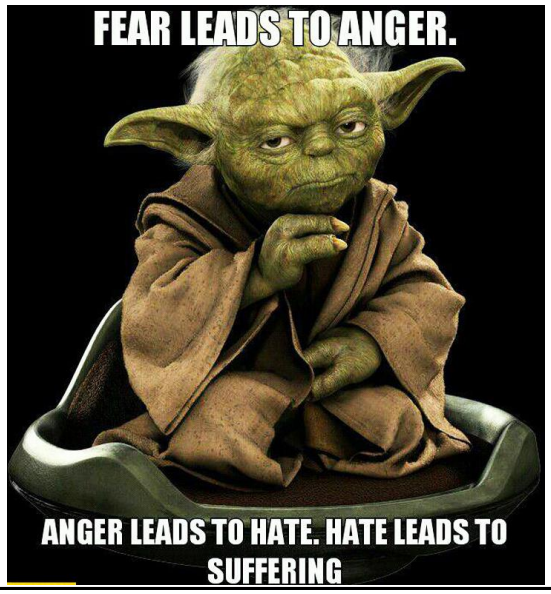
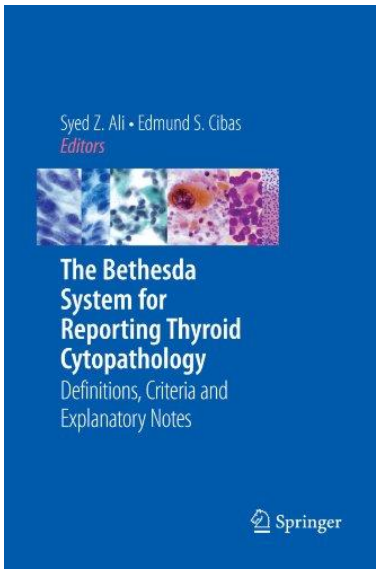
Actual problems of the morphological diagnostics of the thyroid tumors – The Highlights of WHO Classification, 4th edition, 2017.

In the beginning there are some important words about thyroid cytology!



The Bethesda 2007 System for Reporting Thyroid Cytopathology



The Bethesda 2007 System for Reporting Thyroid Cytopathology

Category I: Nondiagnostic / Unsatisfactory:
- **Cyst fluid only**
- **Virtually acellular specimen**
- **Obscuring blood**

Category II: Benign:
- **Consistent with benign follicular nodule**
- **Consistent with benign adenomatoid nodule**
- **Consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical context**
- **Consistent with granulomatous (subacute) thyroiditis**
- **Other**

Category III: Atypia of Undetermined Significance / Follicular lesion of Undetermined Significance

Category IV: Follicular Neoplasm / Suspicious for a Follicular Neoplasm
- **Hurthle cell (oncocytic) type**

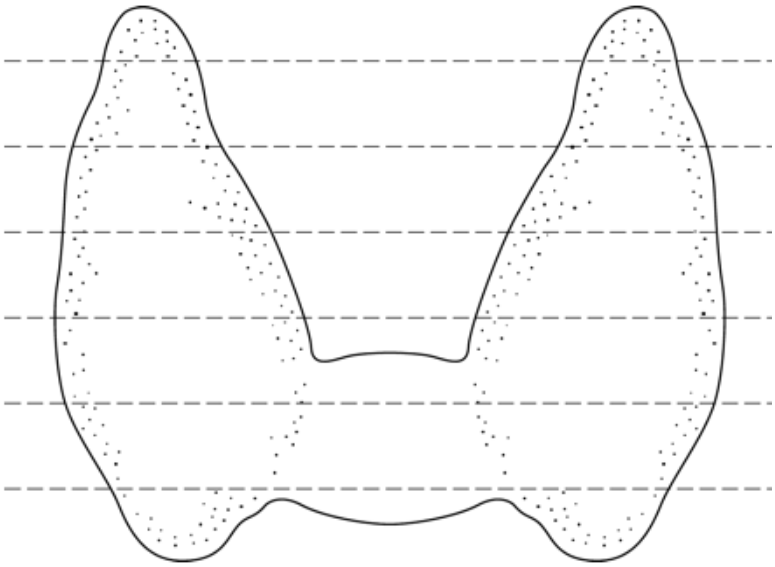
Category V: Suspicious for Malignancy
- Suspicious for papillary carcinoma
- Suspicious for medullary carcinoma
- Suspicious for metastatic carcinoma
- Suspicious for lymphoma
- Other

Category VI: Malignant
- Papillary thyroid carcinoma
- Poorly differentiated carcinoma
- Medullary thyroid carcinoma
- Undifferentiated (anaplasyic) carcinoma
- Squamous cell carcinoma
- Carcinoma with mixed features
- Metastatic carcinoma
- Non-Hodgkin lymphoma
- Other

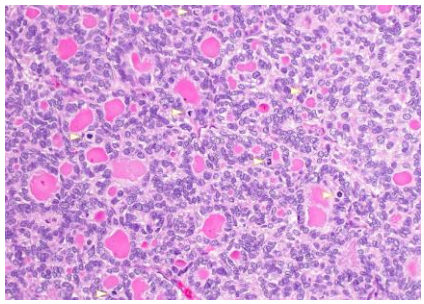
Risk of malignancy and recommended clinical management

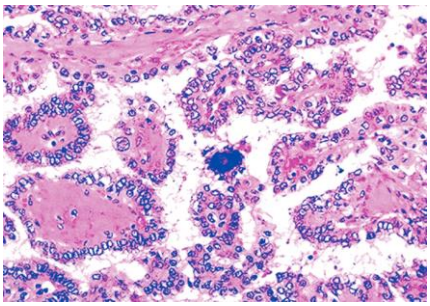
Diagnostic category	Risk of malignancy	Usual management
Non-diagnostic / Unsatisfactory		Repeat FNA, US-guided
Benign	0 -3%	Follow up
Atypia of Undetermined Significance / Follicular Lesion of Undetermined Significance	5 – 15%	Repeat FNA
Follicular Neoplasm / Suspicious for a Follicular Neoplasm	15 – 30%	Lobectomy
Suspicious for Malignancy	60 - 75%	Near-total thyroidectomy or lobectomy with FS (?)
Malignant	97 – 99%	Near-total thyroidectomy with FS (?)

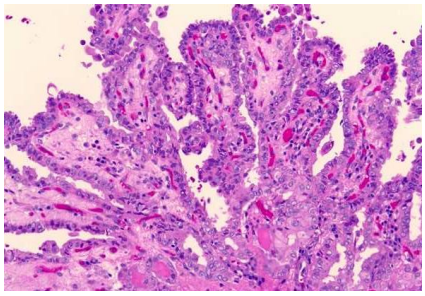
Sectioning of the Thyroid Gland

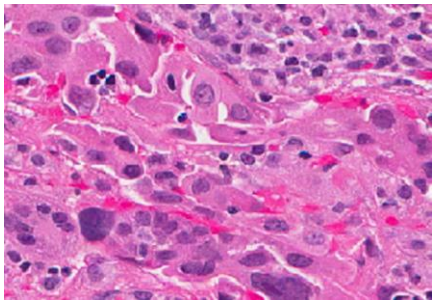


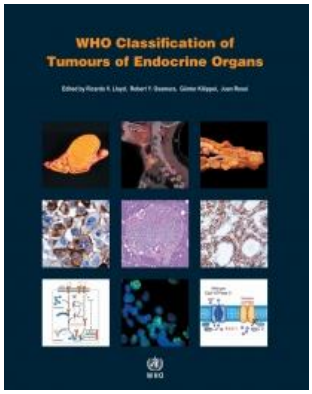
Thyroid Tumors of Follicular Cell Origin











AJSP: Reviews & Reports • Volume 22, Number 4, July/August 2017

Pathology of Endocrine Tumors Update: World Health Organization New Classification 2017—Other Thyroid Tumors

TABLE 1. Modified Version of WHO Classification of Nonmedullary Thyroid Tumors

I. Epithelial Tumors
Follicular cell neoplasms
Benign follicular tumors
Follicular adenoma
Hyalinizing trabecular tumor
Hürthle cell adenoma
Borderline follicular tumors/encapsulated or well-circumscribed follicular-patterned tumors with well-developed or equivocal nuclear features of papillary thyroid carcinoma
FT-UMP
WDT-UMP
NIFTP
Carcinoma
Papillary carcinoma
Follicular carcinoma
Hürthle carcinoma
Poorly differentiated carcinoma
Anaplastic (undifferentiated) carcinoma
Squamous cell carcinoma.
Other epithelial tumors
Salivary gland–type carcinomas
Mucoepidermoid carcinoma
Sclerosing mucoepidermoid carcinoma with eosinophilia
Mucinous carcinoma
Thymic tumors
Ectopic thymoma
Intrathyroid epithelial thymoma/CASTLE
Spindle epithelial tumor with thymus-like differentiation

TABLE 2. Variants of Papillary Thyroid Carcinoma

Variant
1. Conventional/classic
2. Papillary microcarcinoma
3. Encapsulated
4. Follicular
5. Diffuse sclerosing
6. Tall cell
7. Columnar cell
8. Cribriform-morular
9. Hobnail
10. Papillary thyroid carcinoma with fibromatosis/fasciitis-like stroma
11. Solid/trabecular variant
12. Oncocytic
13. Spindle cell
14. Clear cell variant
15. Warthin like variant

The histologic criteria for poorly differentiated carcinoma are (1) a diagnosis of carcinoma of follicular cell derivation (by conventional criteria); (2) solid, insular, or trabecular growth; (3) absence of conventional nuclear features of papillary thyroid carcinoma; and (4) at least 1 of 3 features: convoluted nuclei (ie, "dedifferentiated" nuclear features of papillary carcinoma), mitotic activity 3 or more per 10 high-power fields, or tumor necrosis. An algorithmic approach was devised for practical use to diagnose this carcinoma.

Thyroid cancer TNM, AJCC – 7th and 8th Editions

Seventh edition	Eighth edition
Tumor	
T1a: tumor ≤1 cm limited to the thyroid	**T1a:** tumor ≤1 cm limited to the thyroid
T1b: tumor >1 cm but ≤2 cm limited to the thyroid	**T1b:** tumor >1 cm but ≤2 cm limited to the thyroid
T2: tumor >2 cm but ≤4 cm limited to the thyroid	**T2:** tumor >2 cm but ≤4 cm limited to the thyroid
T3: tumor >4 cm limited to the thyroid or minimal extrathyroid extension (for example, perithyroidal soft tissues or sternothyroid muscle) from a tumor of any size	**T3a:** tumor >4 cm limited to the thyroid **T3b:** gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, thyrohyoid, omohyoid) from a tumor of any size
T4a: gross extrathyroidal extension invading subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve from a tumor of any size	**T4a:** gross extrathyroidal extension invading subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve from a tumor of any size
T4b: gross extrathyroidal extension invading prevertebral fascia or encasing the carotid artery or mediastinal vessels from a tumor of any size	**T4b:** gross extrathyroidal extension invading prevertebral fascia or encasing the carotid artery or mediastinal vessels from a tumor of any size
Node	
Nx: regional lymph nodes cannot be assessed	**Nx:** regional lymph nodes cannot be assessed
N0: no evidence of locoregional lymph node metastasis	**N0a:** one or more cytologically or histologically confirmed benign lymph nodes **N0b:** no radiologic or clinical evidence of locoregional lymph node metastasis
N1a: ipsilateral or bilateral metastasis to level VI (pretracheal, paratracheal, or prelaryngeal/Delphian) lymph nodes	**N1a:** ipsilateral or bilateral metastasis to level VI or VII (pretracheal, paratracheal, or prelaryngeal/Delphian, or upper mediastinal) lymph nodes; this can be unilateral or bilateral disease
N1b: metastasis to unilateral, bilateral, or contralateral lateral neck lymph nodes (levels I, II, III, IV, or V) or retropharyngeal or superior mediastinal lymph nodes (level VII)	**N1b:** metastasis to unilateral, bilateral, or contralateral lateral neck lymph nodes (levels I, II, III, IV, or V) or retropharyngeal lymph nodes
Metastasis	
M0: no distant metastasis	**M0:** no distant metastasis
M1: distant metastasis	**M1:** distant metastasis

Thyroid cancer TNM, AJCC – 7th and 8th Editions

Seventh edition	Age <45 years			Eighth edition	Age <55 years		
I	Any T	Any N	M0	I	Any T	Any N	M0
II	Any T	Any N	M1	II	Any T	Any N	M1
Seventh edition	**Age ≥45 years**			**Eighth edition**	**Age ≥55 years**		
I	T1a/b	N0	M0	I	T1a/b T2	N0/NX N0/NX	M0 M0
II	T2	N0	M0	II	T1a/b T2 T3a/b	N1a/b N1a/b Any N	M0 M0 M0
III	T1a/b T2 T3	N1a N1a N0, N1a	M0 M0 M0	III	T4a	Any N	M0
IVa	T1a/b T2 T3 T4a	N1b N1b N1b N0, N1a, N1b	M0 M0 M0 M0	IVa	T4b	Any N	M0
IVb	T4b	Any N	M0	IVb	Any T	Any N	M1
IVc	Any T	Any T	M1	-	-	-	-

F1000Research F1000Research 2018, 7(F1000 Faculty Rev):86 Last updated: 18 JAN 2018

Check for updates

REVIEW

Recent advances in managing differentiated thyroid cancer [version 1; referees: 2 approved]

Livia Lamartina, Giorgio Grani, Cosimo Durante, Sebastiano Filetti

Dipartimento di Medicina Interna e Specialità Mediche, Università di Roma "Sapienza", Viale del Policlinico 155, 00161 Rome, Italy

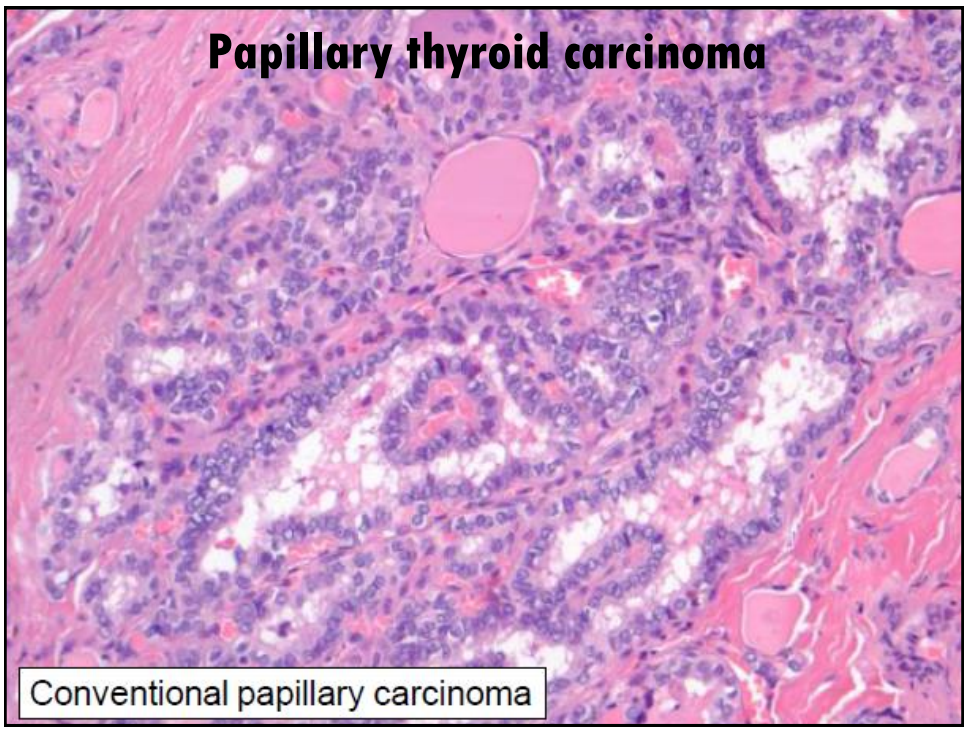
MANAGEMENT STRATEGIES (UPDATE):

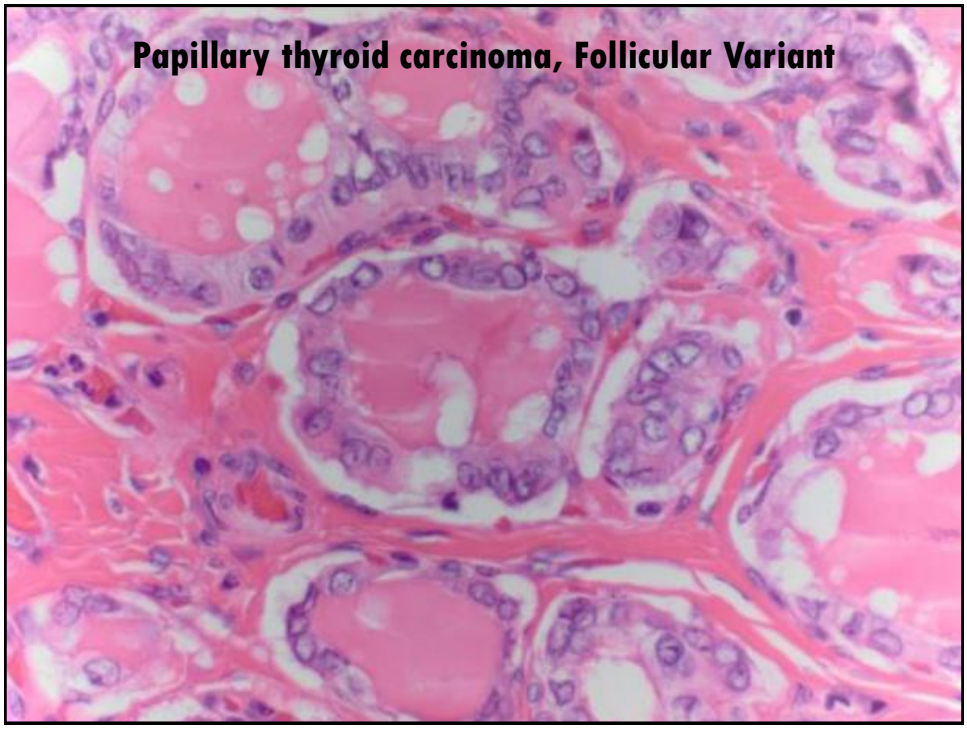
- Active surveillance
- Individualized surgical approaches
- Radioiodine remnant ablation: selective use
- Follow-up tools
- Treatment of distant metastases
- Radioactive iodine-refractory disease

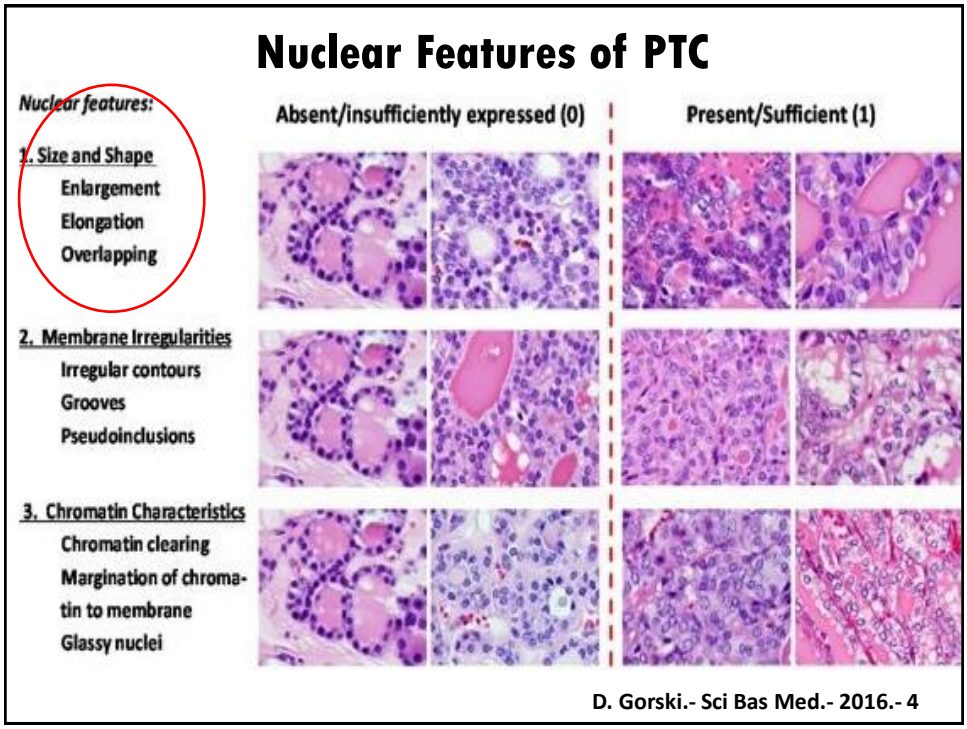
Papillary thyroid carcinoma

1. PTC – more aggressive in M > F
2. Age at the time of diagnosis
3. Tumor size
4. Surgical margins
5. Extra-thyroid extension

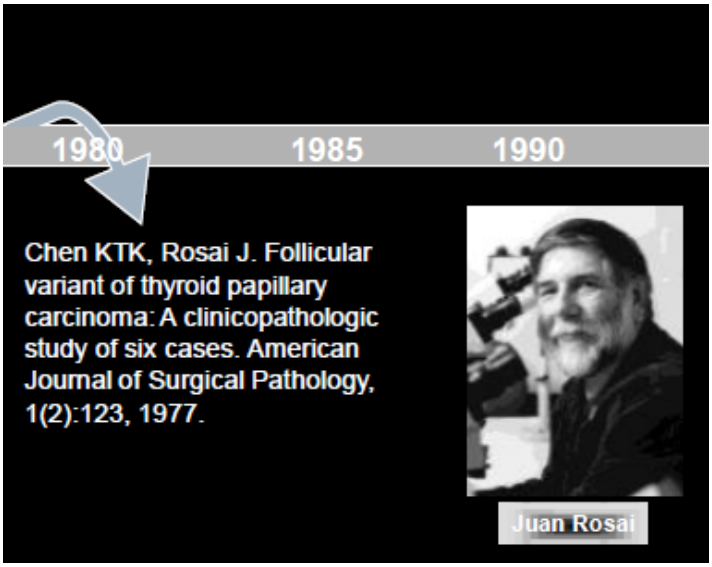
- TNM
- Age, Grade, Extent of disease and Size – AGES




Papillary thyroid carcinoma, Follicular Variant


Nuclear Features of PTC
Nuclear features:
1. Size and Shape
Enlargement
Elongation
Overlapping
2. Membrane Irregularities
Irregular contours
Grooves
Pseudoinclusions
3. Chromatin Characteristics
Chromatin clearing
Margination of chroma-
tin to membrane
Glassy nuclei
Absent/insufficiently expressed (0)
Present/Sufficient (1)
D. Gorski.- Sci Bas Med.- 2016.- 4

Follicular Variant of PTC



Papillary thyroid carcinoma

Variant of papillary thyroid carcinoma

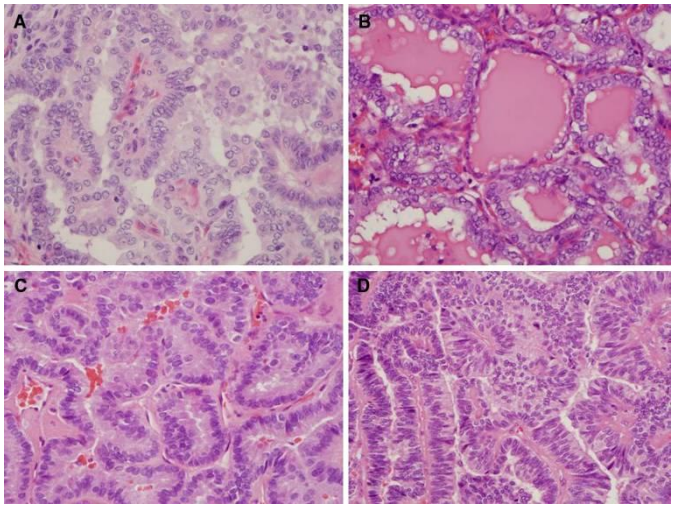
- Conventional
- Follicular variant
- Papillary microcarcinoma
- Tall cell
- Oncocytic
- Columar cell
- Diffuse sclerosing
- Solid
- Clear cell
- Cribriform morular
- Macrofollicular
- PTC with prominent hobnail features
- PTC with fasciitis-like stroma
- Combined papillary and medullary carcinoma
- PTC with dedifferenatiation to anaplastic carcinoma

R.Lloyd. H&N Path 2011.- 5(1).- p.51-56

PROGNOSIS			
Better	*Worse*	*Possibly Worse*	*Too Few Cases Reported to Assess*
PAPILLARY THYROID CARCINOMA			
Encapsulated variant	Tall cell variant	Follicular variant	PTC with lipomatous stroma
Cystic variant	Columnar variant	Solid variant	PTC with fasciitislike stroma
Microcarcinoma variant	Diffuse sclerosis variant	Oncocytic (Hürthle cell) variant	Myxoid variant
Macrocarcinoma variant	Diffuse macrofollicular variant	Associated with Graves disease	Cribriform variant
	Insular cell variant		
	PTC with de-differentiation		
FOLLICULAR THYROID CARCINOMA			
	Oncocytic (Hürthle cell) variant		
	Insular cell variant		

Li Volsi et al 1995

Papillary thyroid carcinoma



R.Lloyd. H&N Path 2011.- 5(1).- p.51-56

Papillary thyroid carcinoma

Mutation status & histology

BRAF – like : conventional and solid
RAS –like : follicular PTC

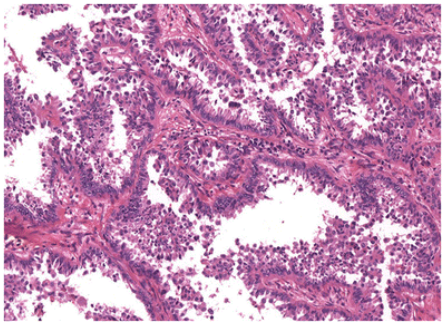
BRAF-like – extra-thyroid extension
RAS – like – metastases

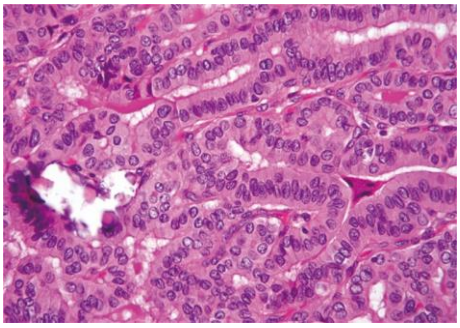
Soares P. et al. Virch Arch.- 2014.- 464.-p.363-346

Papillary thyroid carcinoma

Most aggressive variants of PTC:

Tall cell variant of PTC
Hobnail variant of PTC





Nath MC, Erickson LA. Adv Anat Pathol. 2018 25(3):172-179.

Papillary thyroid carcinoma

Aggressive variants of PTC:

Columnar cell variant of PTC
Solid variant of PTC
Diffuse sclerosing variant of PTC

…But still not universally accepted…

Papillary thyroid carcinoma

Other poor prognostic factors:

1. Vascular invasion
2. High mitotic activity
3. Necrosis

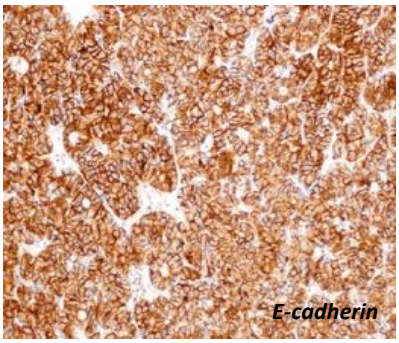
The variant of PTC doesn't matter

Papillary thyroid carcinoma

IHC prognostic markers:

1. *E-cadherin*
2. *Beta-catenin*
3. *Bcl-2*
4. *p53*
5. *Ki-67*
6. *Galectin-3*

HBME-1
CITED-1 etc.
(some authors)



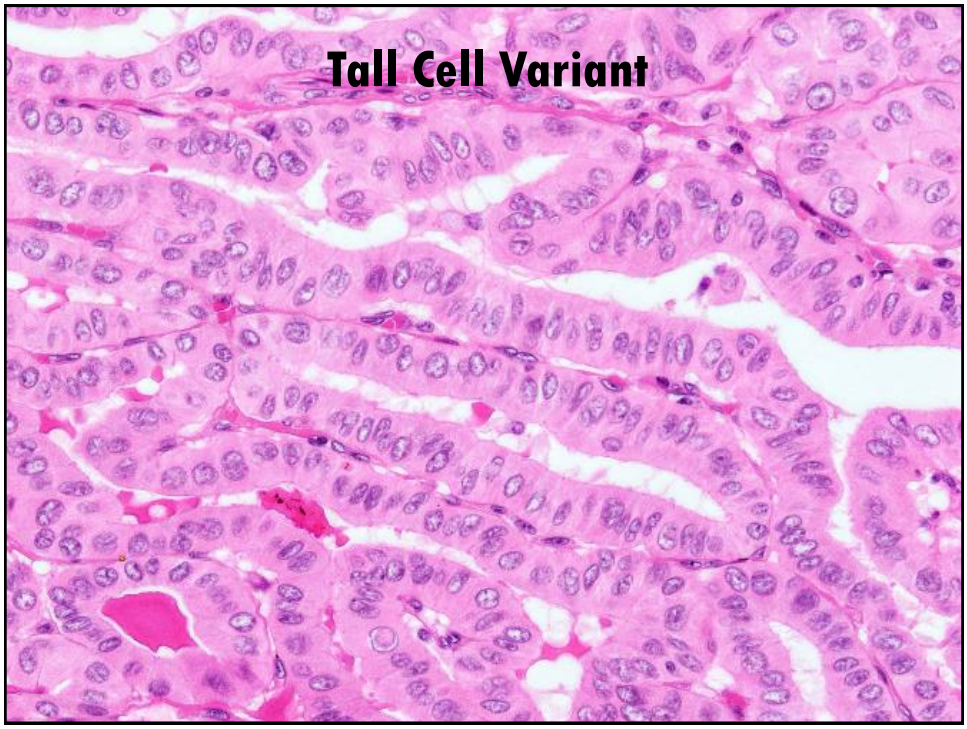
A.Ceyran et al. Int J Exp Path. 2015.- 8(4).- p. 3670–80

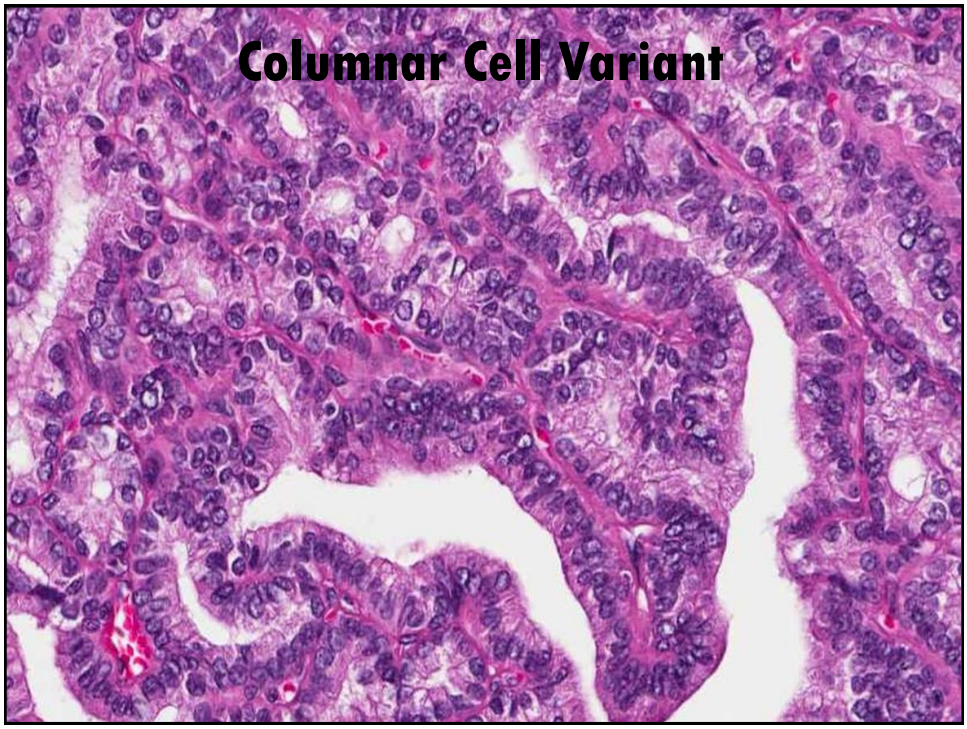
Now some pictures of PTC !

Review

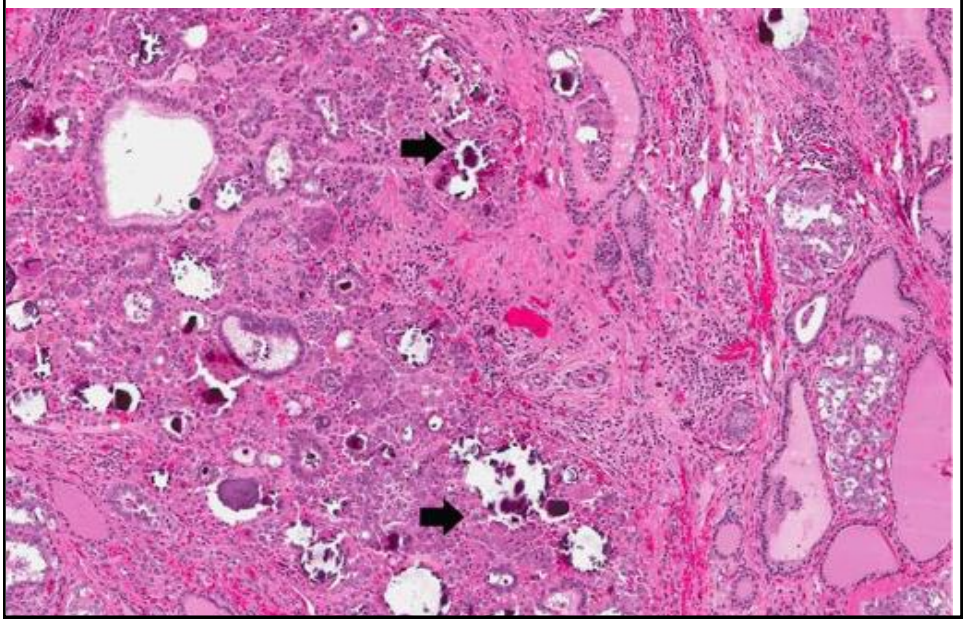
Aggressive variants of follicular cell derived thyroid carcinoma; the so called 'Real Thyroid Carcinomas'

Zubair Baloch,[1] Virginia A LiVolsi,[2] Rashmi Tondon[2]

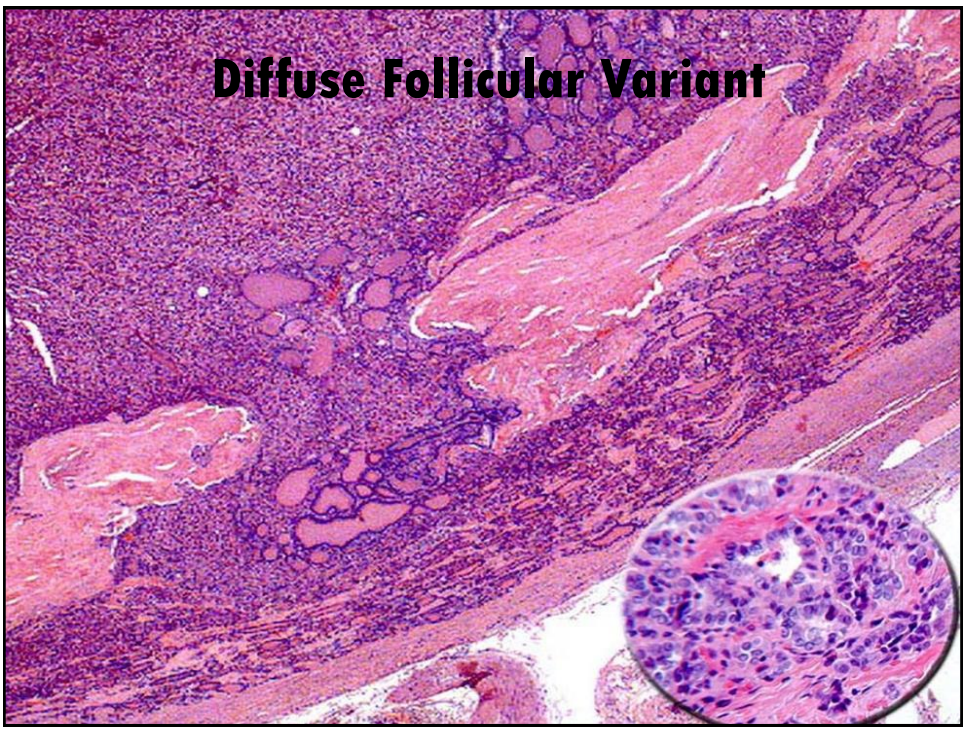

Tall Cell Variant

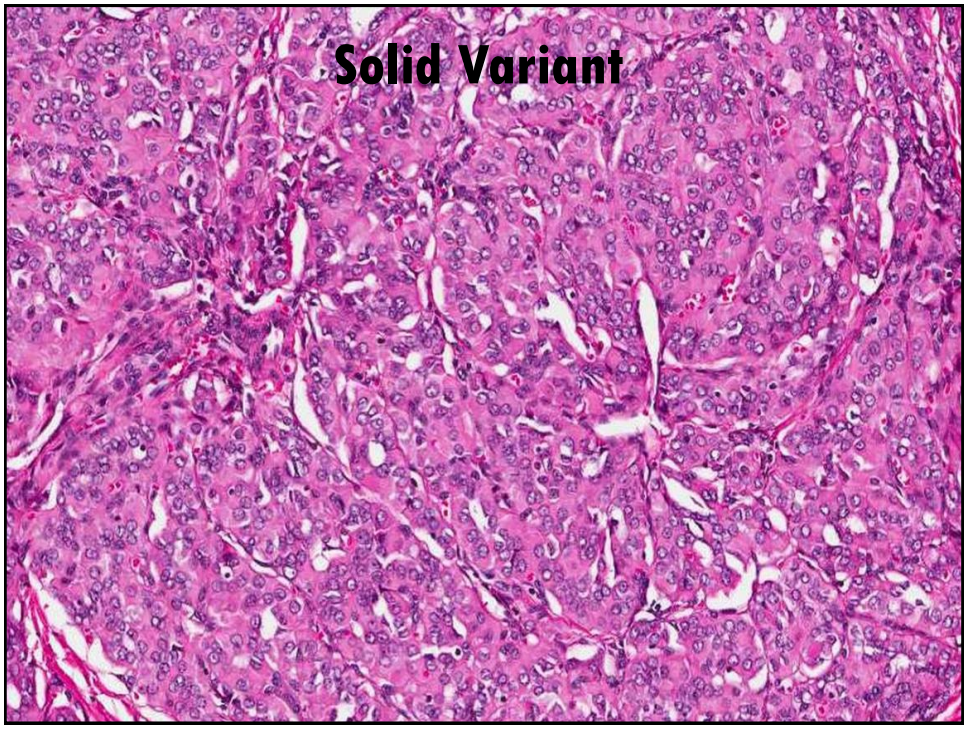

Columnar Cell Variant

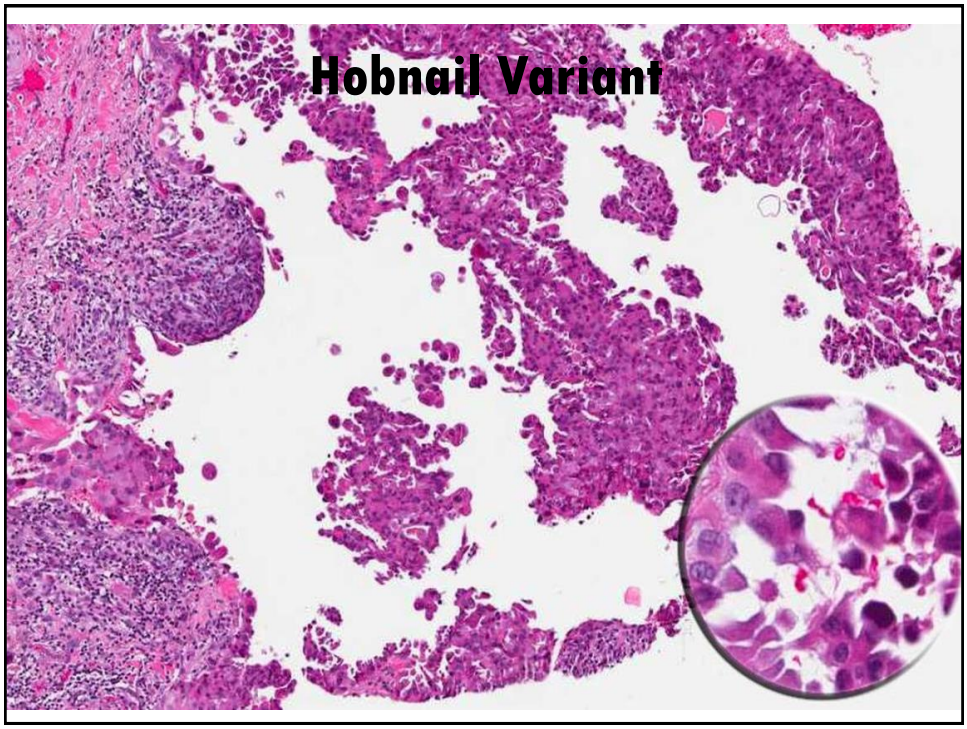
Diffuse Sclerosing Variant



Diffuse Follicular Variant




Solid Variant


Hobnail Variant

Follicular thyroid carcinoma

1. FTC is considered to be more malignant than PTC
2. M : F = 1 : 3, Age 40-60
3. Rarely associated with radiation exposure
4. LN MTS – very uncommon (not like PTC)
5. Distant (Bone, Lung) MTS – common (not like PTC)

6. Hurtle cell follicular carcinoma is the separate entity

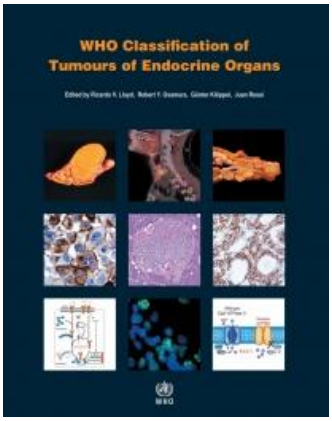
7. FT-UMP is the new entity (между аденомой и раком)
8. WDT-UMP is also new entity (между папиллярным и фолликулярным раками)

Follicular thyroid carcinoma

1. About 10-15 % of thyroid malignant tumors
2. Combined vascular and capsular invasion – worse prognosis
3. Age over 50 years old – worse prognosis
4. Type of surgery and radioiodine therapy – no influence
5. Hurthle cell lesions should be considered as the separated entities!

G.Stenson et al. Endocrine.- 2016.- 53.- p.505–511

WHO Classification, 2017



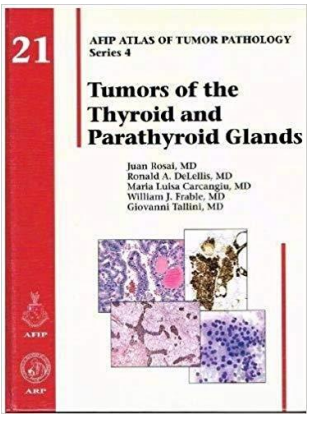
Three types:

- **Minimally invasive follicular carcinoma**
  With capsular invasion only

- **Encapsulated angioinvasive:**
  Tumors with limited vascular invasion (< 4) have a better prognosis than those with extensive vascular invasion

- **Widely invasive:**

AFIP Classification, 2016

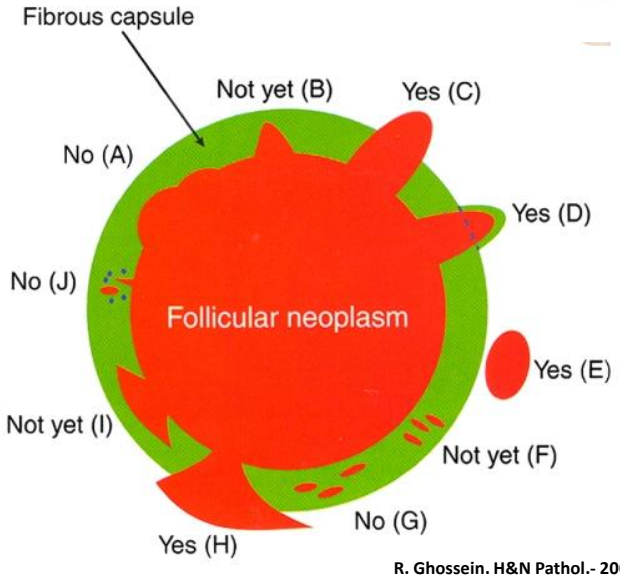


Two types :

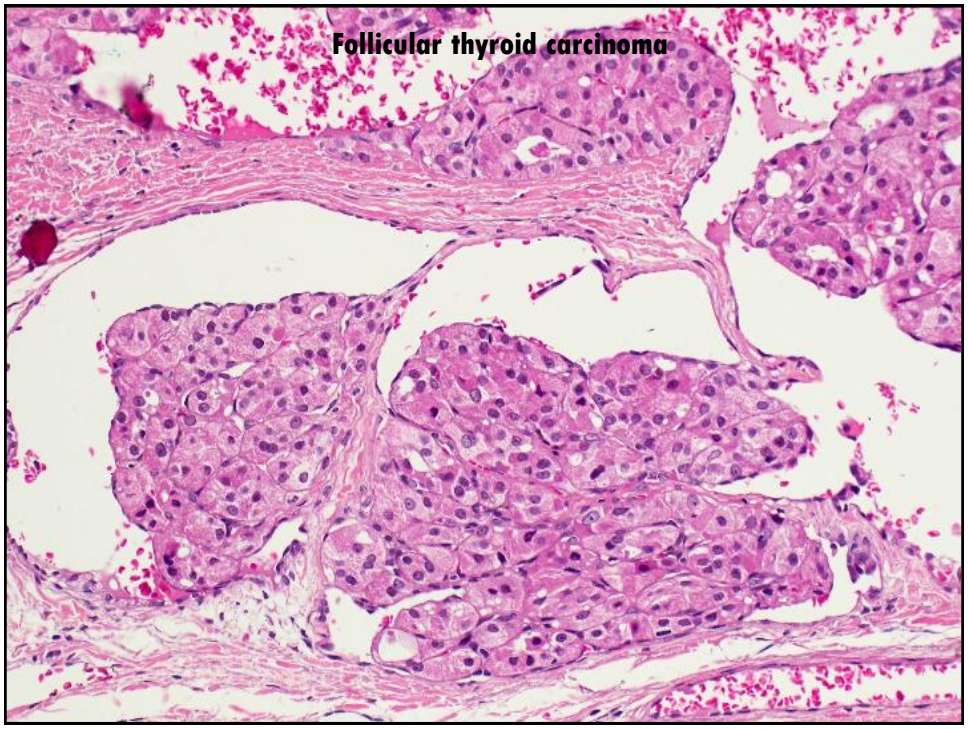
- **Minimally invasive follicular carcinoma**
  - **With capsular invasion (not obvious, need to search)**
  - **With limited (fewer than 4 vessels) vascular invasion**
  - **With extensive (4+ vessels) vascular**

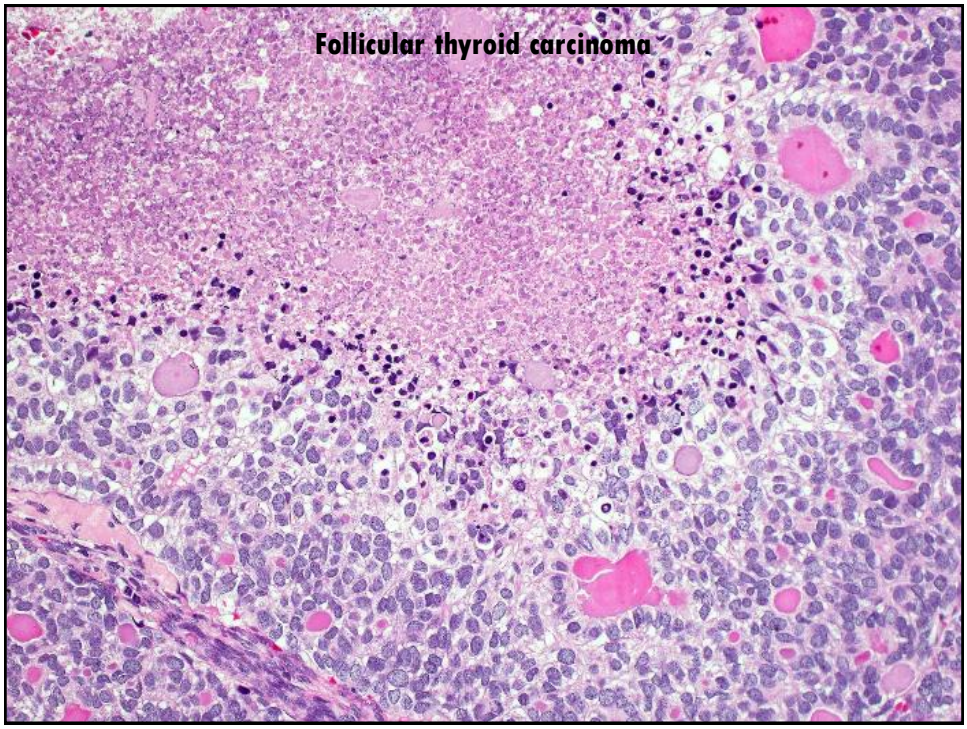
- **Widely invasive**

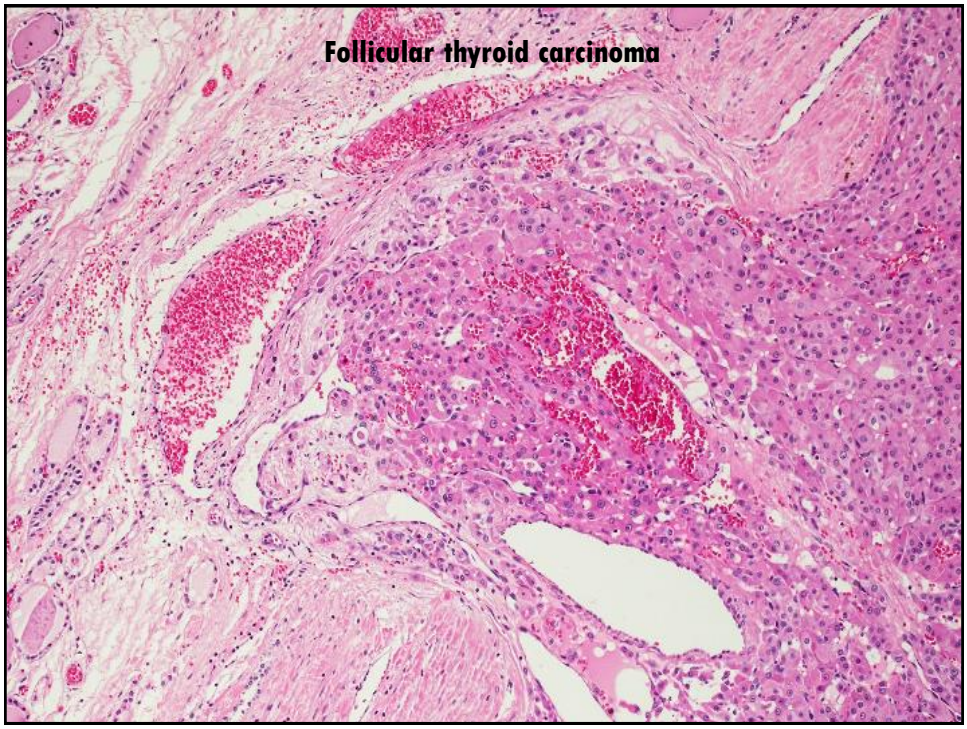
Capsular Invasion in FTC

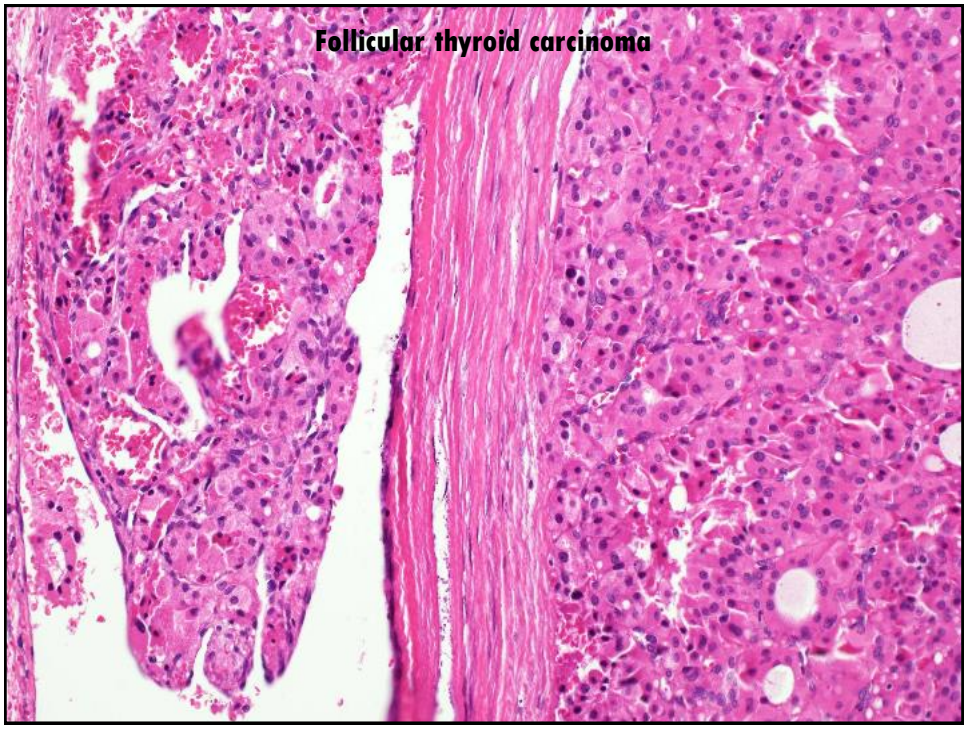


R. Ghossein. H&N Pathol.- 2009.- 3(1).-p. 86–93.




Follicular thyroid carcinoma

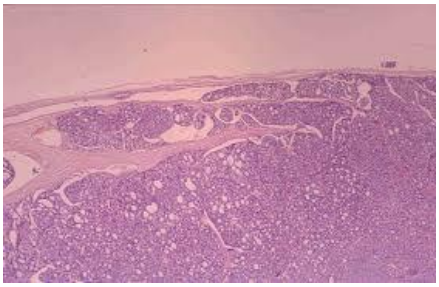

Follicular thyroid carcinoma



Follicular tumor – with UMP

-"**Grey zone" of thyroid follicular tumors**

- Well-circumscribed thyroid tumor
- Well or partially developed PTC-type nuclear features
- Questionable capsular or vascular invasion



Pathology Res Prac 2015.-Issue 4.-p.320-325

Hurthle Cell Nodules

- **Hyperplasia**
- **Adenoma**
- **Papillary carcinoma**
- **Follicular carcinoma**
- **Medullary carcinoma**

Oncocytic changes is metaplasia

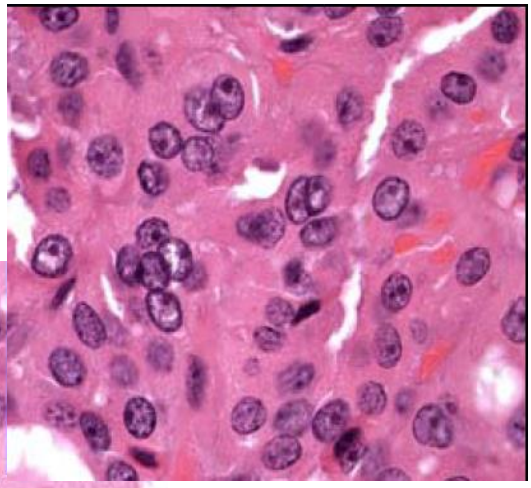
Metaplasia:

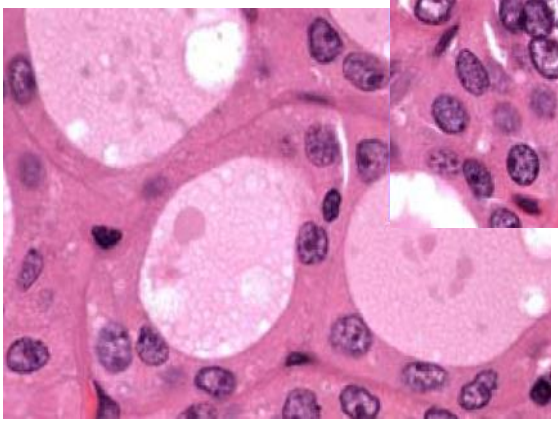
- ***An adaptive substitution of cell more sensitive to stress by other (related) cells better able to withstand the adverse environment***

- ***Reversible***

Oncocytes

- ***Nuclear features of Papillary carcinoma***





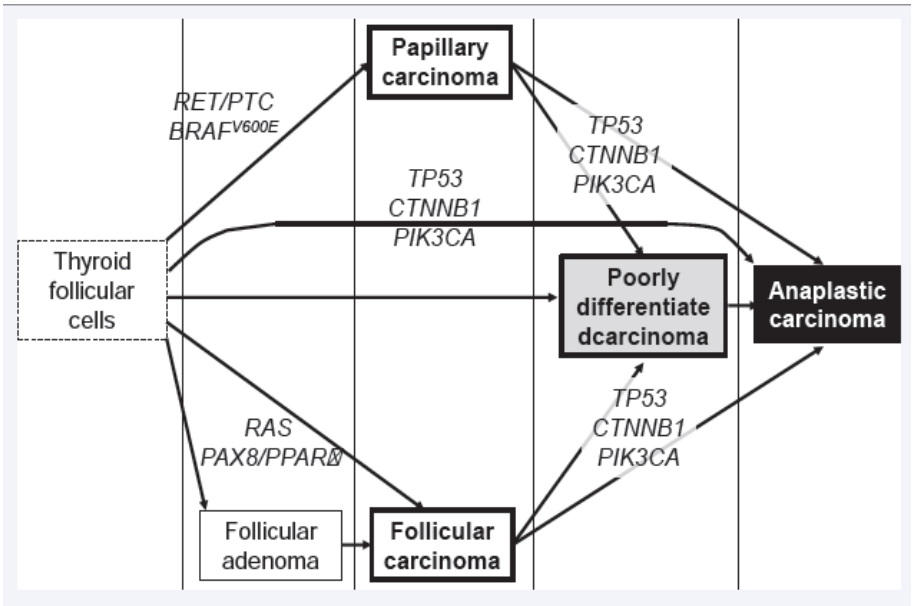
- ***Prominent nucleoli***

Oncocytic Tumors of Endocrine Tissues - Diagnosis

- ***Classify as for other lesions without oncocytic changes***
- ***Usually not difficult – capsular or vascular invasion etc.***
- ***Papillary carcinoma may be difficult, because oncocytes have hyperchromatic nuclei***

Oncocytes - Summary

- **Oxyphils are Oncocytic**
- **They can be follicular epithelial cells or C cells in thyroid**
- **They may have molecular basis**
- **They can form tumors – benign or malignant**
- **They may impact radioactive iodine uptake**
- **They are NOT a distinct cell type, but now they are distinct tumor type**



Ann Clin Pathol 3(1): 1045 (2015)

Poorly differentiated carcinoma

- Heterogeneous group – between PTC/FTC and Und.TC
- Follicular cell origination
- In WHO classification since 2004
- Prevalence – 1% (US) up to 6% (Italy)
- F >> M, m. age – 56
- The 5-year survival – 60-85%

Poorly differentiated carcinoma

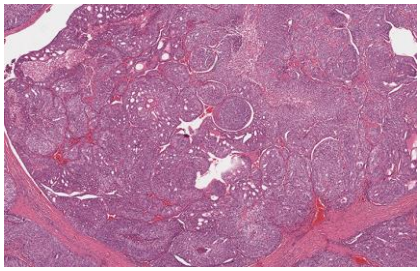
Prognostic factors in PDTC:

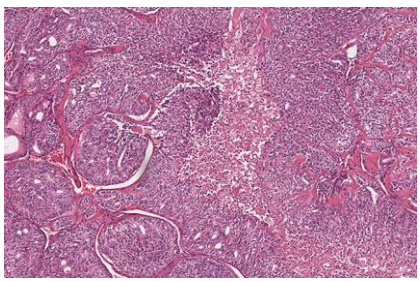
1. Age > 45 years old
2. High stage
3. Extra-thyroidal extension
4. Distant metastases
5. Response on post-operative Iodine therapy
6. SST5 -expression

Poorly differentiated carcinoma

Histology:

insular/trabecular/solid
High mitotic score
Areas of necrosis
Atypia





Turin Proposals:

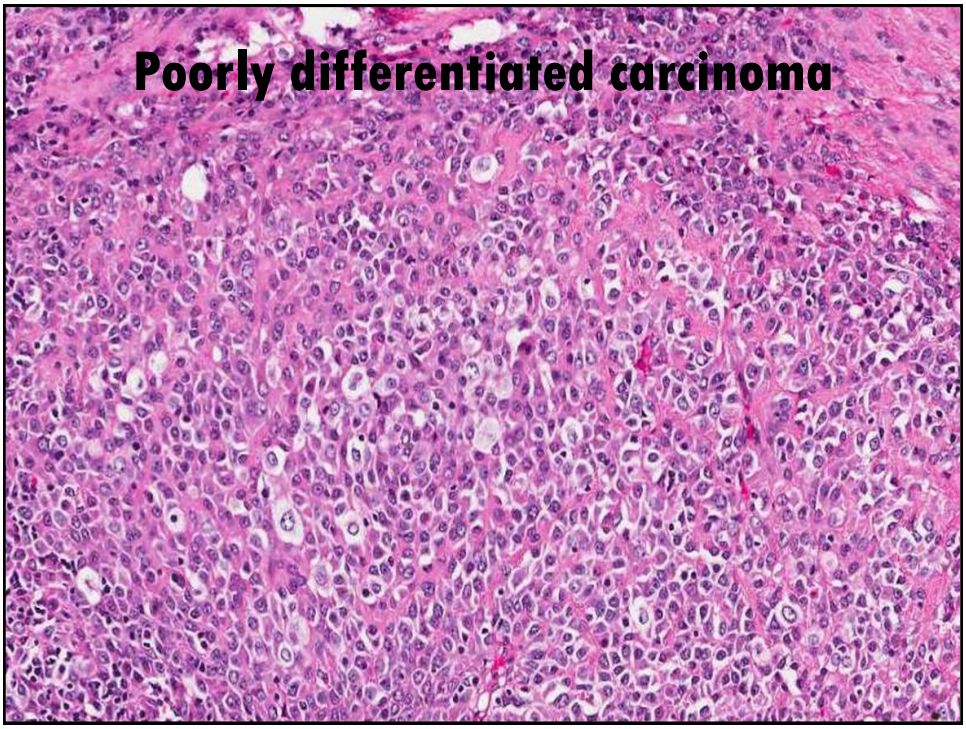
1. Pattern of growth
2. Absence of PTC nuclei
3. > 3 / 10 HPF, necrosis, hyperchromatic nuclei

Poorly differentiated carcinoma

Prognostic and predictive factors:

1. *RAS point mutations (N-RAS)*
2. *BRAF/ RET-PTC (Residual PTC)*
3. *TERT mutations*
4. *IMP3 expression*

5. *Genetic heterogenity (>2 mutations) is not a feature for PDTC!*



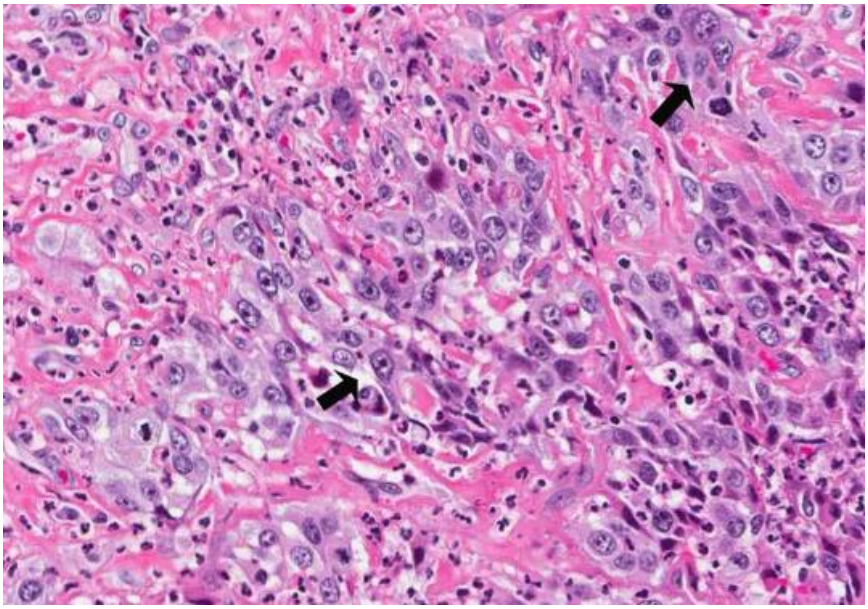
Anaplastic thyroid carcinoma

- *Follicular cell origin*
- *Extremely poor prognosis!*

IHC Prognostic Markers:

- CD70 (49% cases)
- CD27 (in tumor infiltrating lymphocytes)
- PDL-1 (29% cases)

Anaplastic carcinoma



Anaplastic thyroid carcinoma

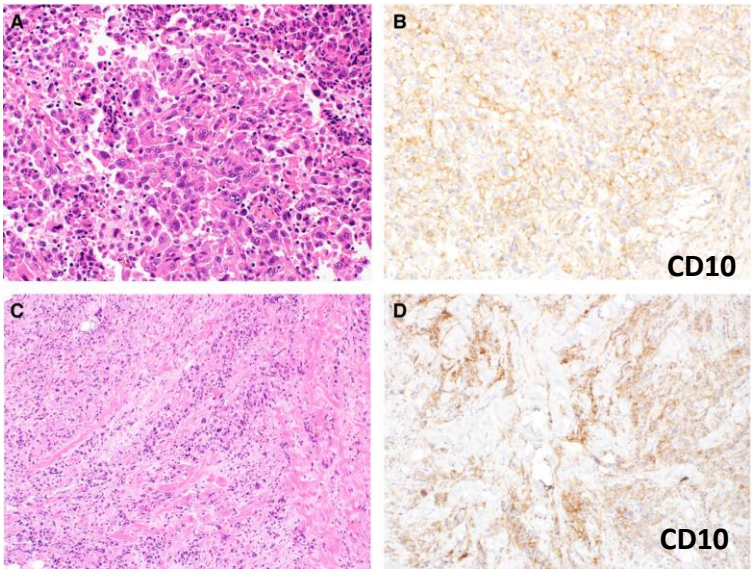
- *Follicular cell origin*
- *Extremely poor prognosis!*

Genetic alterations:

- High genetic heterogenity (>2 mutations)
- CDKN2A, CDKN2B, CCNE1, KDR, KIT, PDGFRA, CD274, JAK2, PDCD1LG2 etc.

Pozdeyev et al. Clin Cancer Res 2018.-Apr.-3

Anaplastic thyroid carcinoma



Nakazawa T, et al. Histopathology. 2018.-73(3).-p.492-499

Sir William Osler, M.D. said...

As is our pathology
so is our practice...
what the pathologist thinks today, the physician does tomorrow.

Thank you very much for the attention!