LGT, Landa I, Carrillo Albornoz PB, Riaz N, Nikiforov YE, Patel K, Umbricht C, Zeiger M, Kebebew E, Sherman E, Ghossein R, Fagin JA, Chan TA.

Cancer Cell 2018

Widespread chromosomal losses and mitochondrial DNA alterations as genetic drivers in Hürthle cell Carcinoma

Gopal RK, Kübler K, Calvo SE, Polak P, Livitz D, Rosebrock D, Sadow PM, Campbell B, Donovan SE, Amin S, Gigliotti BJ, Grabarek Z, Hess JM, Stewart C, Braunstein LZ, Arndt PF, Mordecai S, Shih AR, Chaves F, Zhan T, Lubitz CC, Kim J, Iafrate AJ, Wirth L, Parangi S, Leshchiner I, Daniels GH, Mootha VK, Dias-Santagata D, Getz G, McFadden DG

Cancer Cell 2018

Genetic profile of oncocytic (Hurthle cell) carcinomas different from other thyroid carcinoma

Genetic alterations in Hurthle cell tumors compared to other thyroid cancers					
Gene	**Prevalence stratified by thyroid histology**				
	PTC	**FTC**	**PDTC**	**ATA**	**HCC**
RET point mutation RET rearrangements	0% Sporadic 20% Radiation induced 50-80%				0%
BRAF mutations	30-70%	0%	0-15%	10-35%	0%
RAS mutations	10%	45%	20-35%	50-60%	9%
PIK3CA point mutation or amplification		10-30%		25-45%	0%
PPARG rearrangement		25-60%			0%

PTC-papillary thyroid cancer
FTC-follicular thyroid cancer
PDTC-poorly differentiated thyroid cancer
ATC-anaplastic thyroid cancer

Lower follicular carcinoma type canonical mutations

Genetic profile of Hurthle cell carcinomas different from other thyroid carcinoma

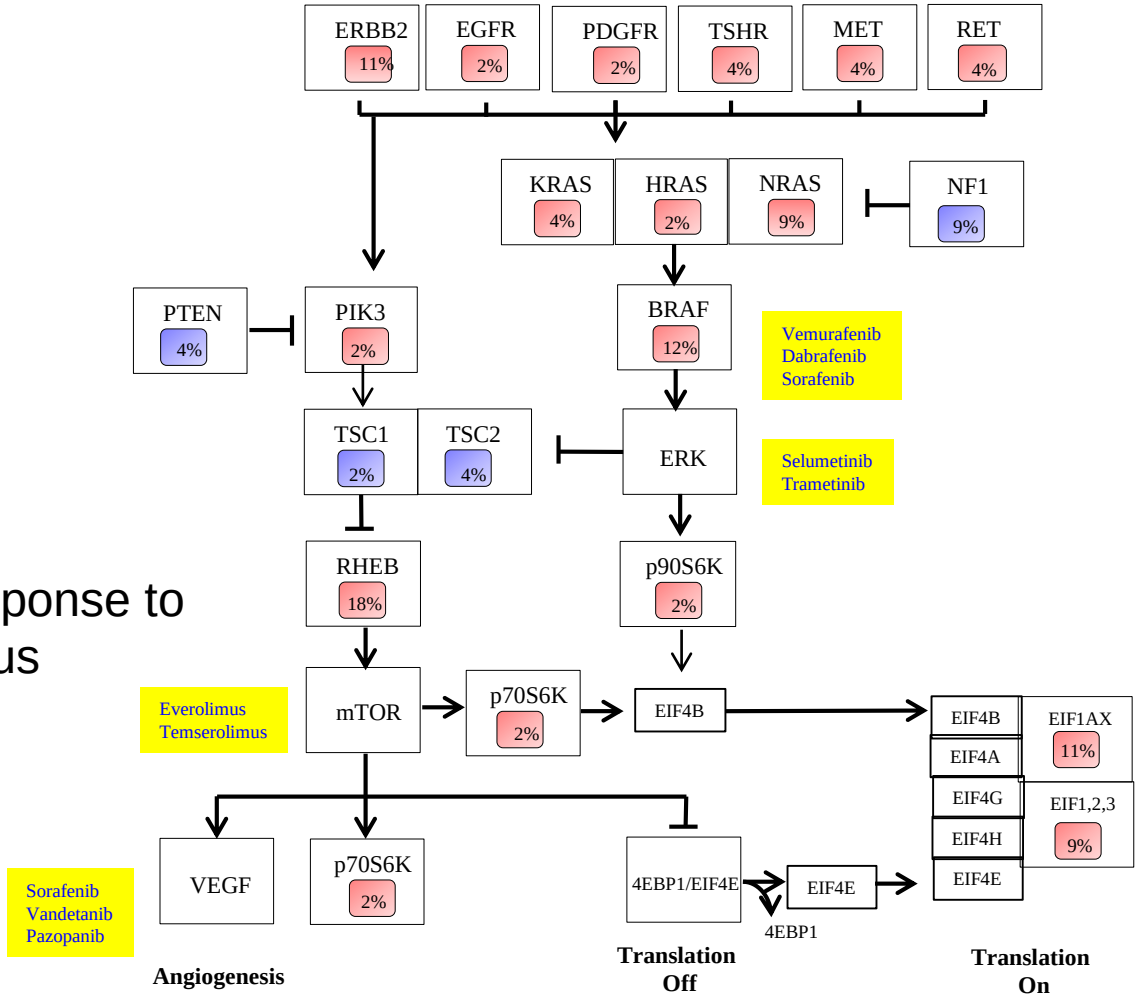
- Widespread chromosomal loss leading to haploidy or uniparental disomy: 54%

-Frequent mitochondrial DNA mutations: 67%

Gopal et al. Cancer Cell 2018
Ganly et al Cancer Cell 2018

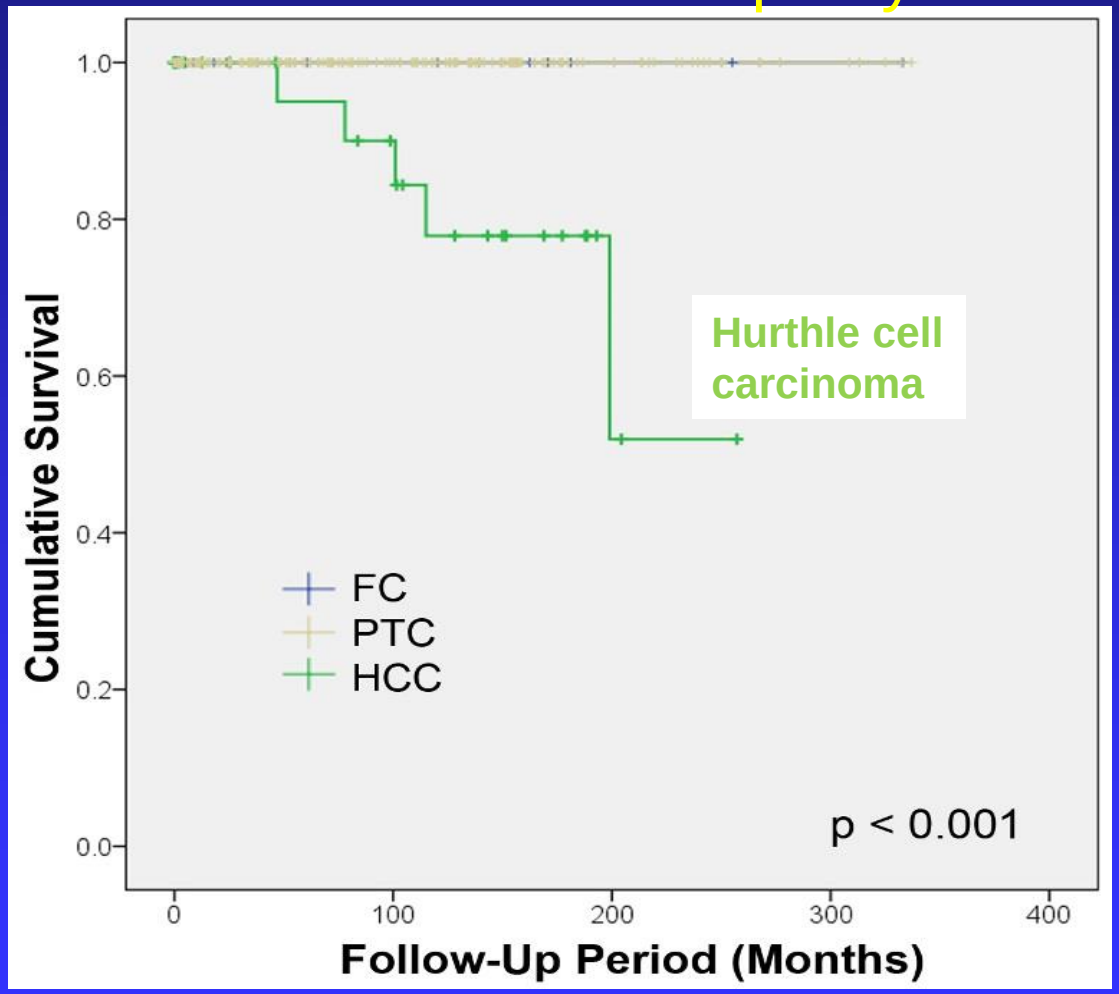
RTK/PIK3/RAS Pathway altered in 55% tumors

Good response to Everolimus



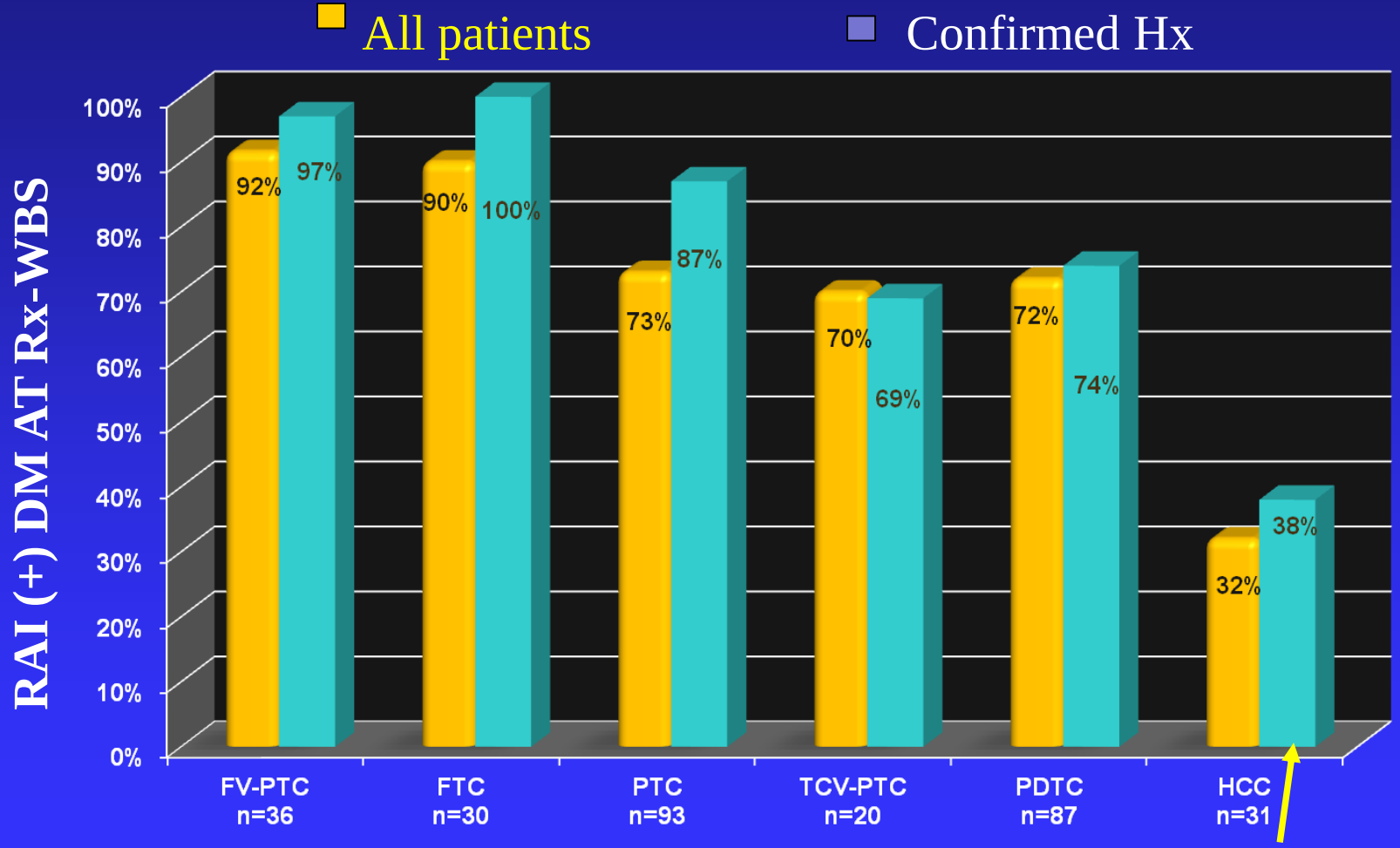
Ganly et al Cancer Cell 2018

Tumor type and recurrence free survival in encapsulated PTC, follicular carcinomas and Hurthle cell carcinoma (N=267) . Median follow up: 6 years



Xu B et al. *Hum Pathol.* 2015

RAI(+) distant metastases by histology



Third controversy: Is Oncocytic (Hurthle cell) carcinoma a subtype of follicular carcinoma?

- Follicular carcinoma *seems very different* from Hurthle cell carcinoma at molecular level, and in regard to RAI avidity and recurrence rates

WHO 2017-2022

- Hurthle cell tumors not subtypes of follicular carcinomas

HURTHLE CELL TUMOR

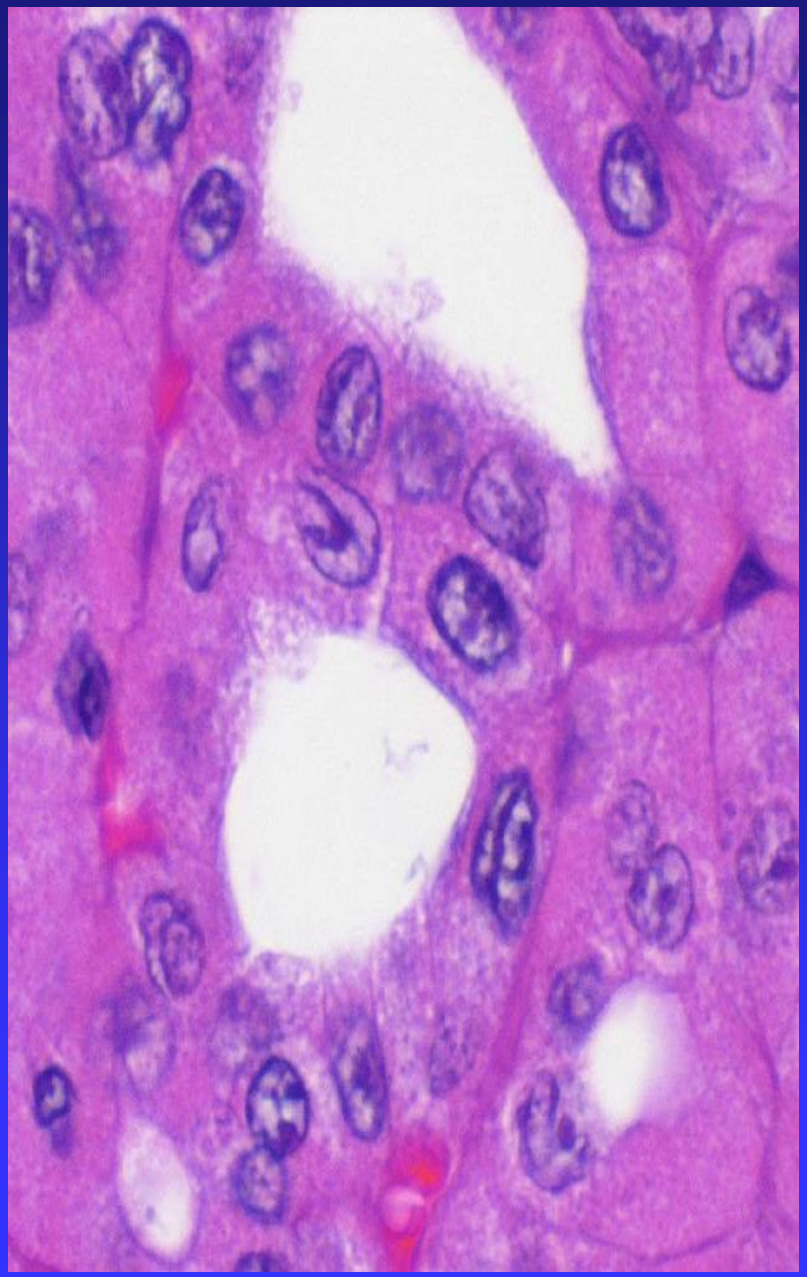
- Traditional Microscopic Criteria of Capsular and Vascular Invasion Define Malignancy.

- Extent of vascular invasion Stratify Patients into Prognostic Categories….*as long as distant metastases are excluded at presentation.*

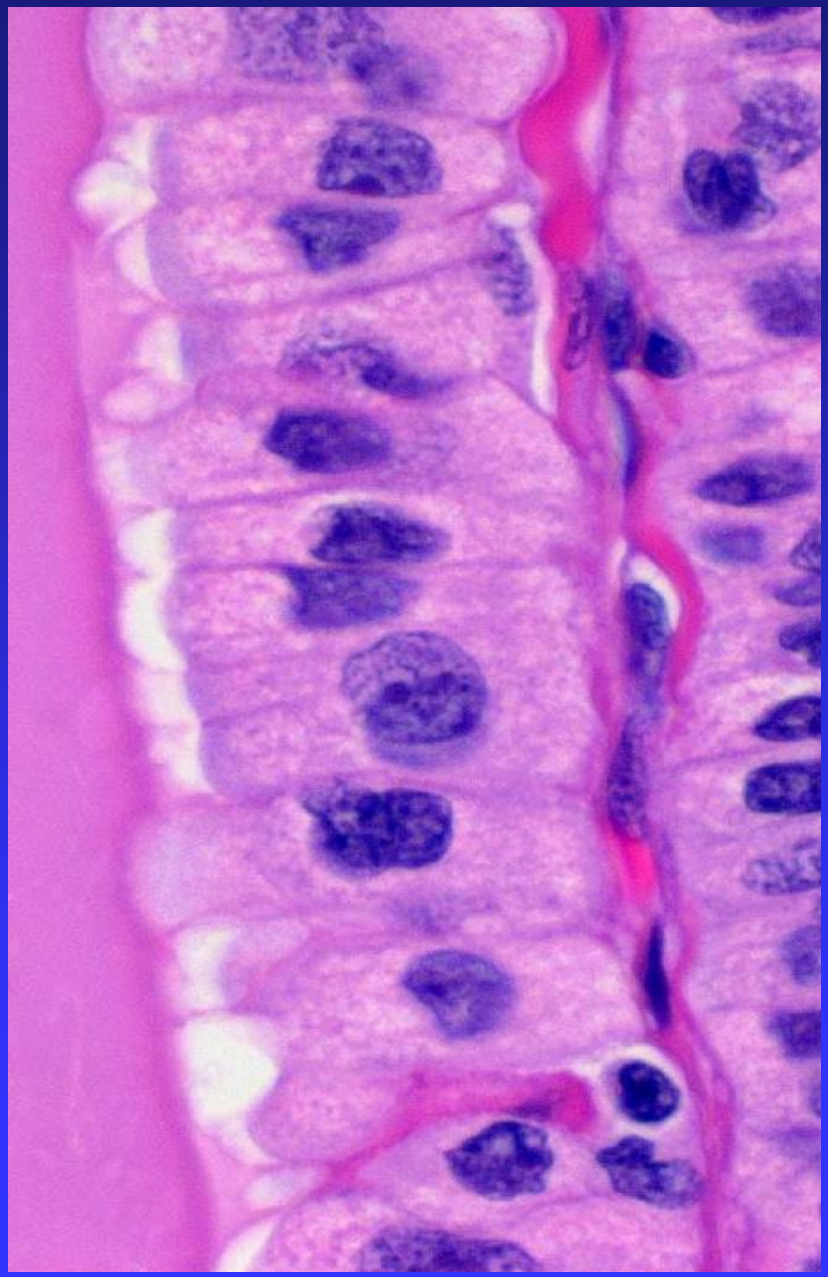
Papillary Carcinoma, Oncocytic Variant Definition

- An oncocytic tumor **with** the nuclear features of papillary carcinoma but the cell are not tall (papillary or follicular growth pattern)

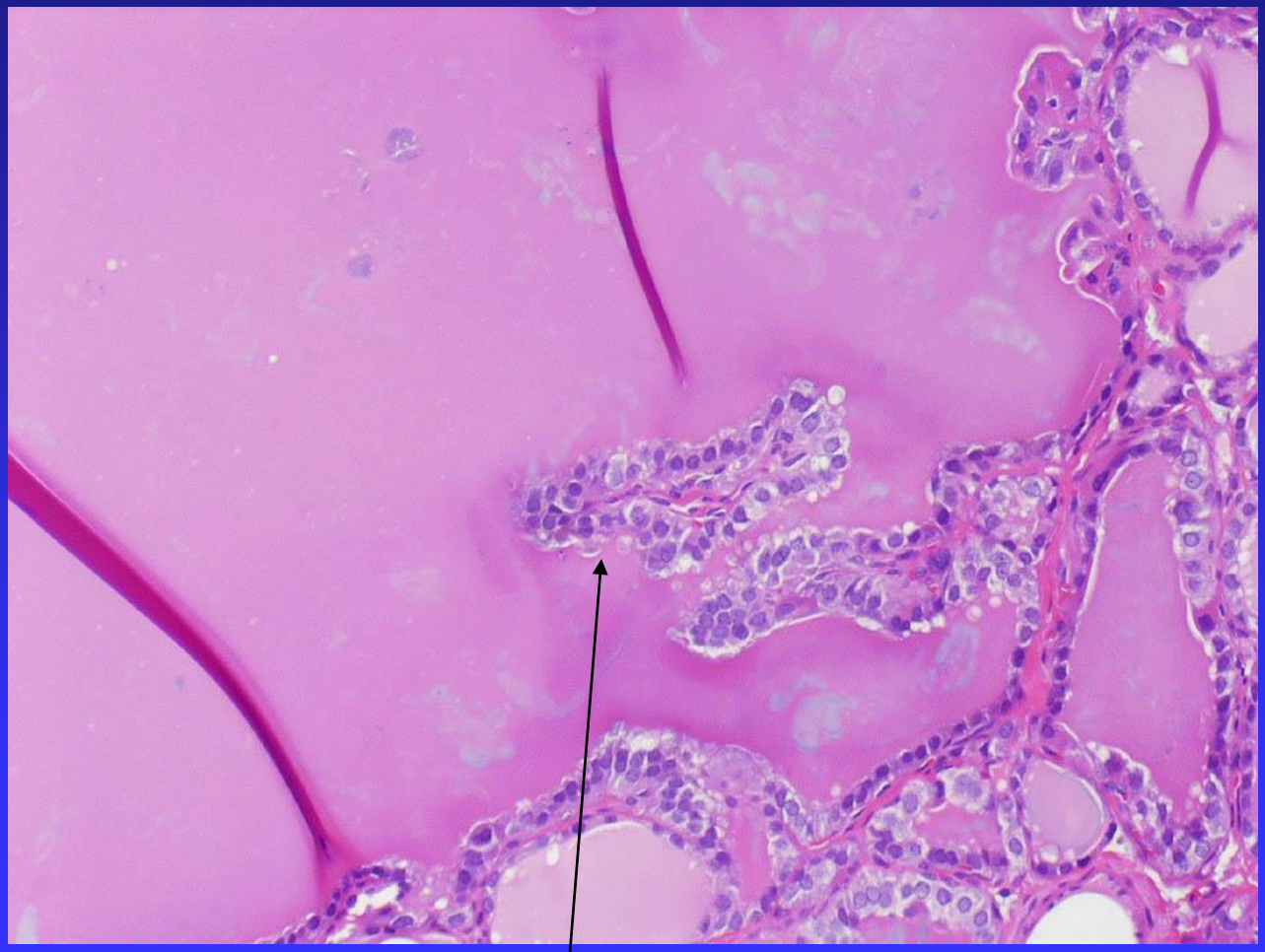
Oxyphilic variant



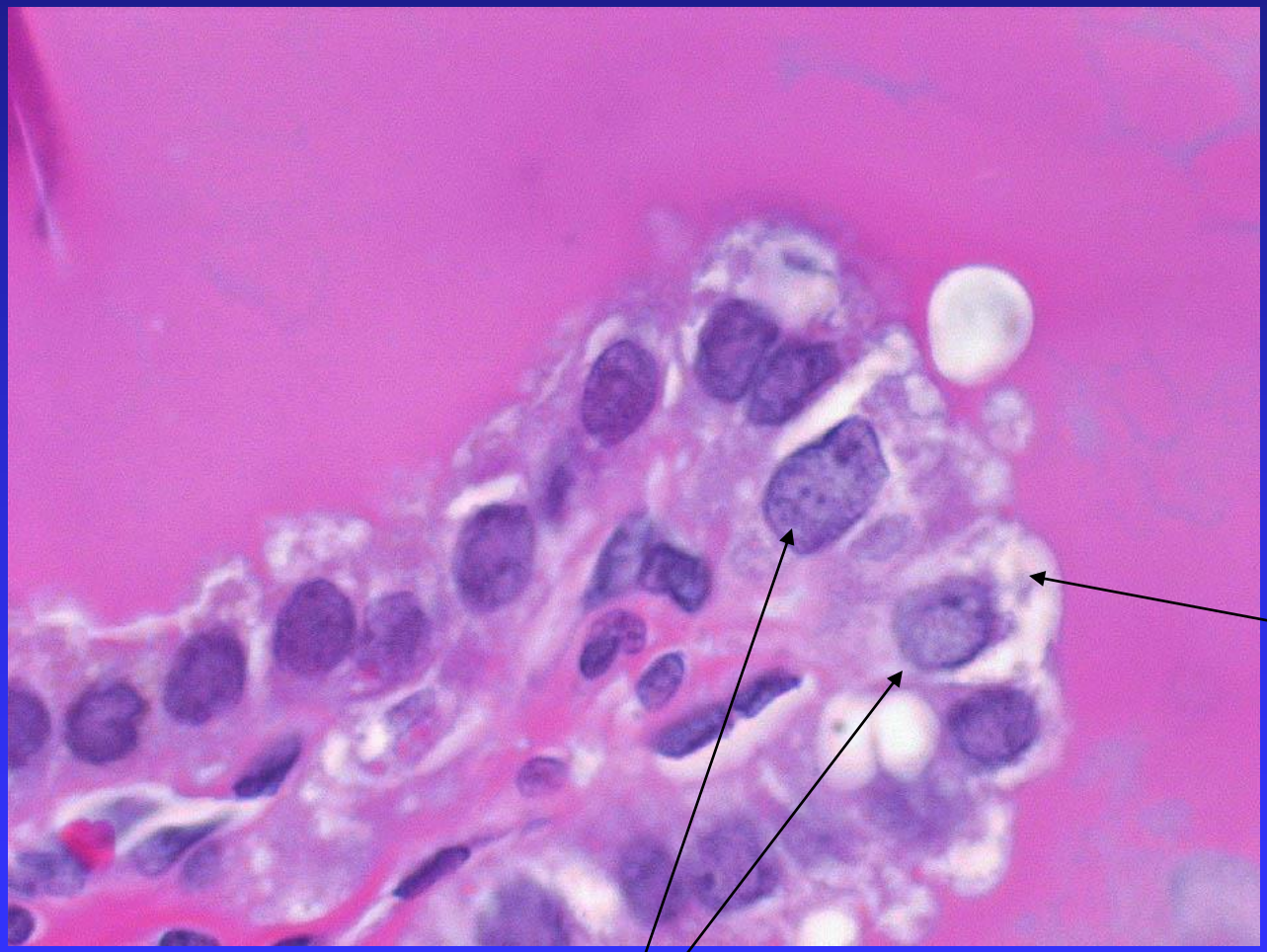
Tall cell variant



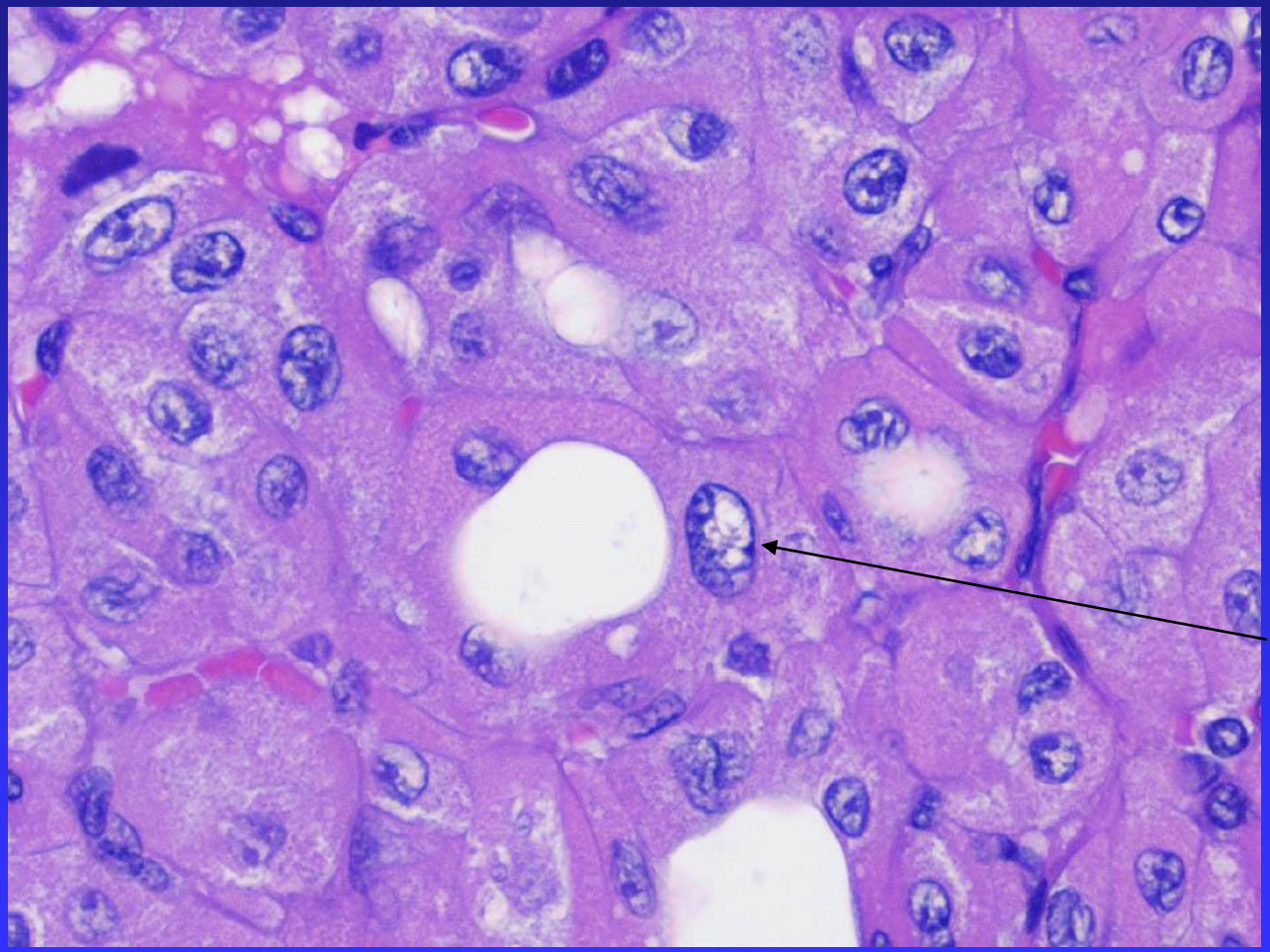
PAPILLARY CARCINOMA, CLASSICAL WITH ONCOCYTIC FEATURES



PAPILLARY CARCINOMA, CLASSICAL WITH ONCOCYTIC FEATURES



PAPILLARY CARCINOMA, FOLLICULAR VARIANT WITH ONCOCYTIC FEATURES



"Old clinicians used to say that the classification of thyroid cancer was very simple. There was a group of well differentiated, slow growing tumors that never killed anybody, and a group of rapidly growing tumors that killed everybody"

L. Woolner

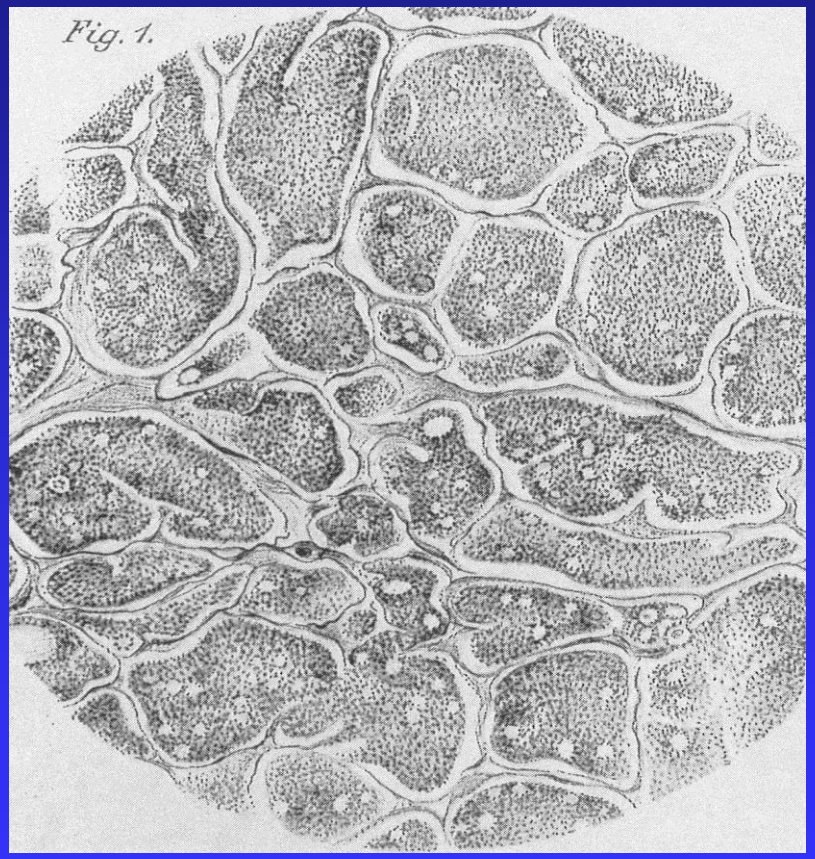
Dept. of Pathology

Mayo Clinic

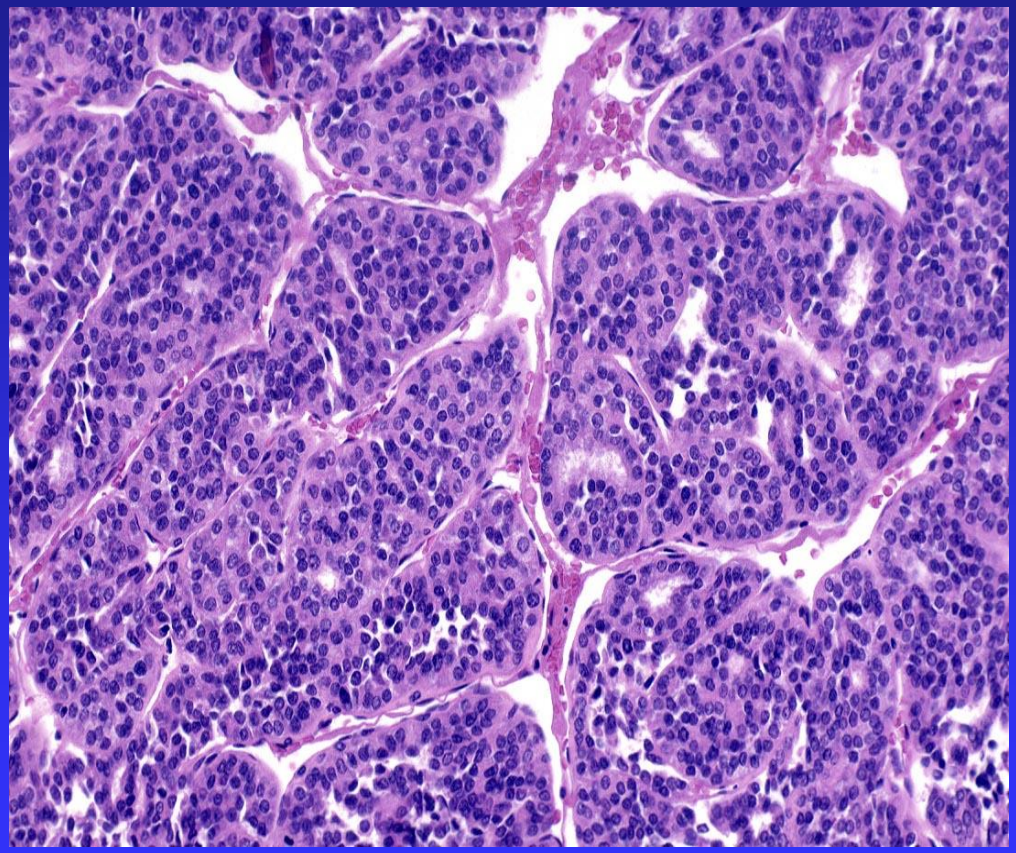
Poorly Differentiated Thyroid Carcinomas

- Tumors of follicular cell origin showing histologic and prognostic features intermediate between Well Differentiated Thyroid Carcinomas and Anaplastic Carcinoma.

“Wuchernde struma”
T. Langhans
1907



Insular carcinoma
Carcangiu, Zampi,Rosai
1984



HISTOLOGIC FEATURES OF POORLY DIFFERENTIATED THYROID CARCINOMAS

- Solid/trabecular/insular growth
- Necrosis
- Capsular invasion
- Vascular invasion

If all the above are present, everybody agrees on the Poorly differentiated diagnosis

THE BIG QUESTION

- WHAT DEFINES POORLY DIFFERENTIATED THYROID CARCINOMAS?

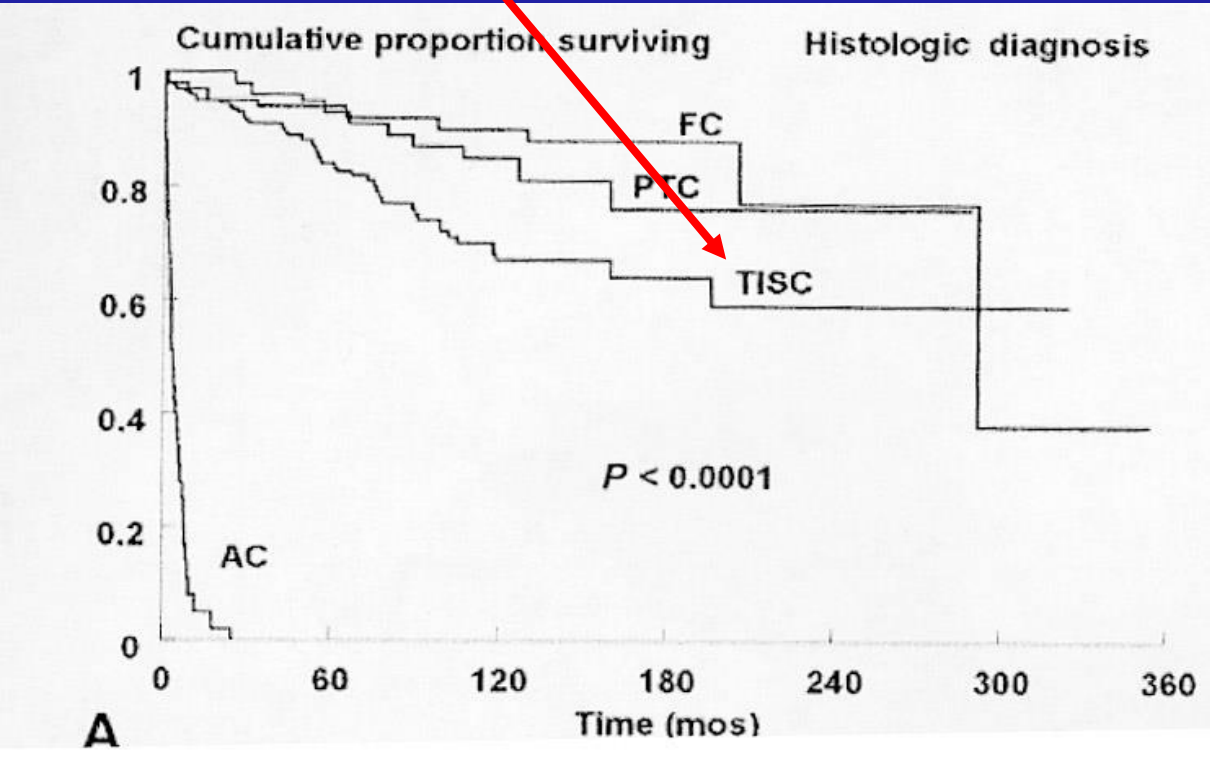
-SOLID GROWTH PATTERN ALONE

OR

- MITOSIS/NECROSIS ALONE

Trabecular/solid/insular poorly differentiated thyroid carcinomas irrespective of mitosis/necrosis

83% at 5 years



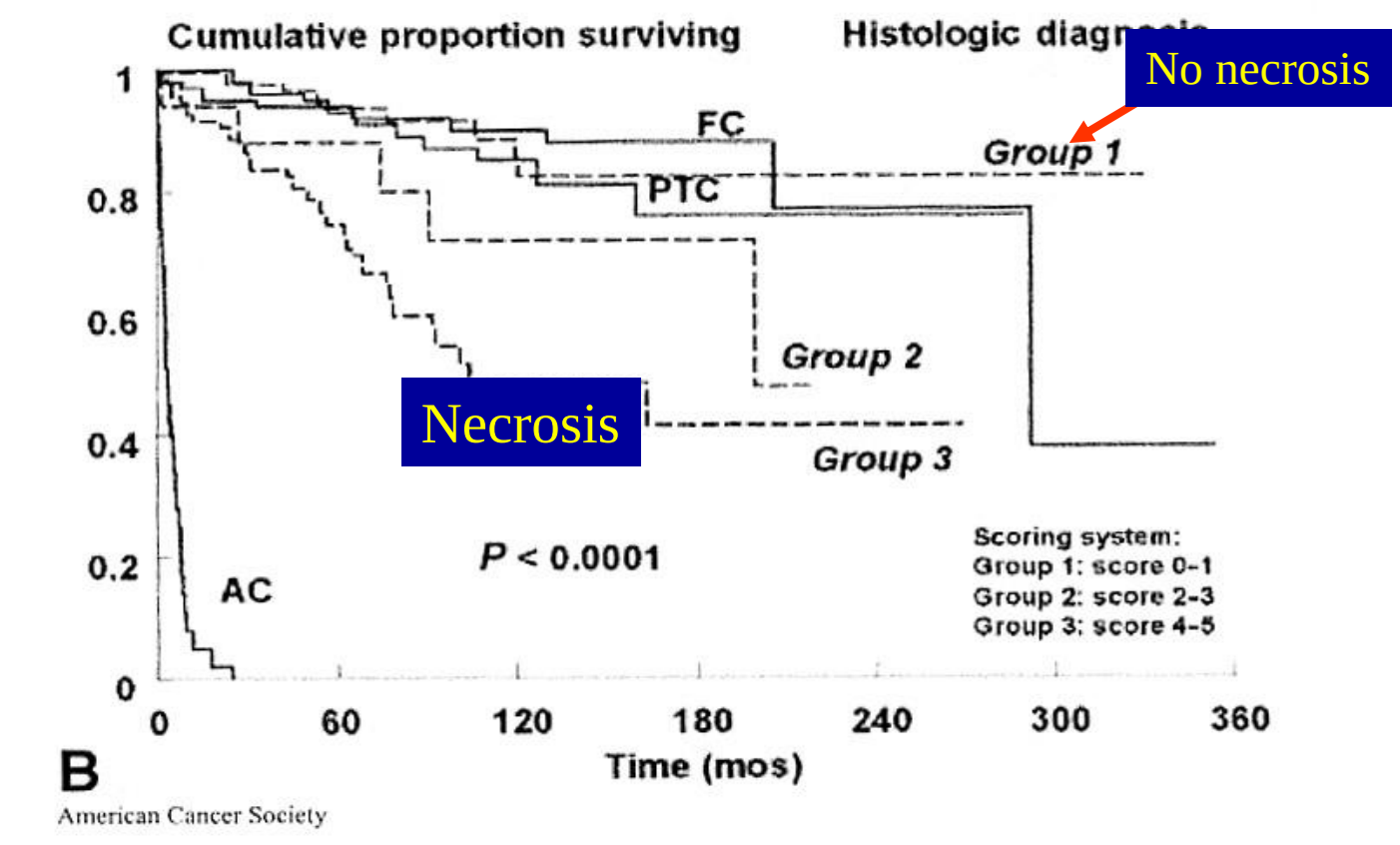
Volante et al. *Cancer* 2004;100:950-7.

Scoring of poorly differentiated thyroid carcinomas (Volante et al)

- Necrosis: 3 points
- Mitosis > 3 per 10 HPF, age >45: 1 point each

- Group 1: 0-1 (NO NECROSIS)
- Group 2: 2-3 (Necrosis or mitosis/age>45)
- Group 3: 4-5 (Necrosis and mitosis/age>45)

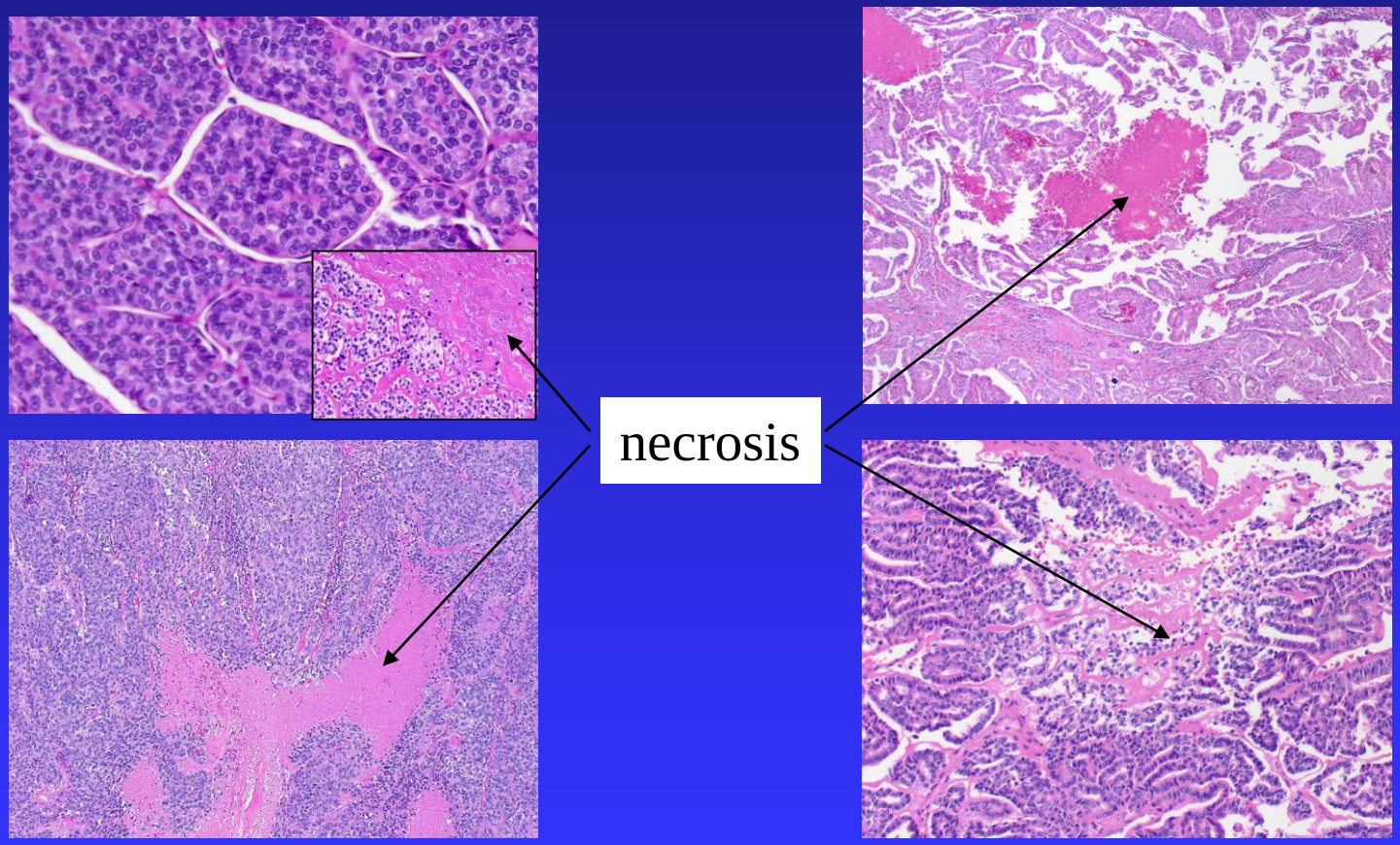
Trabecular/solid/insular poorly differentiated thyroid carcinomas



“POORLY DIFFERENTIATED THYROID CARCINOMAS: DEFINED ON THE BASIS OF MITOSIS AND NECROSIS. A clinico-pathologic study of 58 cases.

D. Hiltzik, D. Carlson, M. Tuttle, S. Chuai, N. Ishill, J. Shah, A. Shaha, B. Singh, R. Ghossein. *Cancer (March) 2006.*

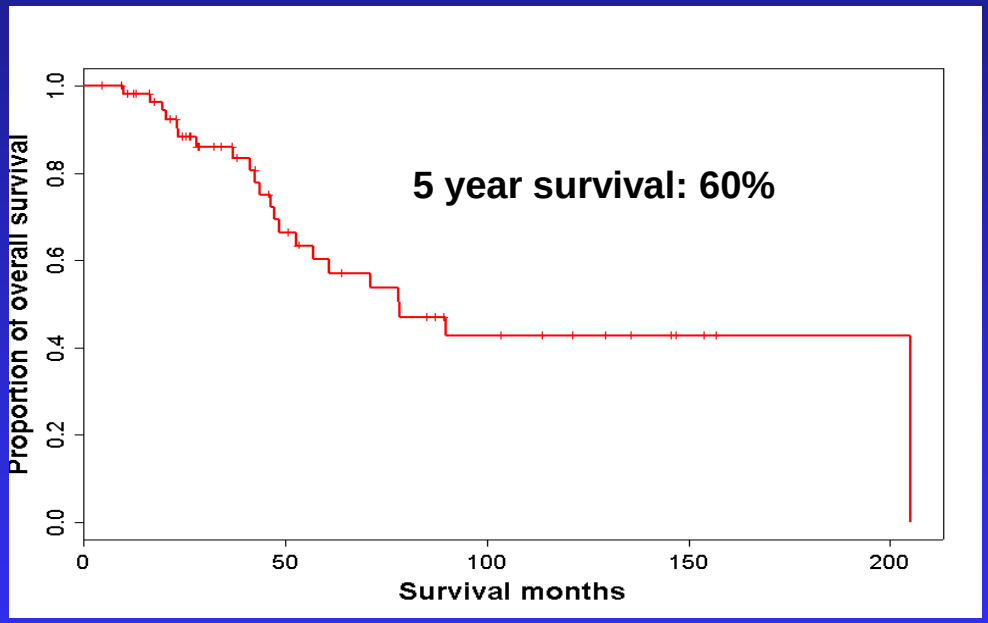
Poorly differentiated thyroid carcinomas defined on the basis of mitosis (≥ 5/10 HPF) and/or necrosis (MSKCC)



Fulfill also Turin

Hiltzik, D. Carlson, M. Tuttle, S. Chuai, N. Ishill, J. Shah, A. Shaha, B. Singh, R. Ghossein. *Cancer (March) 2006.*

Overall survival
Poorly differentiated thyroid ca defined on the basis of mitosis and necrosis



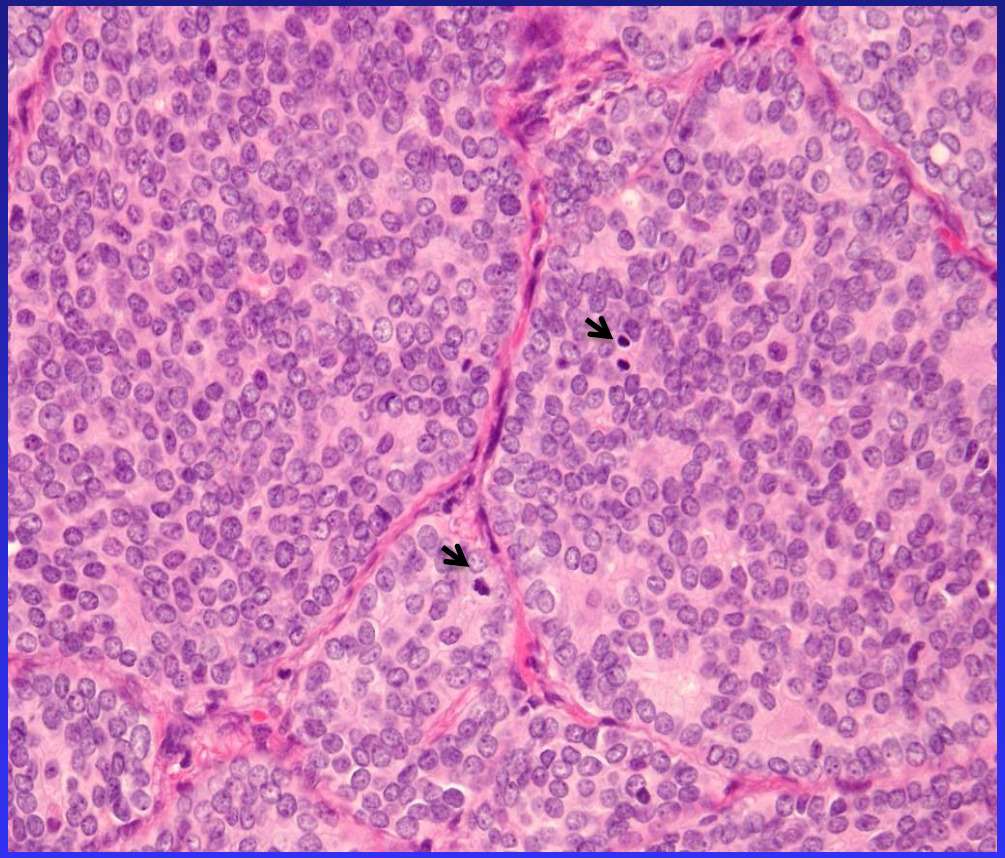
Predictors of survival within PDC

- Tumor > 4cm p=0.02
- Absence of a capsule p=0.001
- Extra-thyroid extension p=0.001
- Margins p=0.001

Factor with no influence on survival

Growth pattern (solid vs foll/pap) p=1

Poorly Differentiated Carcinoma



Turin proposal

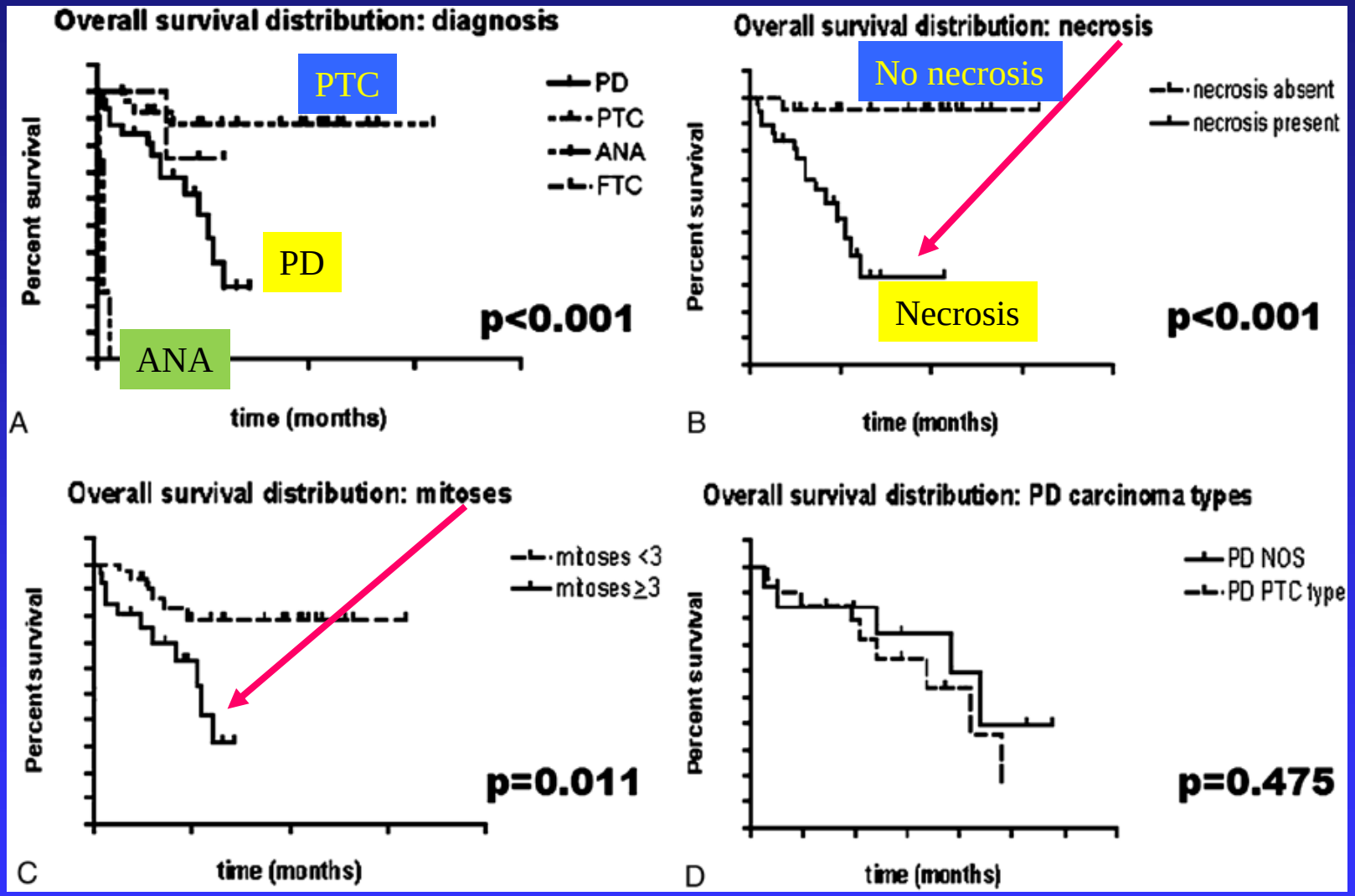
Solid/nested/insular growth pattern, and
Absence of nuclear features of PTC, and
At least one of the following features:

- Convoluted nuclei
- Mitotic index of ≥ 3/10 HPFs
- Tumor necrosis

Volante et al., 2007. Am J Surg Pathol 31: 1256 -1264.

Adopted by previous WHO 4th ed

TURIN PROPOSAL



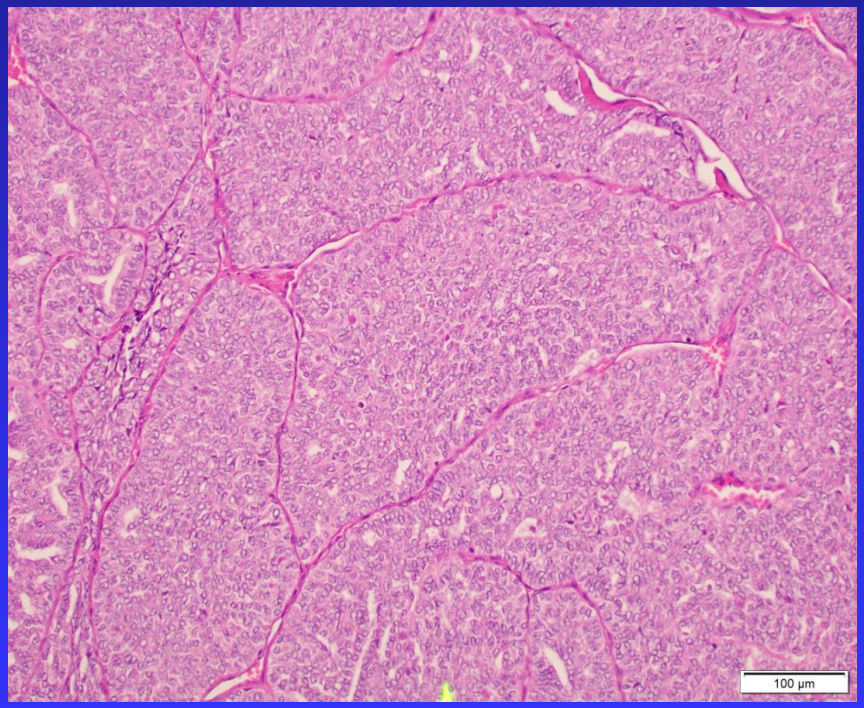
POORLY DIFFERENTIATED THYROID CARCINOMA DEFINED ON THE BASIS OF MITOSIS/NECROSIS

- Main cause of radioactive iodine (RAI) refractory disease (46%).
- Many of these RAI-refractory PDCs (68%) initially diagnosed as classical PTC, Hurthle cell ca, and follicular ca.
- Main cause of death from non-anaplastic thyroid carcinoma (55%).

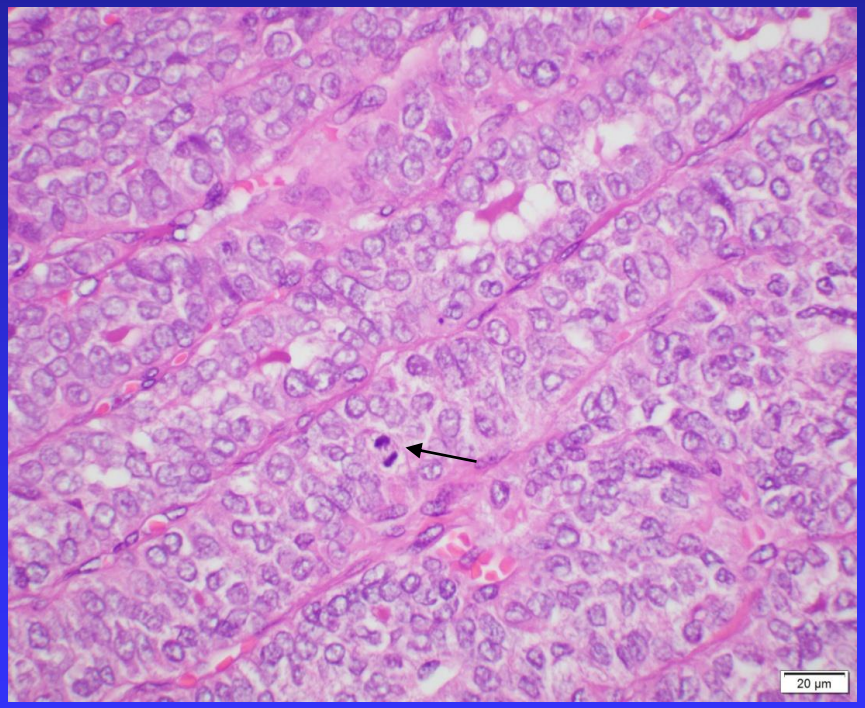
- Rivera M, Ghossein R, Schoder H et al. Histopathologic characterization of RAI refractory PET positive thyroid carcinomas. *Cancer 2008*
- Xu B et al. Clinico-Pathologic Features of Fatal Non-Anaplastic Follicular Cell-Derived Thyroid Carcinomas. *USCAP* 2016.

72 year old man with 5.5 cm mass

Solid nested growth

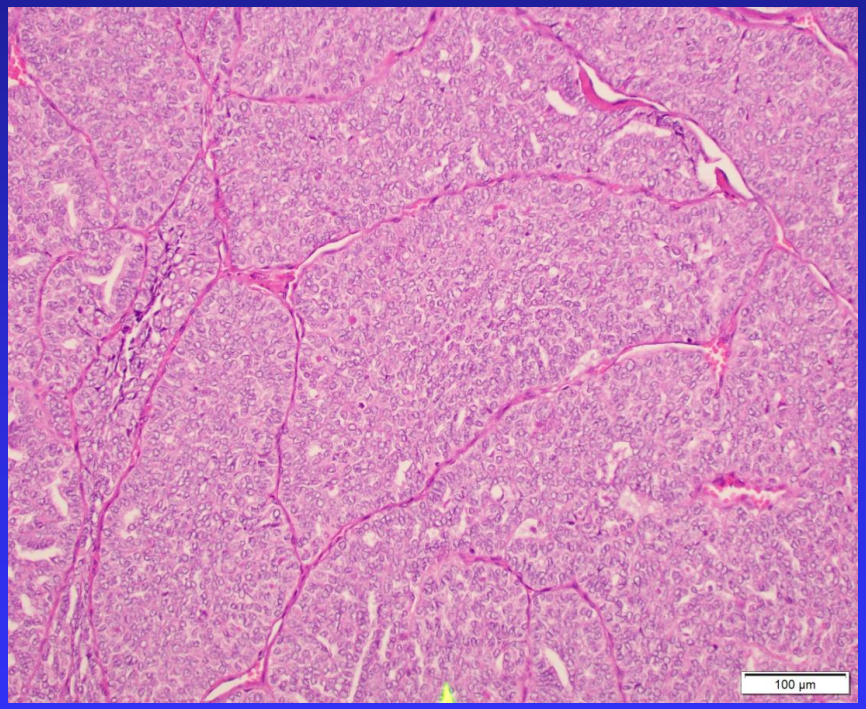


High mitotic rate and clear nuclei

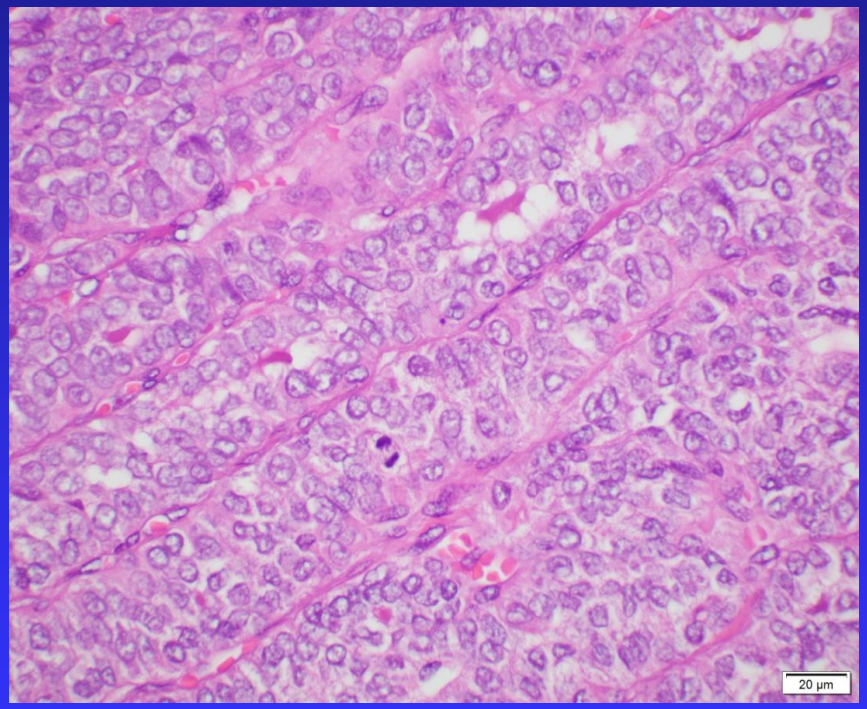


72 year old man with 5.5 cm mass

Turin proposal: Papillary carcinoma (clear nuclei)



MSKCC: Poorly diff carcinoma



Outcome

- Vertebral and lung metastasis
- D.O.D 4 years after diagnosis

WHO 2022
High grade follicular cell derived non-anaplastic thyroid carcinomas

- Invasive carcinoma of thyroid follicular cells
- High grade features as defined by mitotic count and tumour necrosis
- No anaplastic histology.

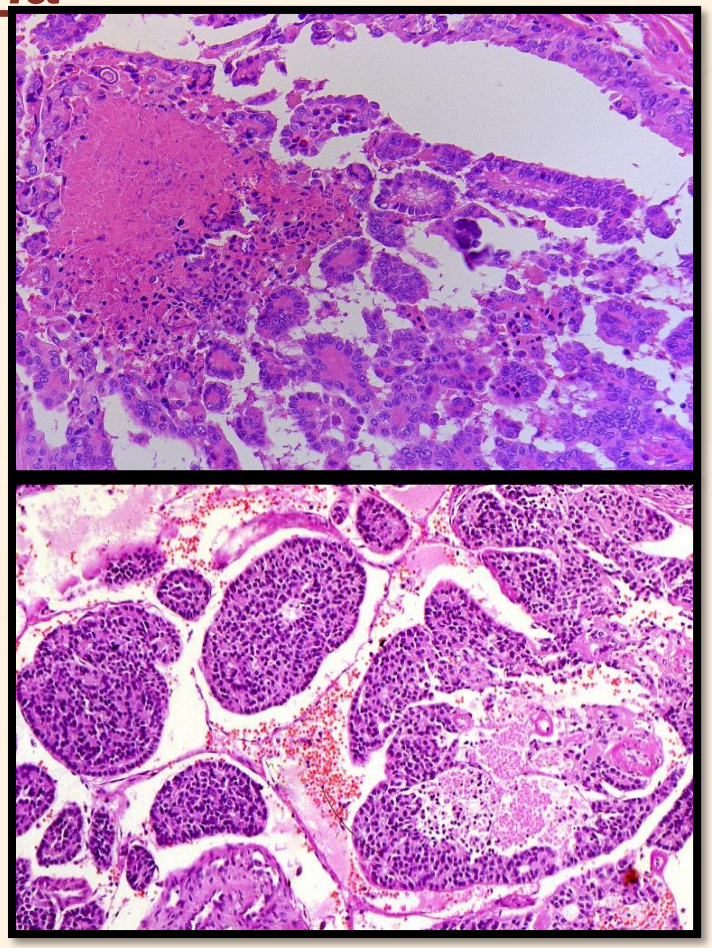
WHO 2022
High grade follicular cell derived non-anaplastic thyroid carcinomas

- Poorly Differentiated Thyroid Carcinoma (PDTC)

- High grade differentiated thyoid carcinomas (HGDTC)

WHO 2022 high grade follicular cell derived non-anaplastic thyroid carcinoma

	PDTC (Turin criteria)	High grade differentiated thyroid carcinoma
Growth Pattern	Solid/trabecular/insular required	Papillary, follicular, solid*
Nuclear Cytology	No features of PTC required	Any
Tumor Necrosis, Mitosis and Convoluted Nuclei	one of the following three features: Mitotic count ≥3/2 mm^2 Tumor necrosis Convoluted nuclei	one of the following two features: Mitotic count ≥5/2 mm^2 Tumor necrosis
Anaplastic features	Absent	Absent



High grade follicular cell derived non-anaplastic thyroid carcinoma
Molecular profile

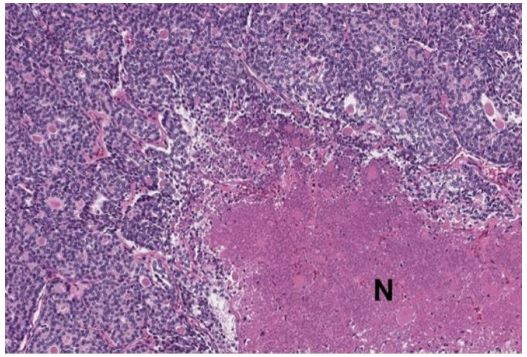
Subtype	*BRAF* V600E	*RAS*[a]	*TERT*	*TP53*	*EIF1AX*	*PTEN*	*PIK3CA*
Poorly differentiated thyroid carcinoma (PDTC)	6%	44%	44%	15%	15%	6%	2%
High grade differentiated thyroid carcinoma (HGDTC)	81%	6%	39%	3%	3%	0%	3%

High grade (HG) thyroid carcinomas (n=364)

- *TERT* and *TP53* mutation: 55% and 11%
- Adverse independent prognostic factors are: older age, male sex, extensive necrosis, infiltration, vascular invasion, positive margin, lymph node metastasis, *PTEN*, *TP53*, and *TERT* mutations

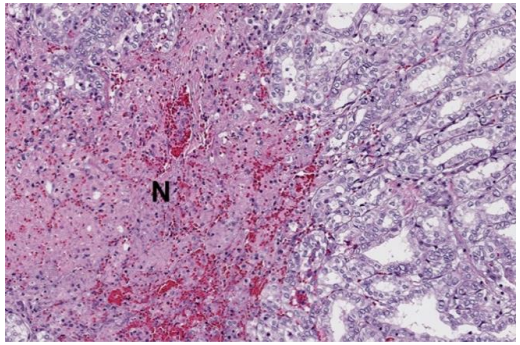
Similar overall and disease specific survival

Poorly differentiated carcinoma



- *RAS*-predominant
- RAI avid
- Higher frequency of distant metastasis
- Lower rate of nodal metastasis

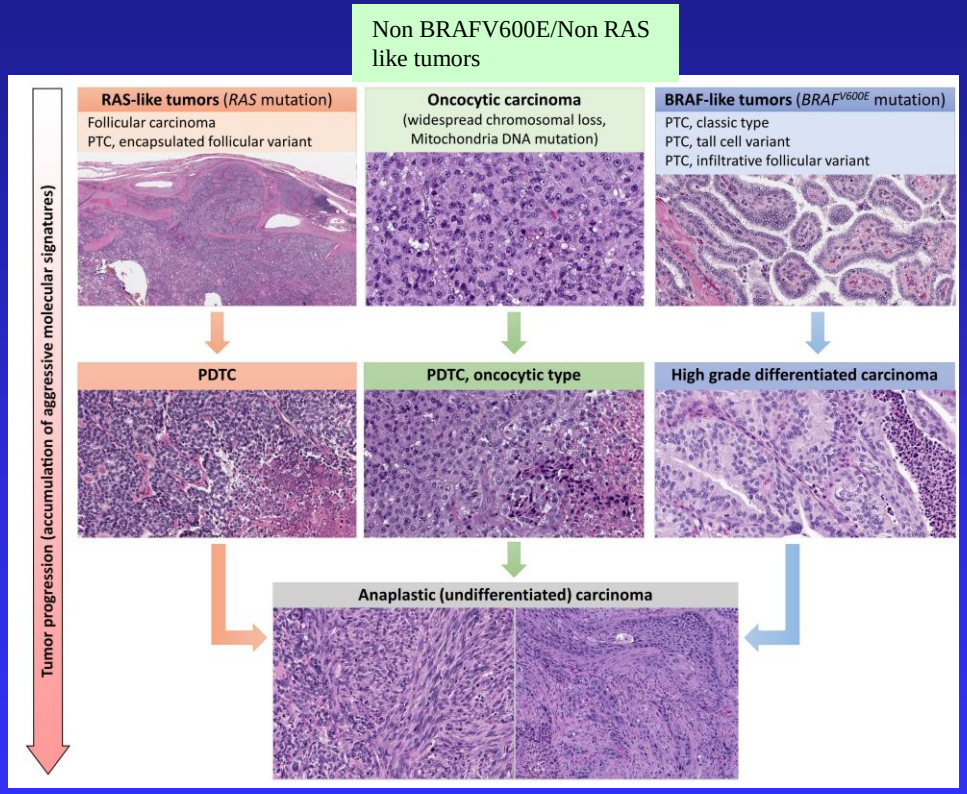
HG differentiated carcinoma (n=164)



- *BRAF* V600E-predominant
- RAI non-avid
- Lower frequency of distant metastasis
- Higher rate of nodal metastasis

Xu B, David J, Dogan S, Landa I, Katabi N, Saliba M, Khimraj A, Sherman EJ, Tuttle RM, Tallini G, Ganly I, Fagin JA, Ghossein RA. Histopathology. 2022.

Morphology, Molecular Profile, Clinical Behavior



Toward a New nomenclature in tumours that better reflects behavior

- For staging:

  -From anatomic grouping (6,7th AJCC edition) to Anatomic/prognostic grouping (8th AJCC edition)

- For pathologic entities:

  -Based on *prognostically relevant histologic features* rather than clinically irrelevant histopathology. (Pathologist=Clinician with a microscope)

The wisdom of Julian Huxley

‘*Cancer (malignancy) must be defined operatively in terms of what the tumor cells do, not what they look like; otherwise the term ceases to have biological meaning*’

Huxley J. Biological Aspects of Cancer. New York, NY: Harcourt, Brace and Co; 1958:14.

THE END