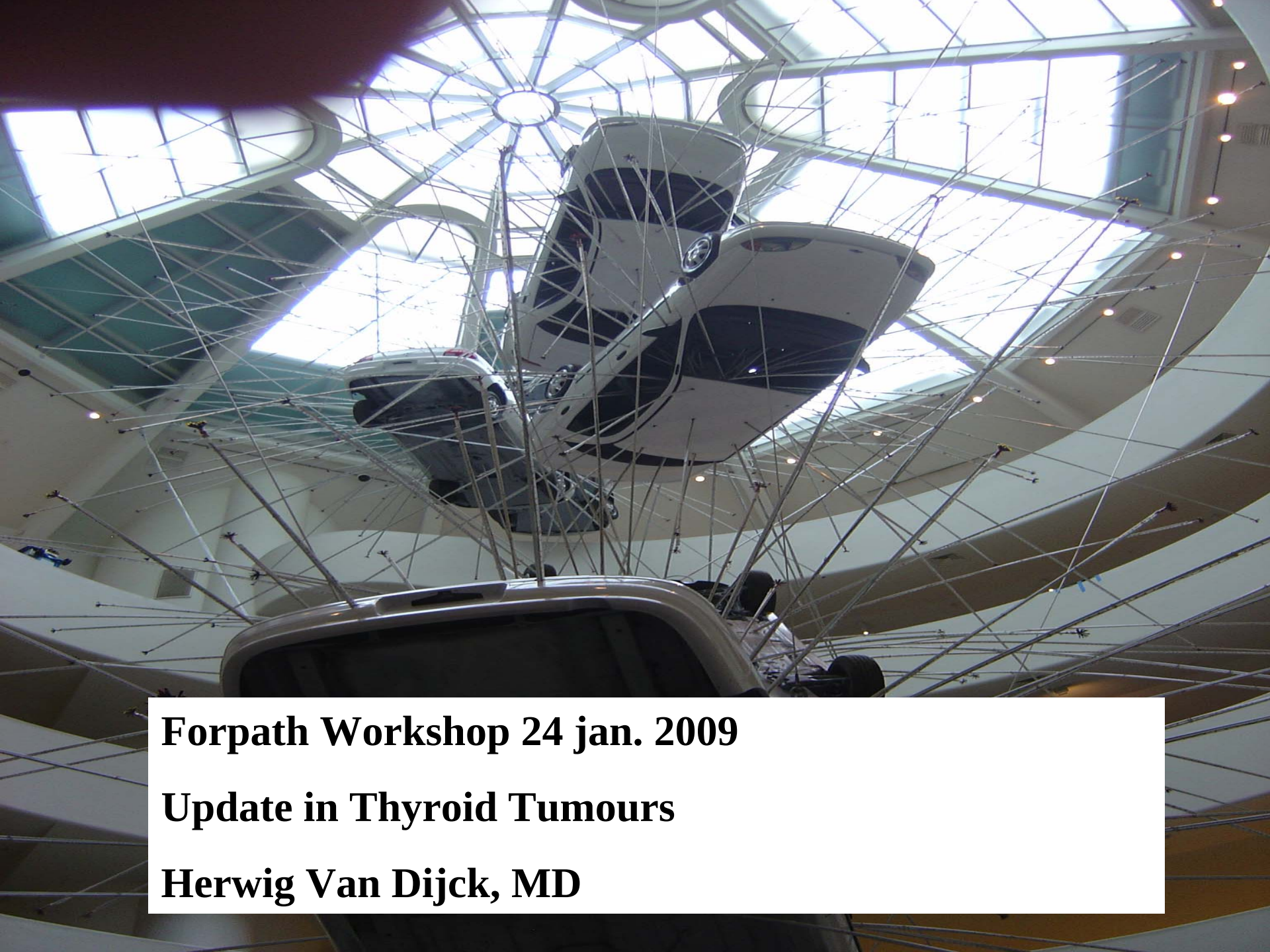


Forpath Workshop 24 jan. 2009

Update in Thyroid Tumours

Herwig Van Dijck, MD

Summary of today

- 1.**Macroscopy**
- 2.**Benign lesions**

2.1 Endocrine Organ

2.2 Terminology

2.3 AD Nodule v FA

2.4 Thyroiditis

2.5 Atypia in benign lesions

2.6 Lymph node containing thyroid tissue

- 3.**Malignant Lesions**

3.1 General remarks

3.2 Hurthle diff.

3.3 FC and FT-UMP

3.4 PTC

3.5 WD-TUMP, WD Ca

3.6 Pitfalls

3.7 Prognosis

3.8 Med Ca

3.9 PDC

3.10 UDC

3.11 Other

Summary of Part 1 bis

3.11 IHC

3.12 TNM

3.13 Meta

3.14 HTT

3.15 Conclusions of the first part

1. Macroscopy

Isthmus should be sectioned in the sagittal plane.

Arch Pathol Lab Med. 2006 Jul;130(7):1057-62.

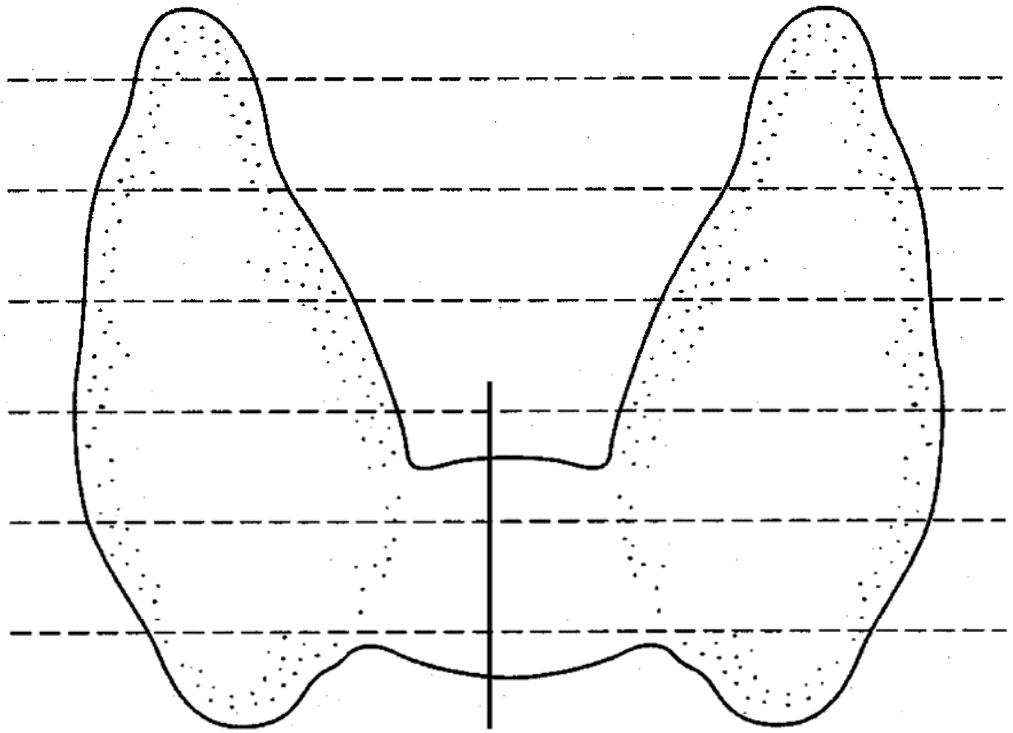
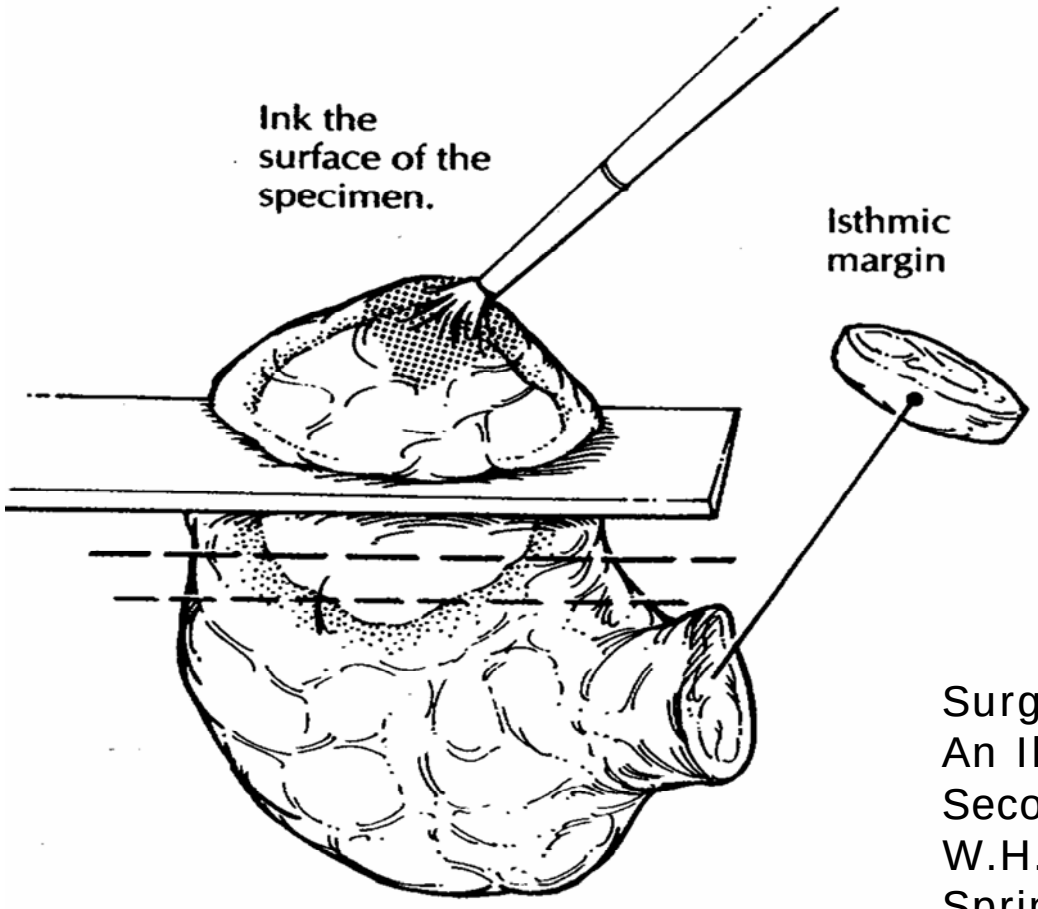


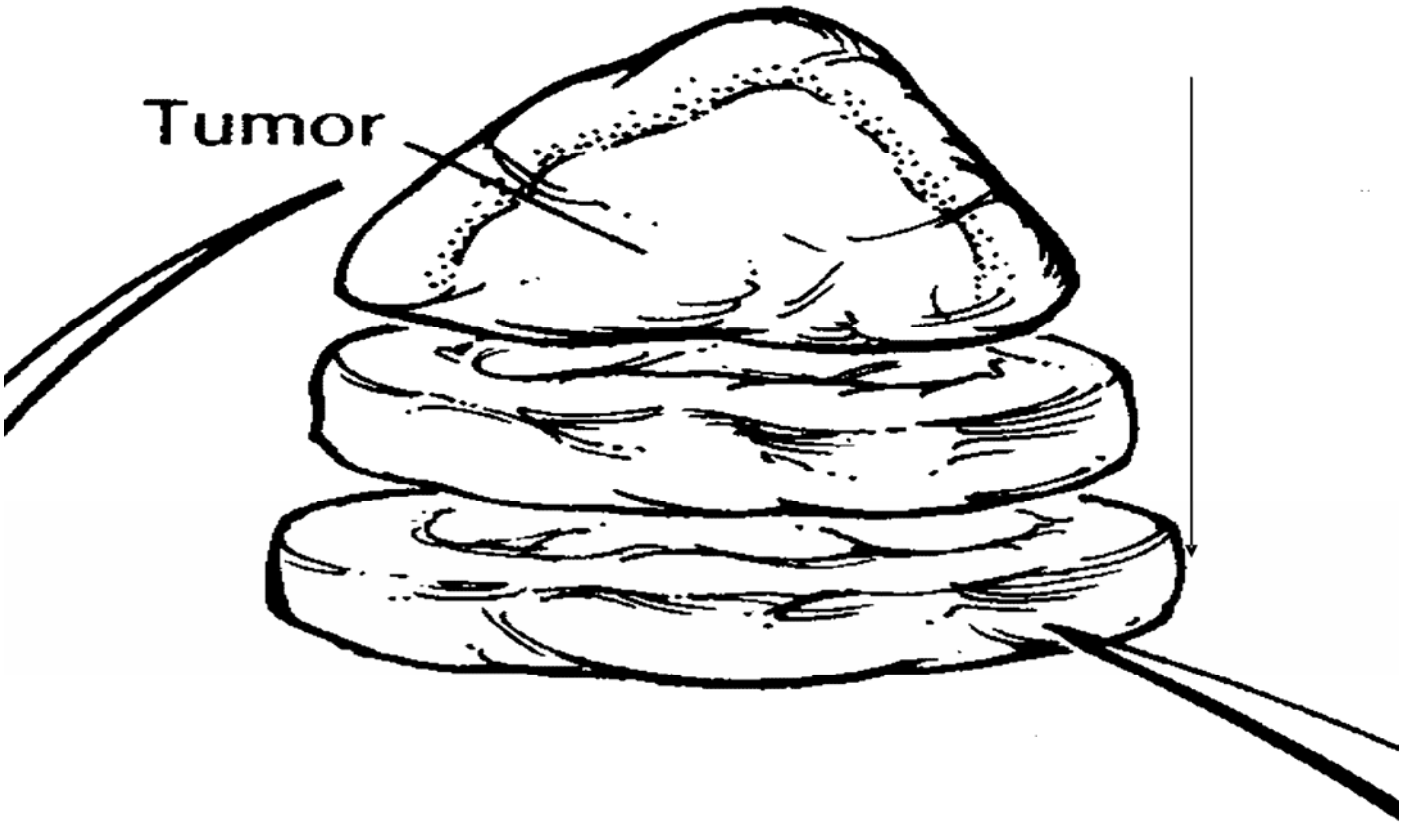
Figure 3 Where possible, the thyroid gland should be sectioned horizontally as demonstrated above.

J Clin Pathol. 2003 Jun;56(6):401-5.

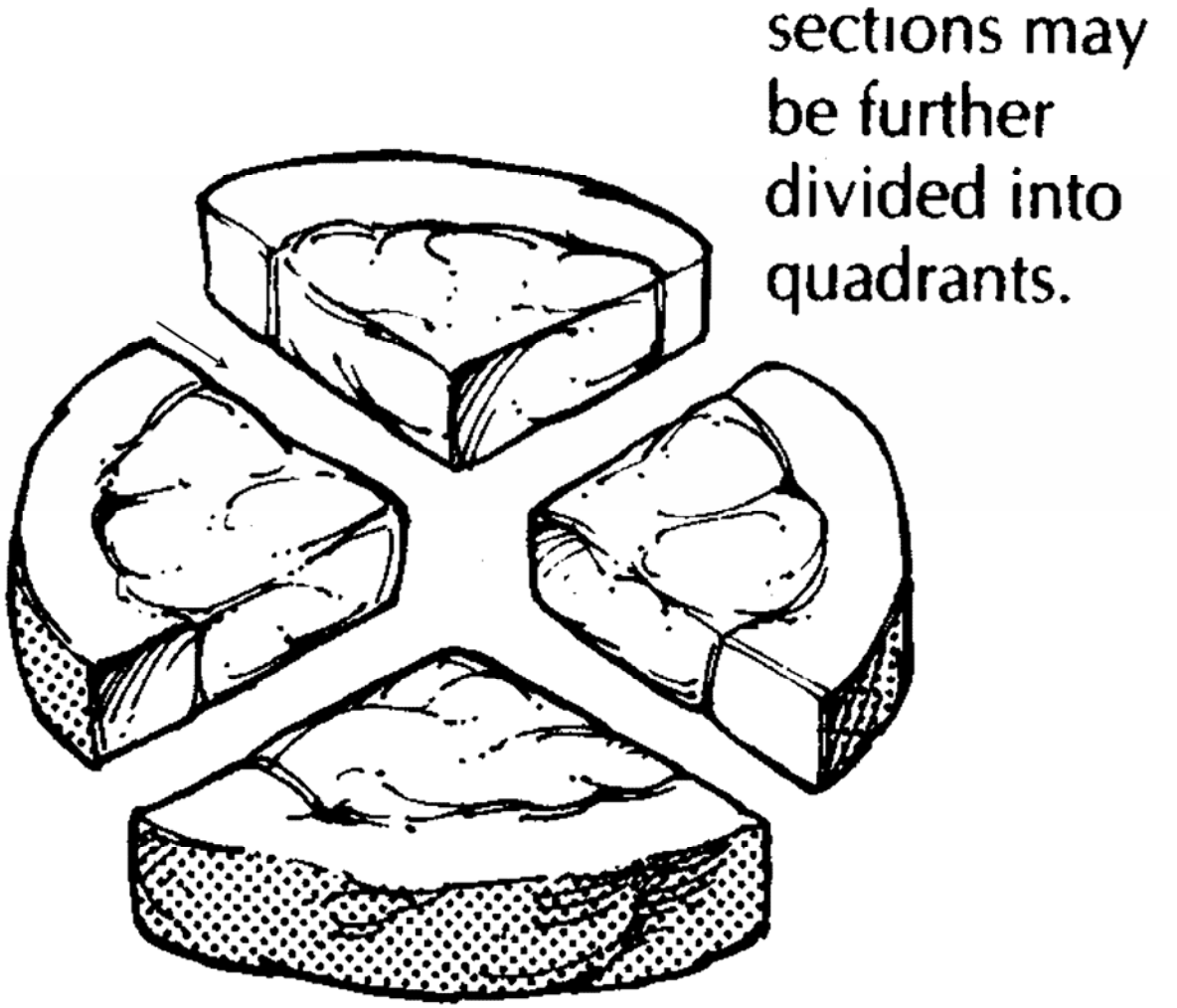


Surgical pathology Dissection
An Illustrated Guide
Second edition
W.H. Westra et al.
Springer

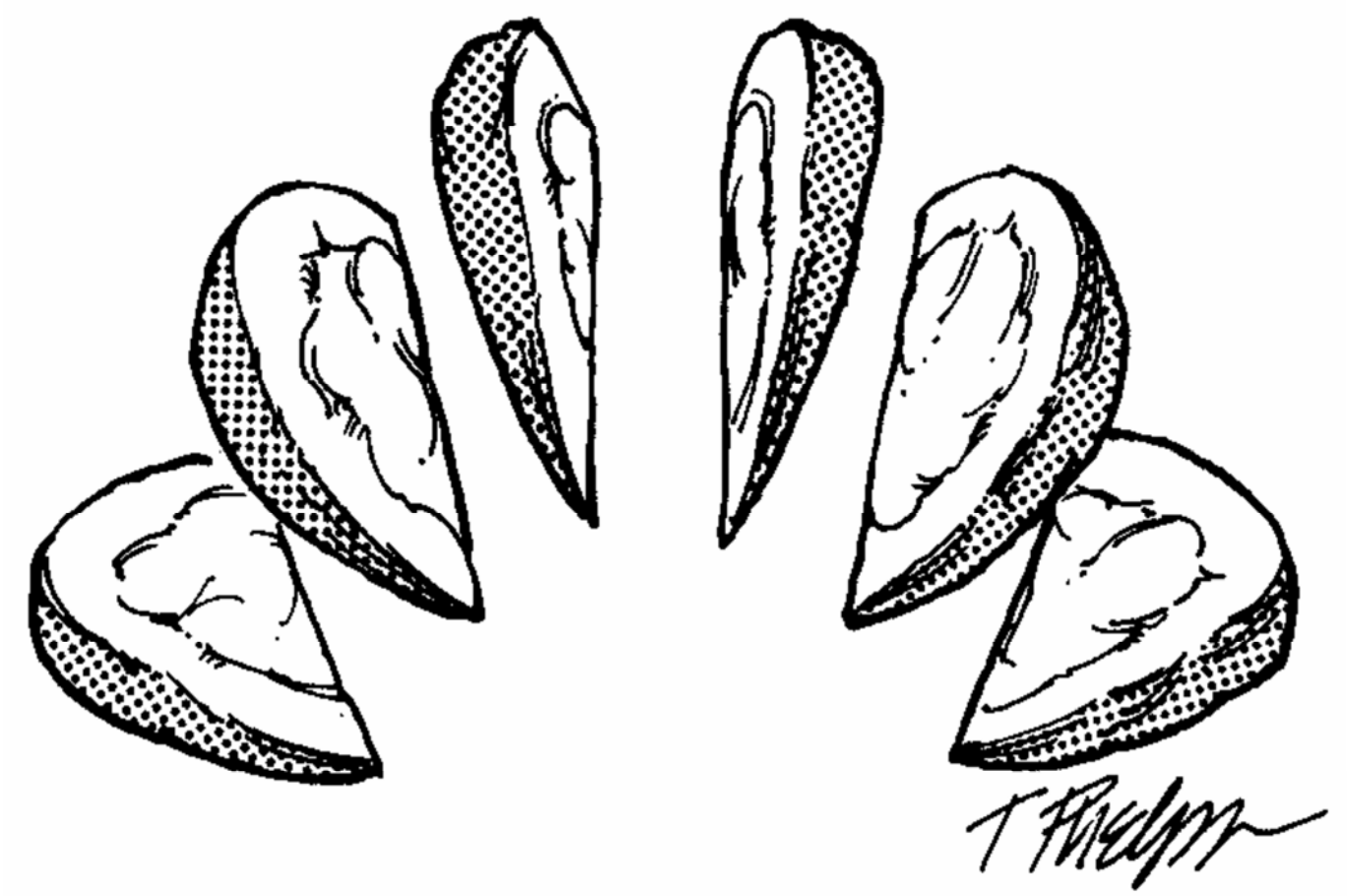
Serially sectioned from superior to inferior.



Always take the whole capsule if it is a thick capsule !



More specific sectioning of a nodule to capture the whole capsule. Like an orange.



1. Macroscopy

- Cross sections of lobes and sagittal sections of isthmus
- Nodules with a capsule *and* special looking nodules: many biopsies especially from the capsule
- *Hum Pathol. 2000 Oct;31(10):1199-201. Recommendations for the reporting of thyroid carcinoma*.

2.1 The Thyroid is an Endocrine Organ

- In endocrine organs, the presence of cellular atypia is not necessarily indicative of malignancy. Rather, large atypical cells are commonly found in reactive conditions and benign tumours, and often merely reflect hyperfunction.

  Seminars in Diagnostic Pathology, Vol 12, no 1, 1995

- There are more mitoses in benign thyroid disease than in malignant thyroid disease.

  Simoes, Paris 2006

2.2 If benign:Terminology, …? Diagnostic equals

- Adenomatous goiter
- Colloid goiter
- Nodular goiter
- Adenomatous hyperplasia

- ….

2.3 Adenomatous nodule
AJSP vol 26 no 11, 2002

- 1.Incomplete capsule: always
- 2.Variable sized follicles: always
- 3.Coarse papillary configuration : very often (Sanderson Polster)
- 4.Abundant edematous or hyalinized stroma may be possible
- 5.Chronic inflammatory cell infiltrate sometimes
- 6.Degenerative changes: very often
- 7.Frequent multiple

2.3 Follicular Adenoma WHO

- 1.Complete capsule of variable thickness
- 2.Architectural pattern and cytological features are different from the surrounding tissue
- 3.Architectural: follicular, trabecular
- 4.Cells: cuboidal, columnar, polygonal and often with dark round nuclei. Enlarged hyperchromatic nuclei may be present
- 5.60% are monoclonal!

2.3 Follicular adenoma WHO

- 6.Central portion due to delayed fixation with large and pale nuclei
- 7.Mitotic figures are rare
- 8.Often richly vascular
- 9.Focal myxoid change, subcapsular
- 10.Secondary changes: edema, fibrosis, hyalinization, haemorrhage, calcification, cartilaginous metaplasia, cyst formation, infarction, ..
- 11.Recurrence rate is very high

2.3 Follicular adenoma versus Adenomatoid nodule(s)

- FA:Growth pattern:
  normofolliculair
  macrofolliculair
  microfolliculair
- FA: Clear capsule
  - Adenomatoid nodules lack a well defined capsule
  - Adenomatoid nodules: follicules are similar to those in the surrounding tissue.

2.3 Special types of FA

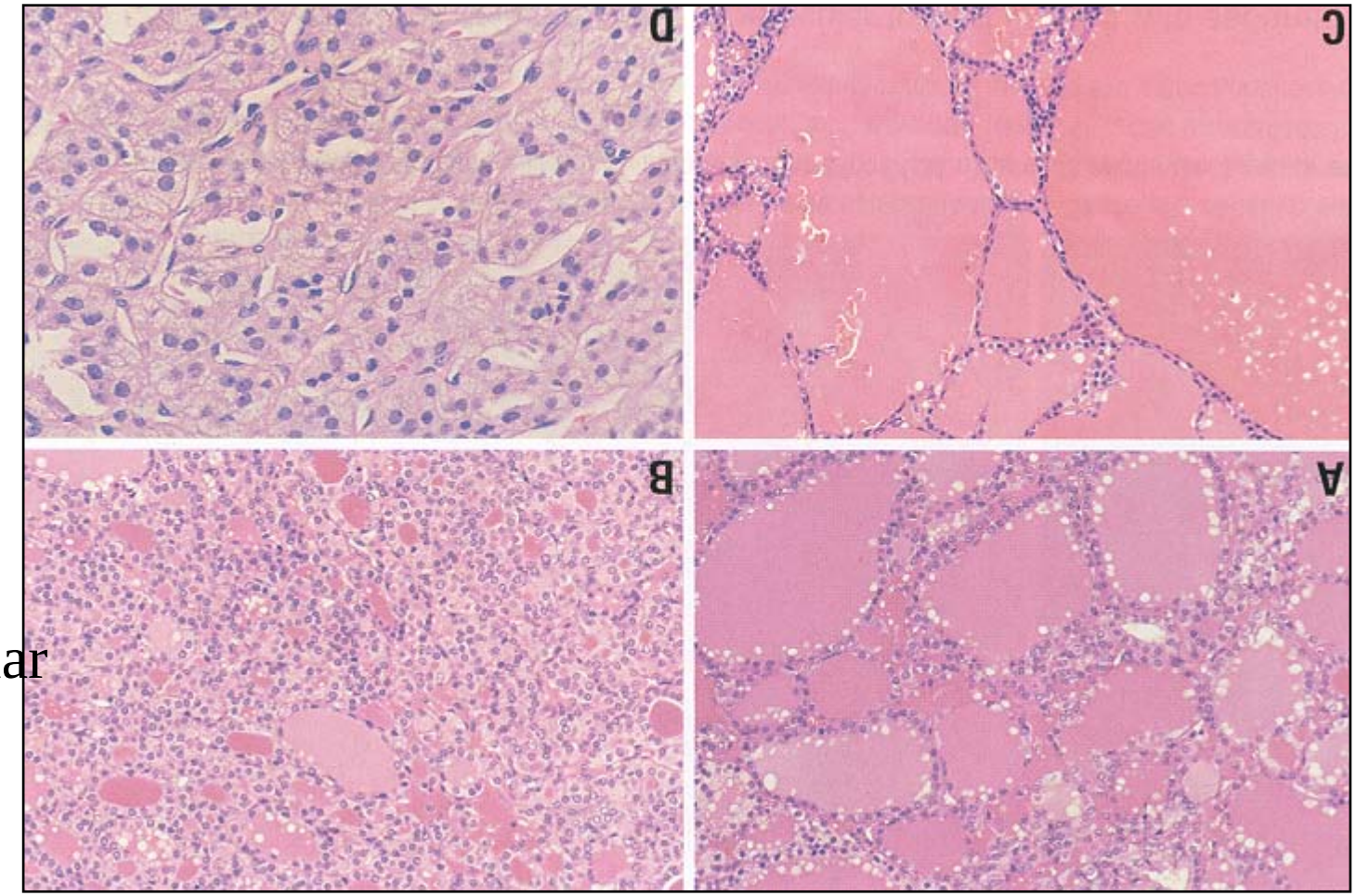
- Fetal adenoma (micro-, trabecular)
- Signet ring cell follicular adenoma
- Mucinous follicular adenoma
- Lipoadenoma
- Clear cell follicular adenoma
- Toxic adenoma (tall cells)
- Oncocytic adenoma

  (Adenomatoid oncocytic nodules often occur in Hashimoto Thyroiditis)
- Follicular adenoma with papillary hyperplasia

FA … follicular … variant

Micro

Macro

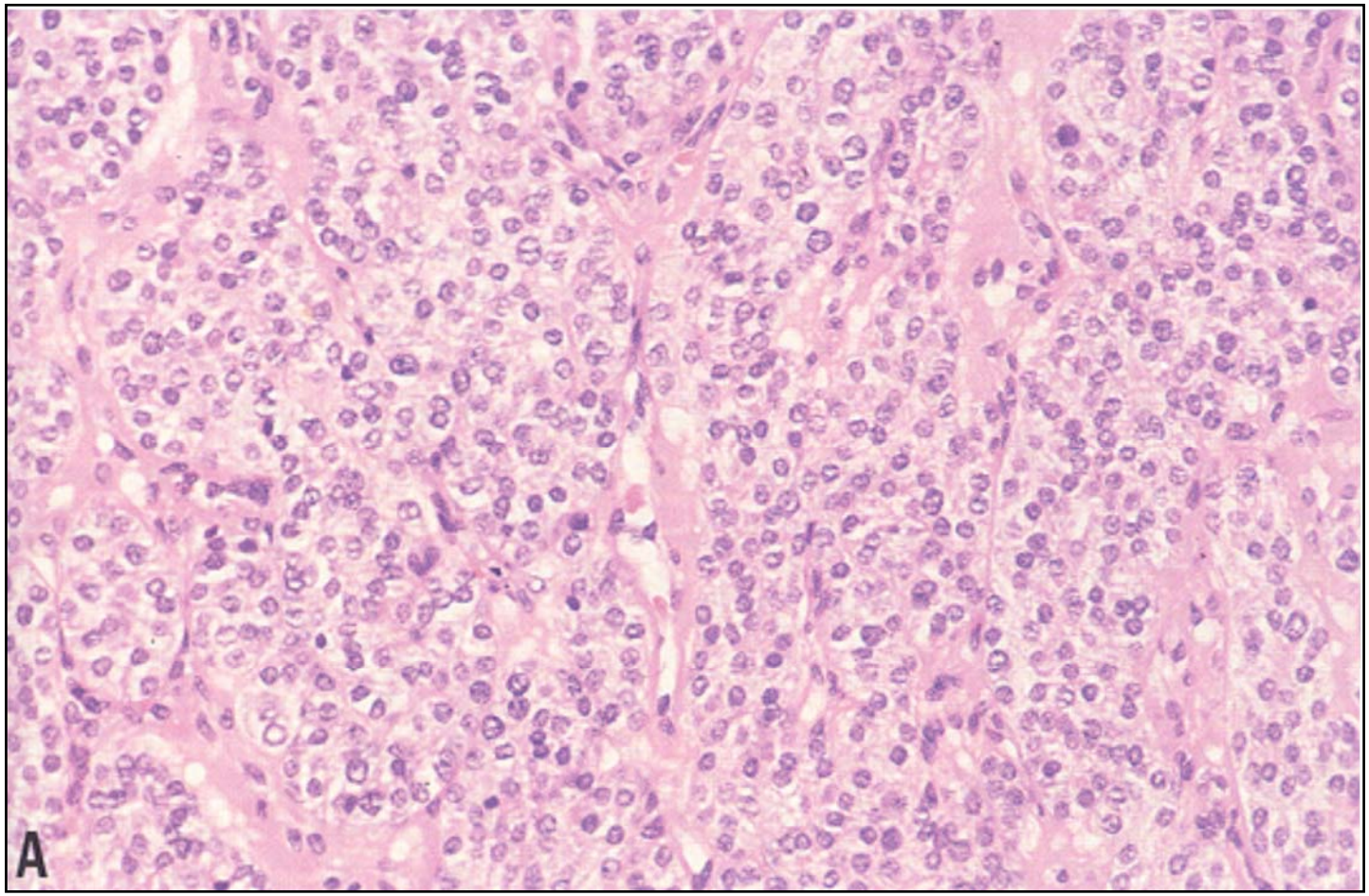


Trabecular

Normo

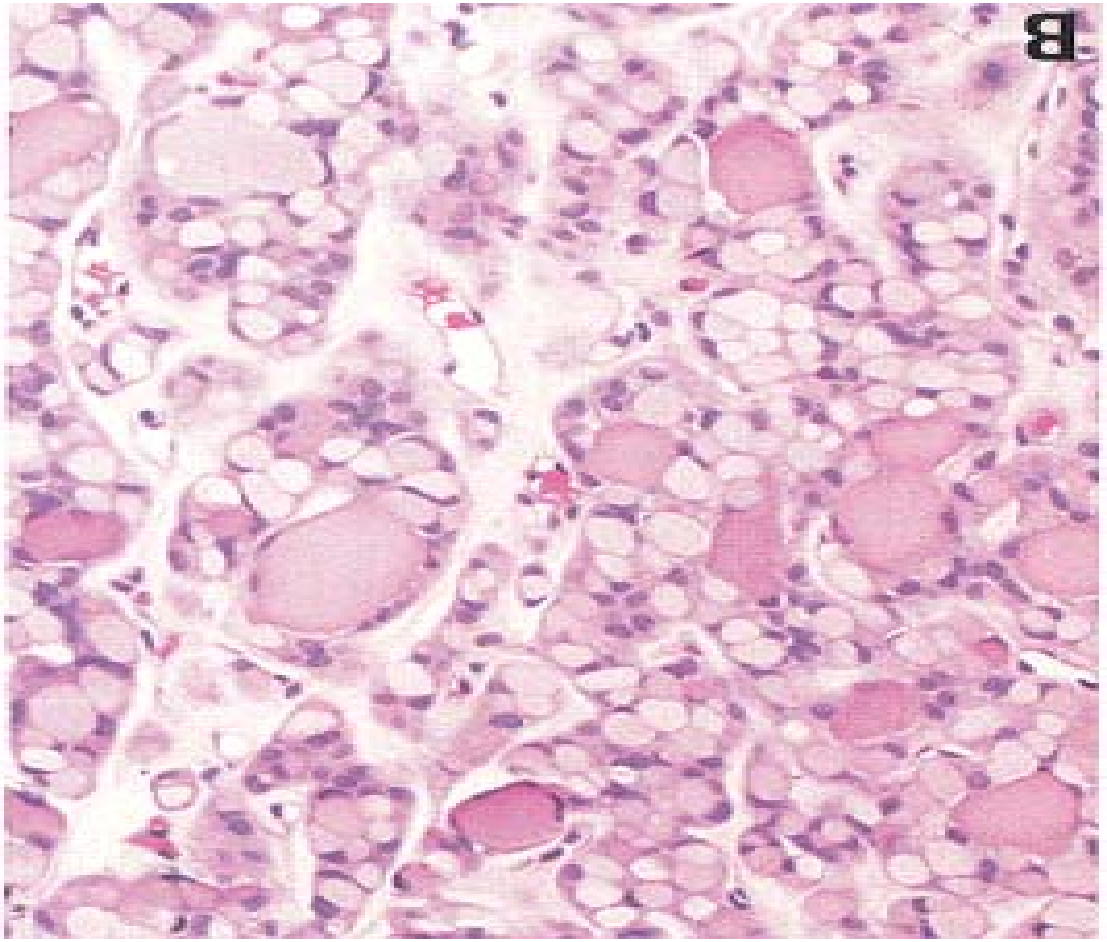
Ref. WHO

FA Embryonal



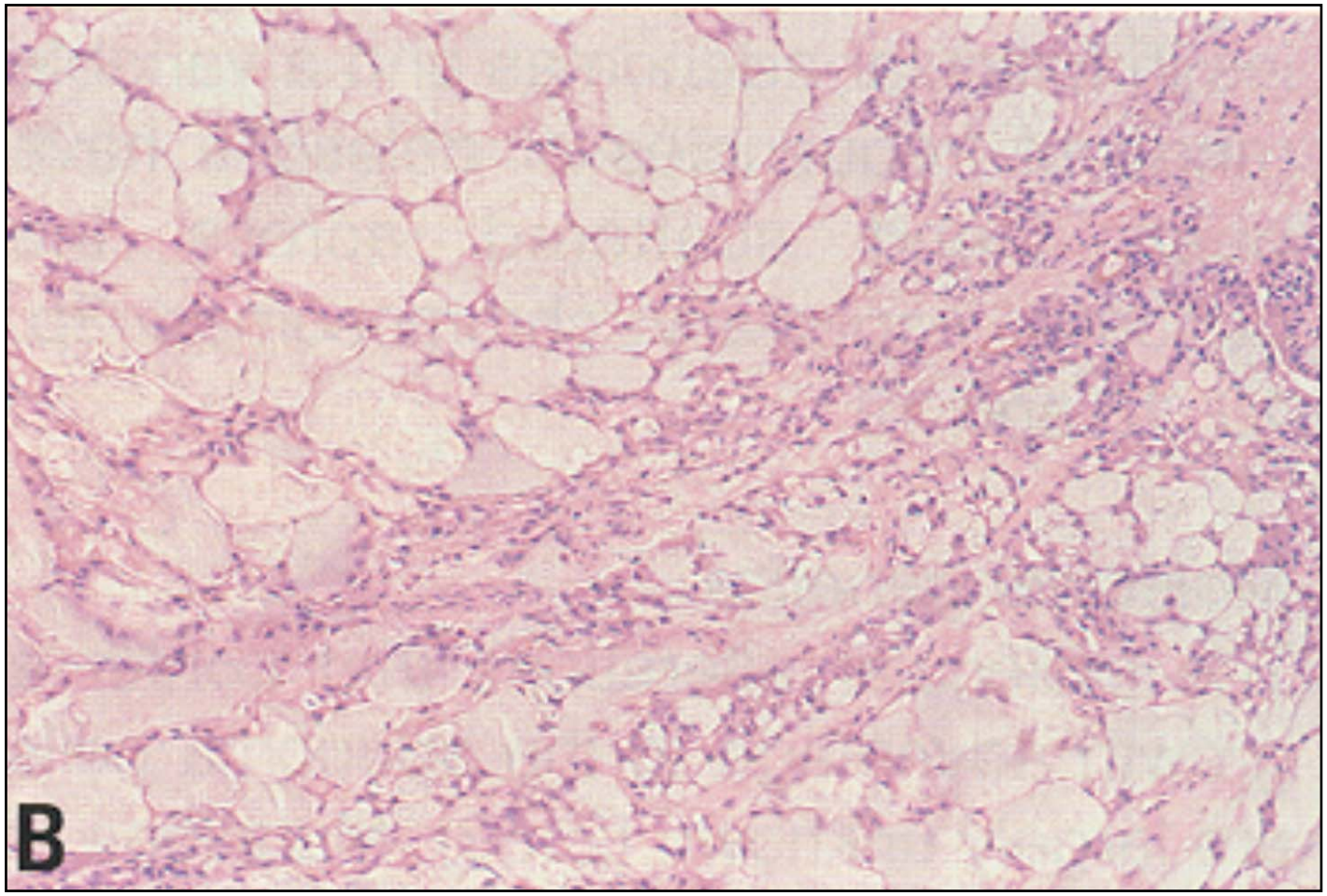
Ref. WHO

Signet ring variant FA



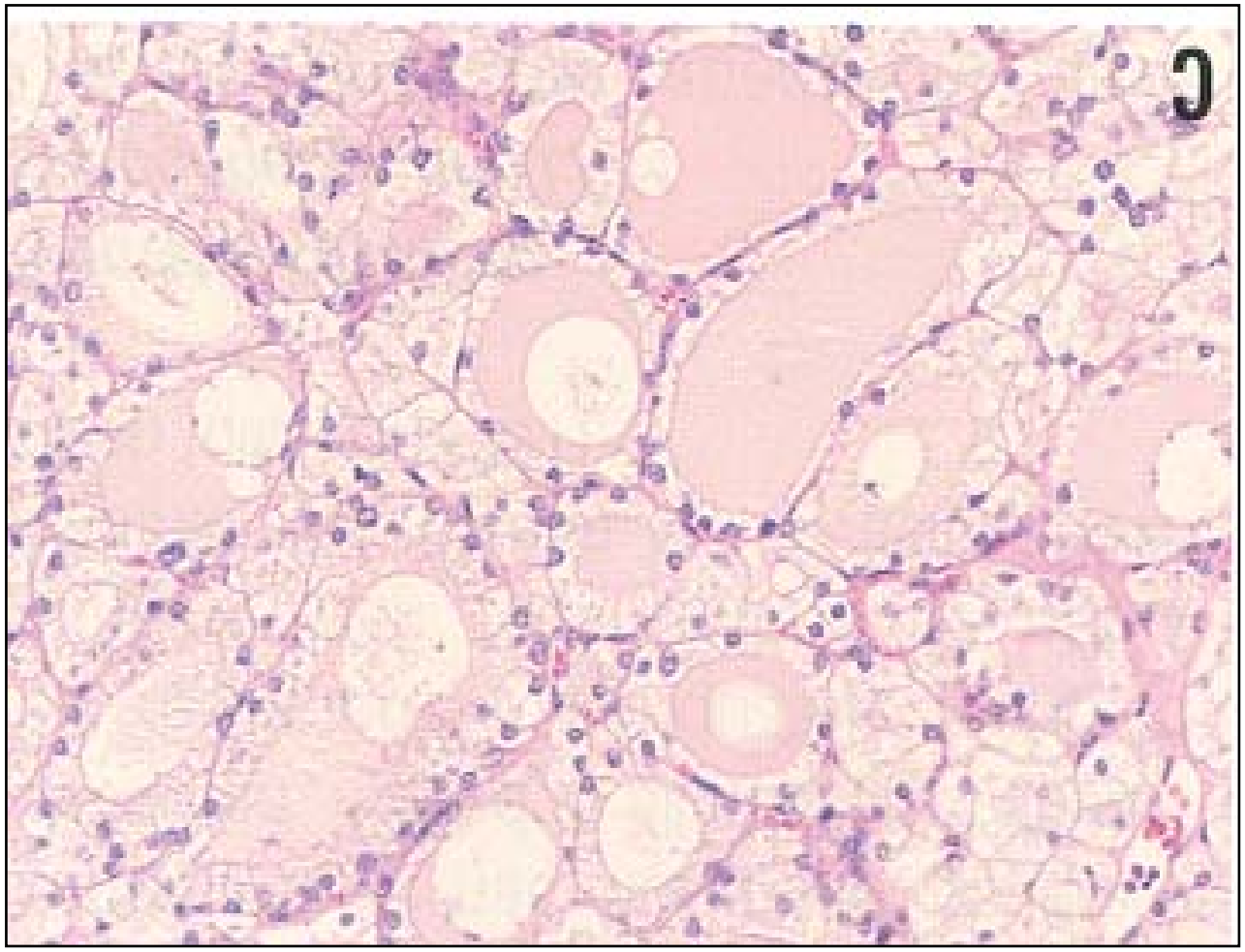
Ref. WHO

Mucinous variant FA



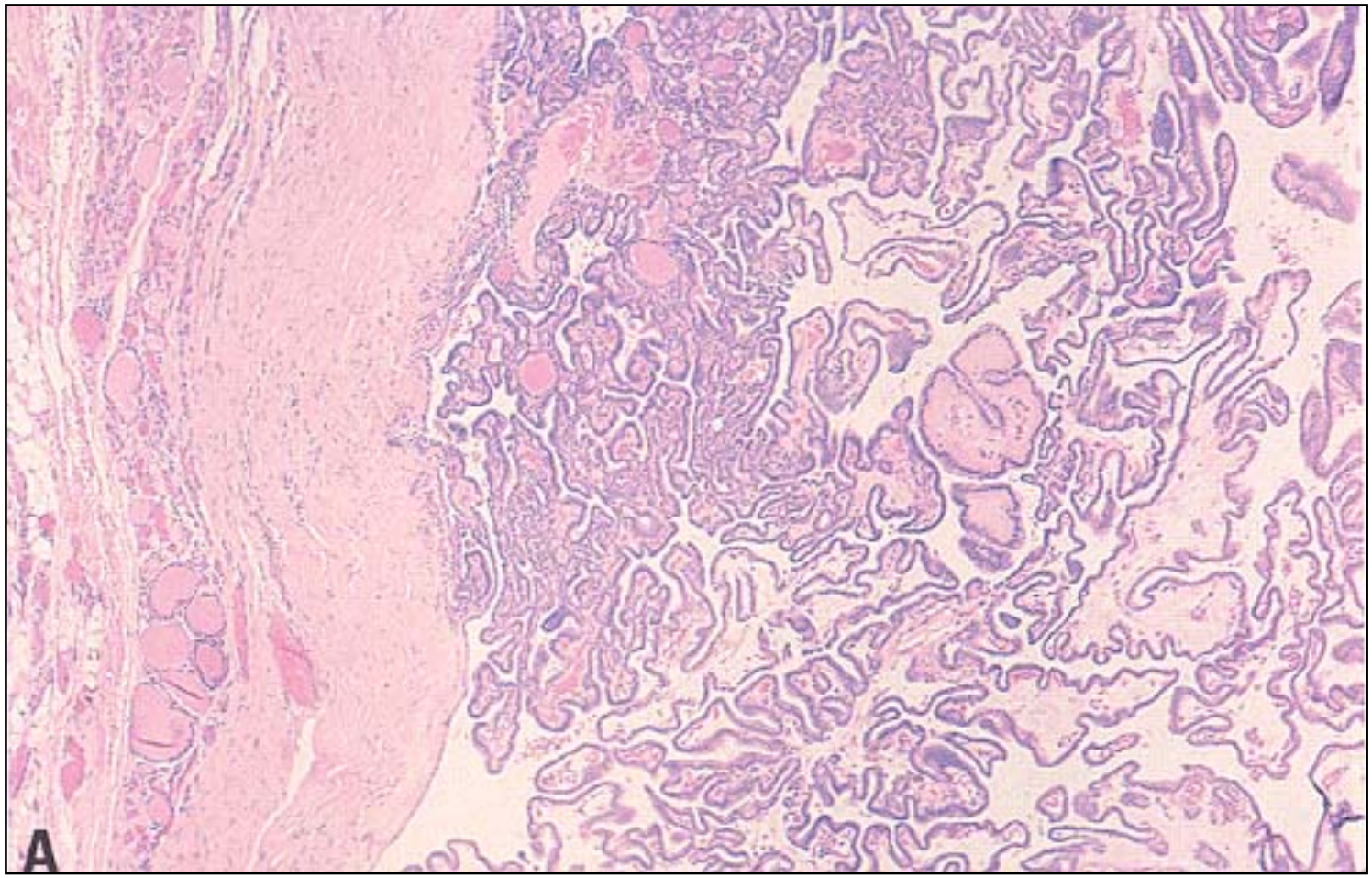
Ref. WHO

Clear cell variant FA



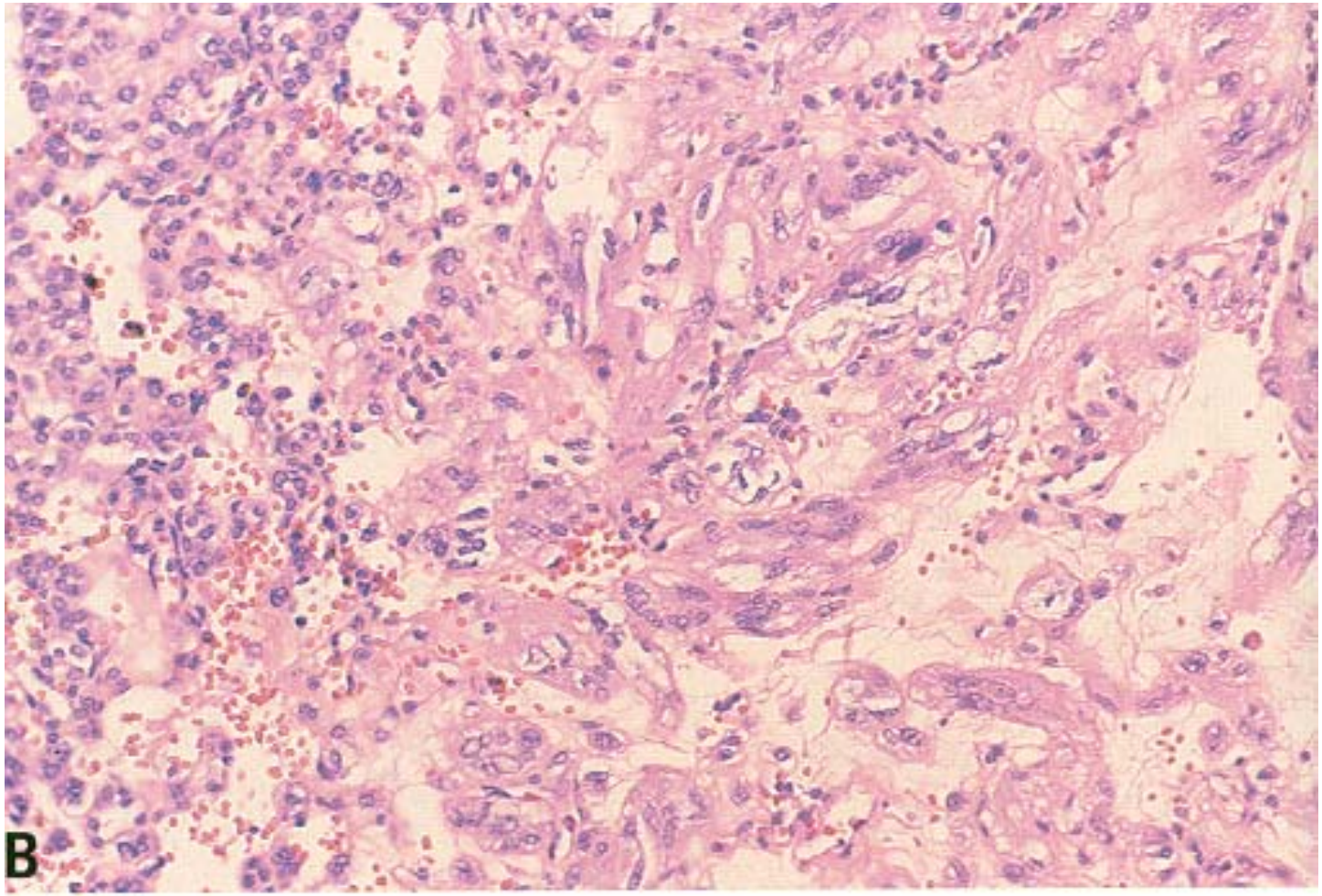
Ref. WHO

Papillary Hyperplasia FA



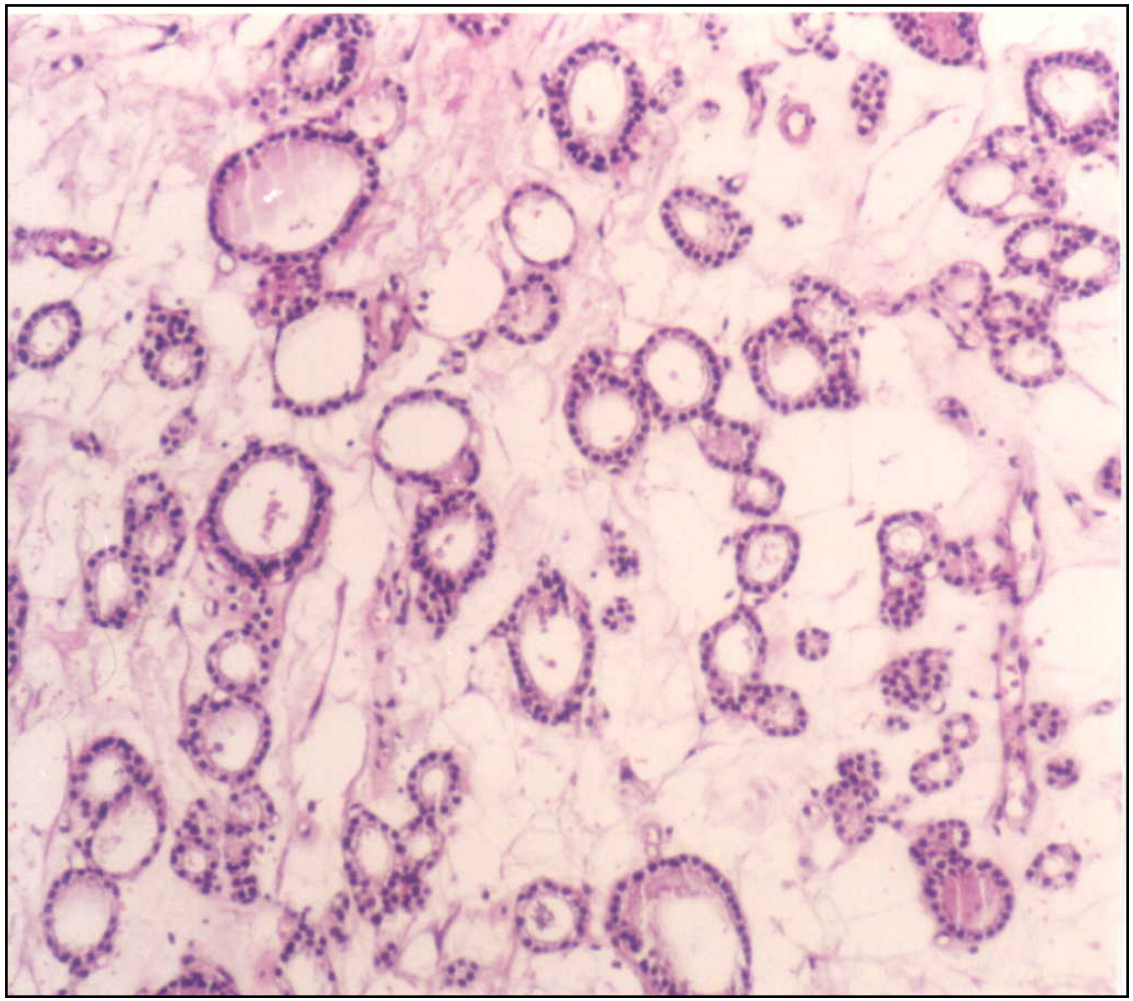
Ref. WHO

FA vascular rich with spindle cells



Ref. WHO

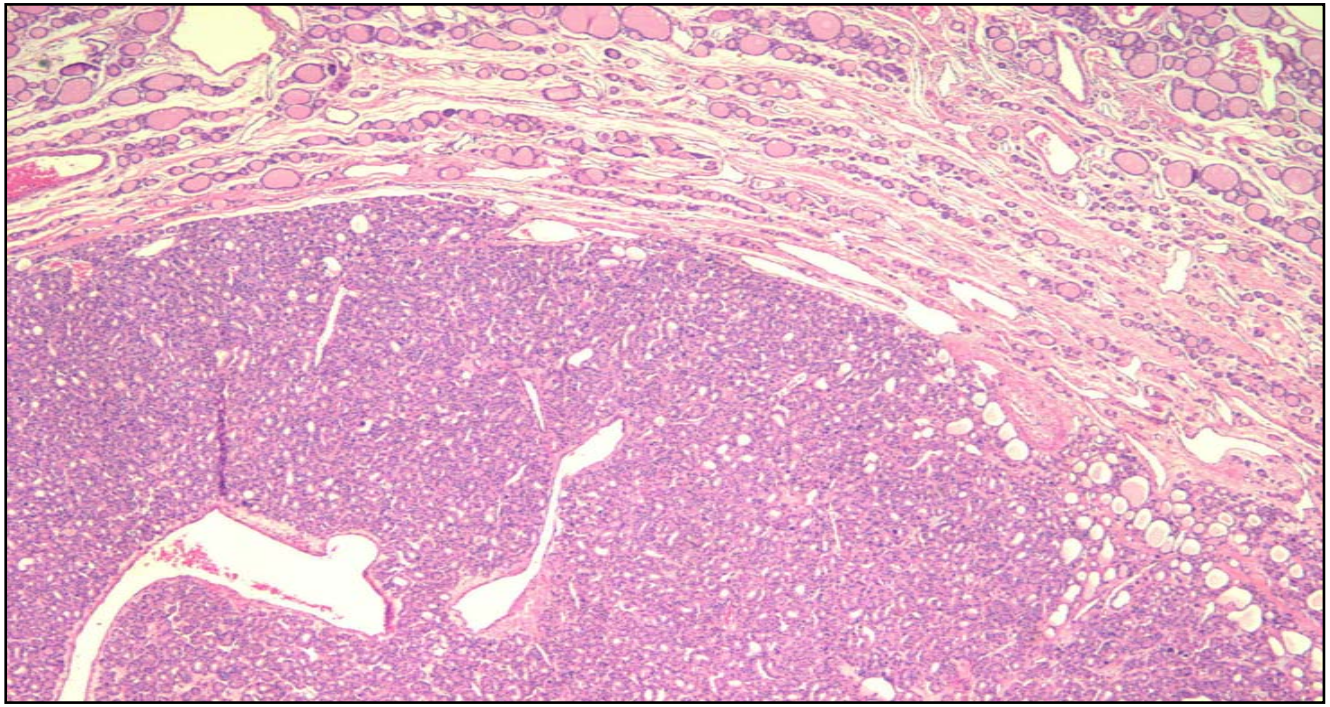
Myxoid variant of FA

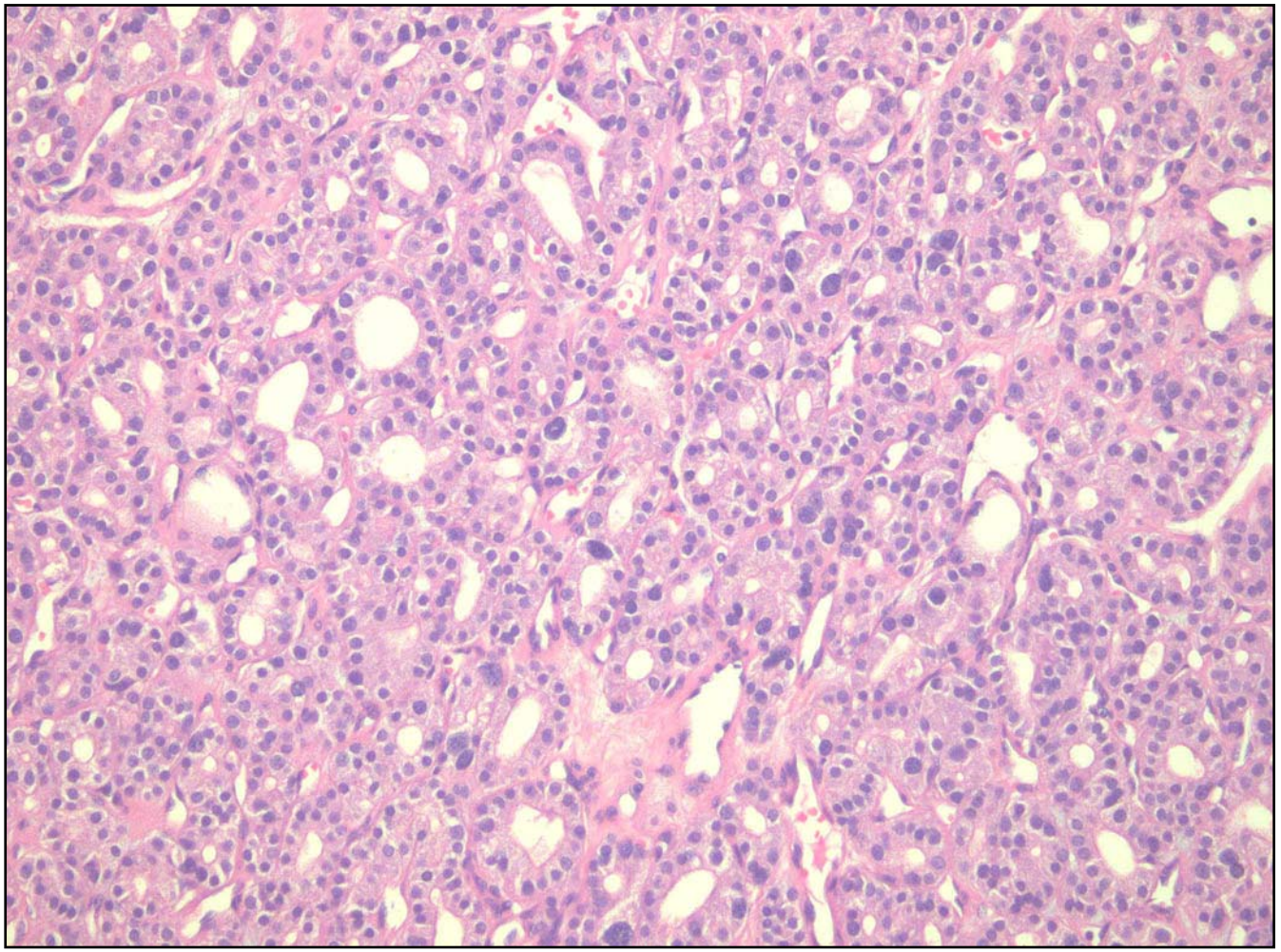


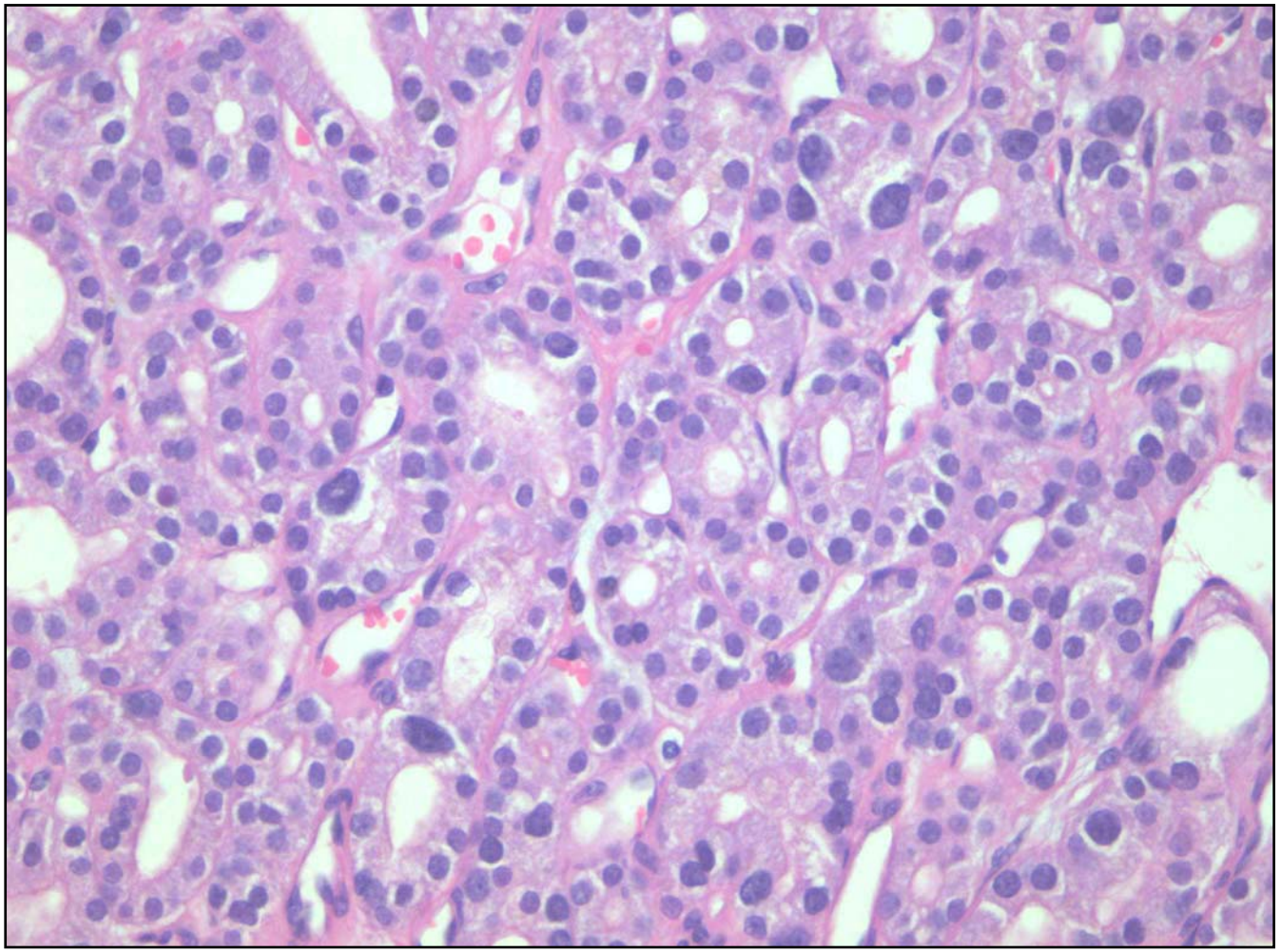
Ref. WHO

Follicular Adenoma with bizarre nuclei

- Small groups of monstrous tumor cells with enlarged hyperchromatic nuclei within an otherwise typical follicular adenoma



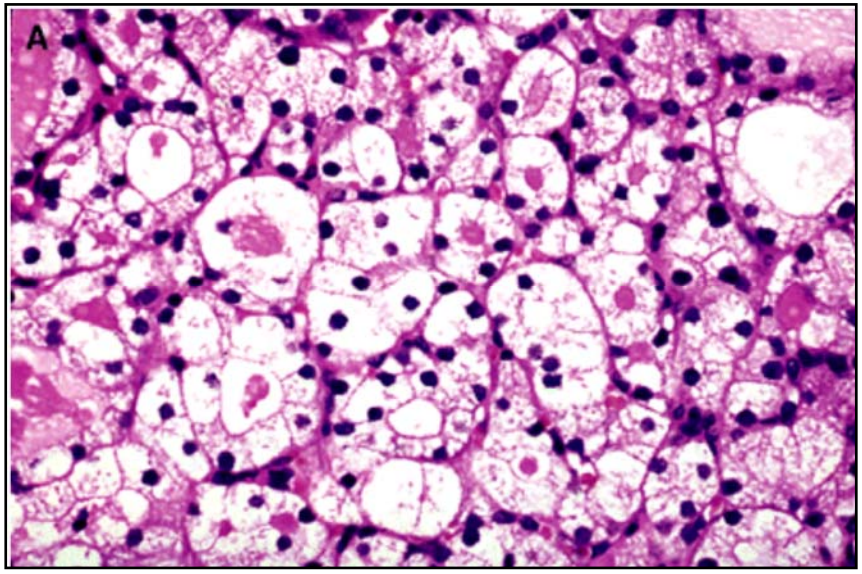


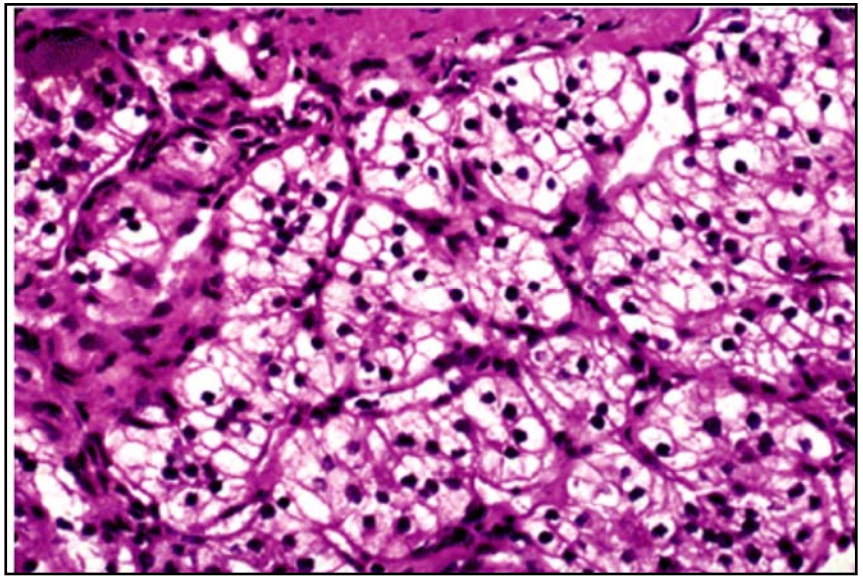


Follicular thyroid adenoma *versus* Parathyroid adenoma

- Arising within the thyroid gland or not
- Microfollicular, clear cell or oncocytic type cells
- Presence of water clear cells
- Chromogranine positivity and parathyroid hormone positivity

Parathyroid Adenoma





2.4 Thyroiditis

- 1.Chronic lymphocytic thyroiditis of Hashimoto is an auto immune disease.

Variants of Hashimoto: fibrous and juvenile.

- 2.Granulomatous thyroiditis of de Quervain
- 3.Palpation thyroiditis (Granulomatous)
- 4.Silent focal lymphocytic thyroiditis
- 5.Post partum thyroiditis

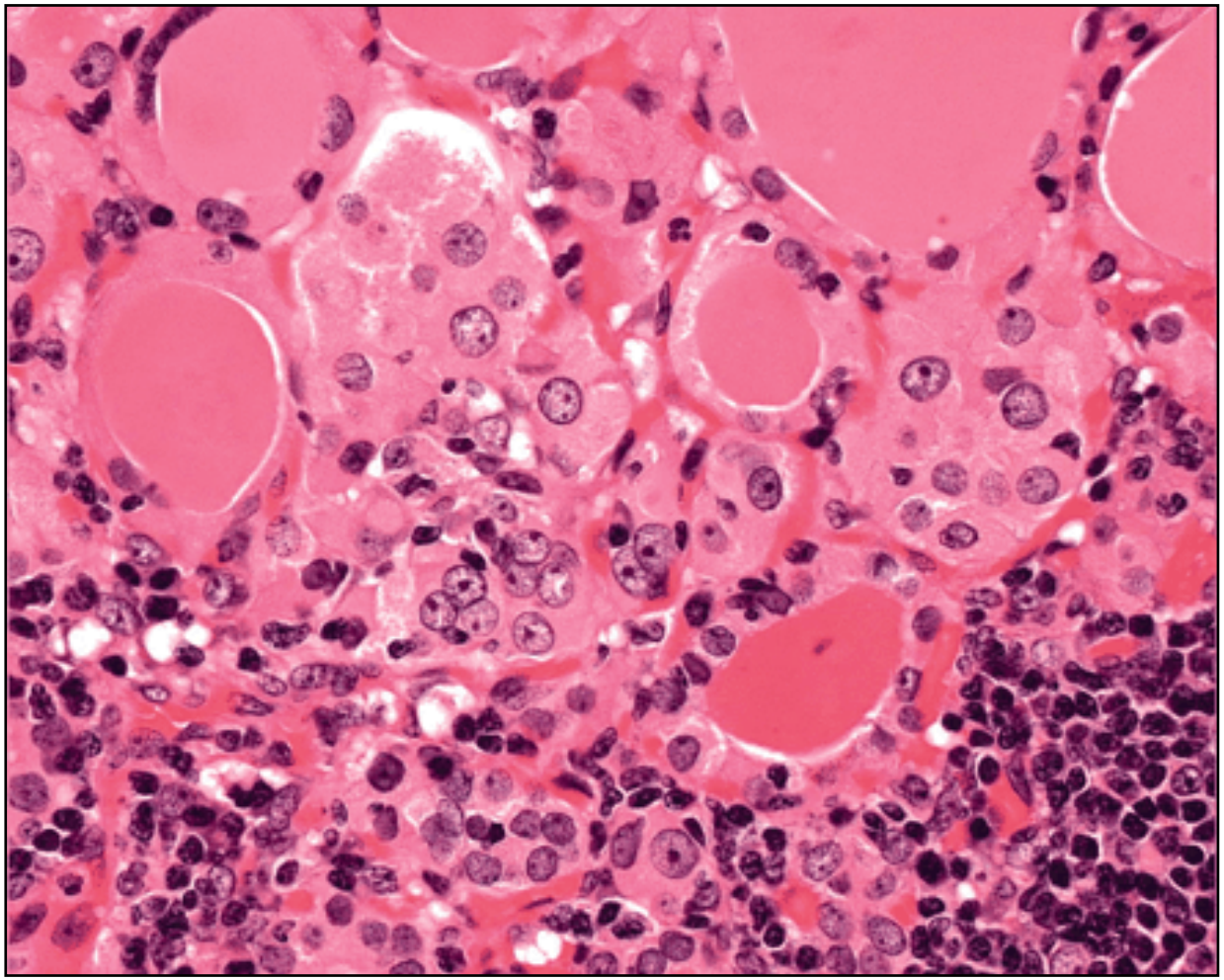
2.4 Thyroiditis

- 6.Riedel's thyroiditis: extensive fibrosis extends to the adjacent muscle with sharp demarcation between affected area and normal areas, granulomatous changes in vessels.

- DD 1.Paucicellular Anaplastic (Undifferentiated) Thyroid Carcinoma of the elderly
- DD 2.PTC with fasciitis like stroma
- DD 3. PTC with extensive fibrosis or Diffuse sclerosing variant. Most are TG negative

2.5 Cytologic appearance in thyroiditis. Atypia is not malignancy

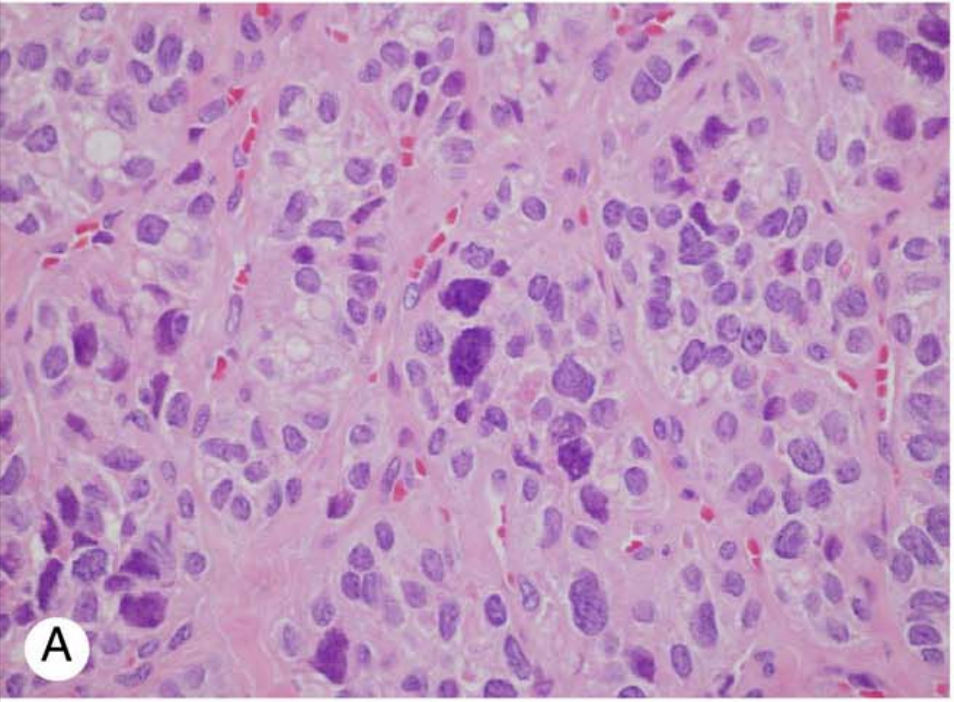
J Clin Pathol 2004, 57, 225-232

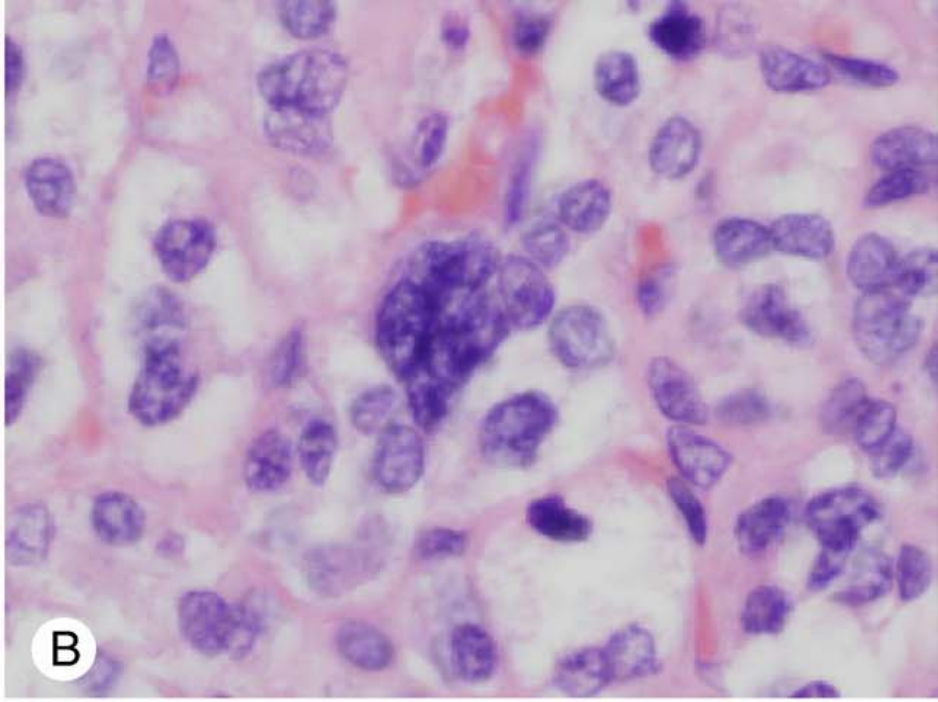


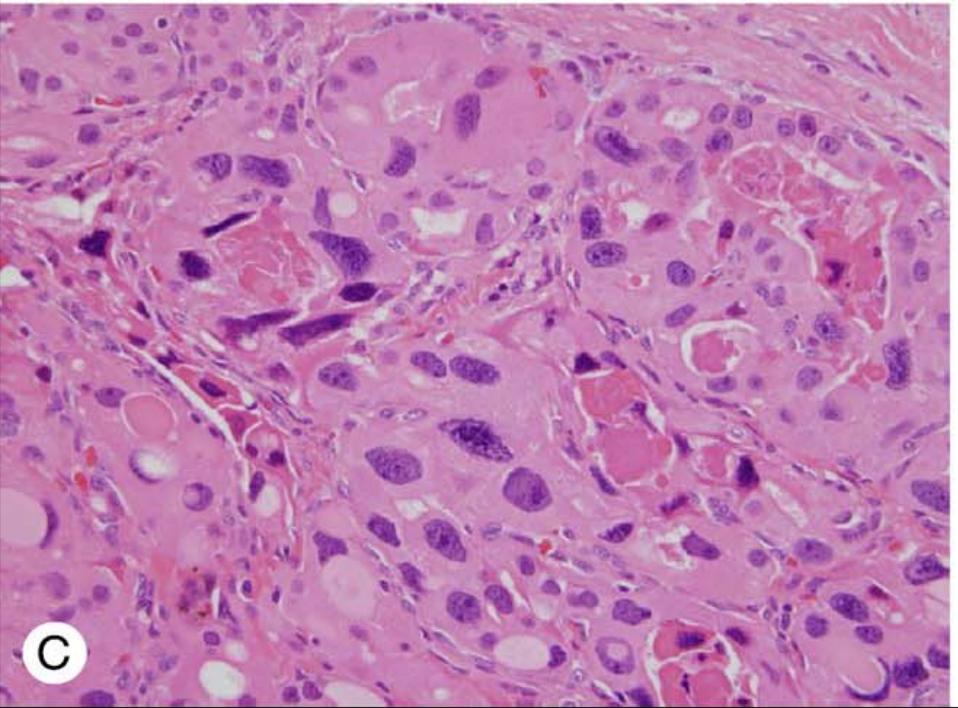
www.jclinpath.com

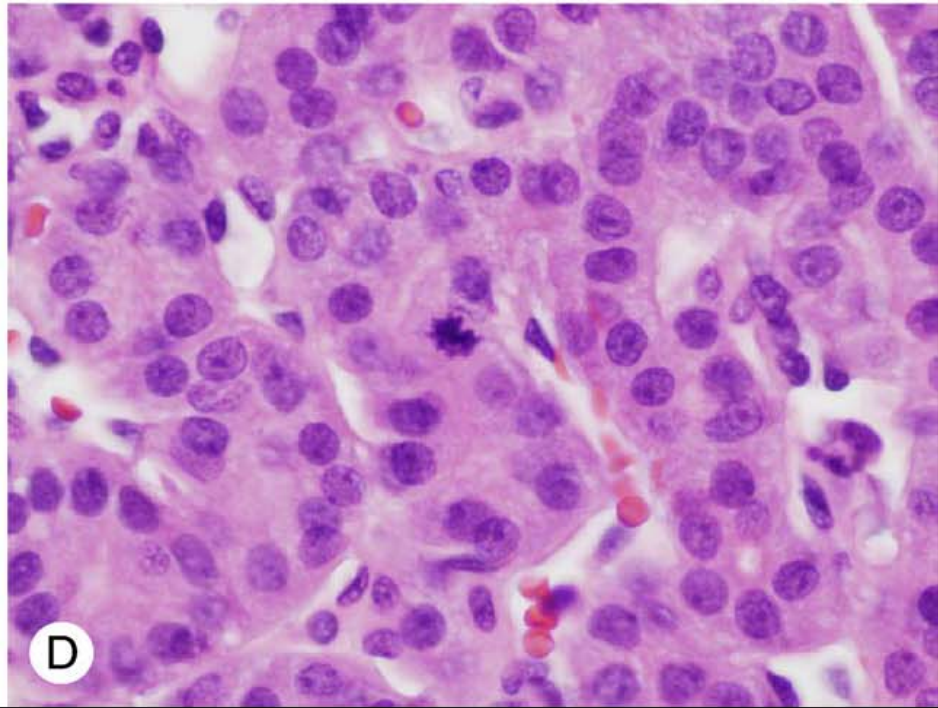
The spectrum of histologic changes in thyroid hyperplasia: a clinicopathological study of 300 cases
Human Pathology (2008) 39, 1080-1087

- Nuclear clearing resembling Orphan Annie nuclei: 15%
- Nuclear grooves and pseudonuclear inclusions focally in 8%
- Cytologic atypia in 7% (nuclear enlargement, multinucleation, nuclear pleomorphism with prominent nucleoli)
- Mitoses in 6% ,1/10 HPF
- Psammoma bodies focally in 4%
- Muscle infiltration in 1%
- Two cases with thyroid in lymph node sinuses


A


B


C


D

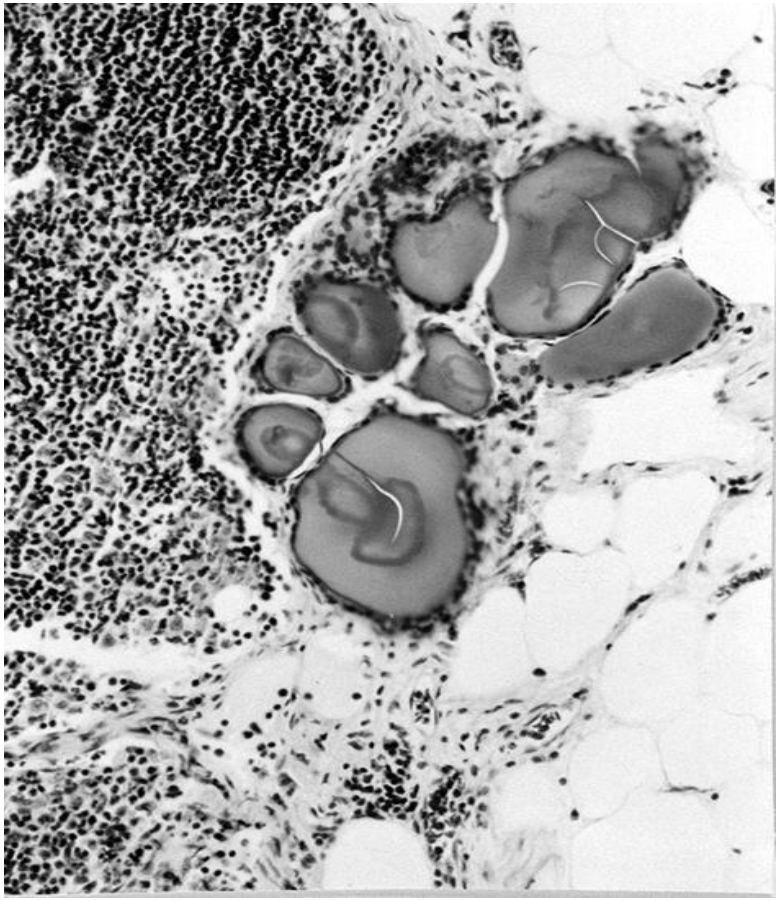
2.6 Lymph nodes (cervical) containing thyroid tissue

- May represent heterotopic thyroid tissue or metastatic carcinoma - evaluate with **extreme** caution

2.6 Heterotopic thyroid

- Small aggregate of follicles with no attributes of papillary carcinoma after detailed examination (i.e. no atypical nuclei, no papillary architecture, no psammoma bodies), and limited to capsule/periphery of one or two lymph nodes

Ectopic thyroid follicles in cervical lymph node have normal architecture and cytology and appear as a small cluster in nodal capsule



Pathology outlines.com

3. Thyroid Carcinoma

3.1 Thyroid Carcinoma

- 1% of all malignancies
- 8th place of malignancies of women
- 80% is PTC
- Increasing

- Arch Pathol Lab Med 30 july 2006, p 1057

Thyroid Carcinoma: WHO book on Endocrine Tumours, 3rd edition, 2004

1. Follicular carcinoma FC
2. Papillary carcinoma PTC
3. Medullary carcinoma Med. Ca
4. Poorly differentiated ca PDC
5. Undifferentiated ca UDC

....

3.2 (Hürthle cell carcinoma)

- Doesn't exist anymore as a separate entity. (WHO 2004)
- *Hürthle cell variant …*
- *… with Hürthle cell differentiation*
- Alle entities benign or malignant

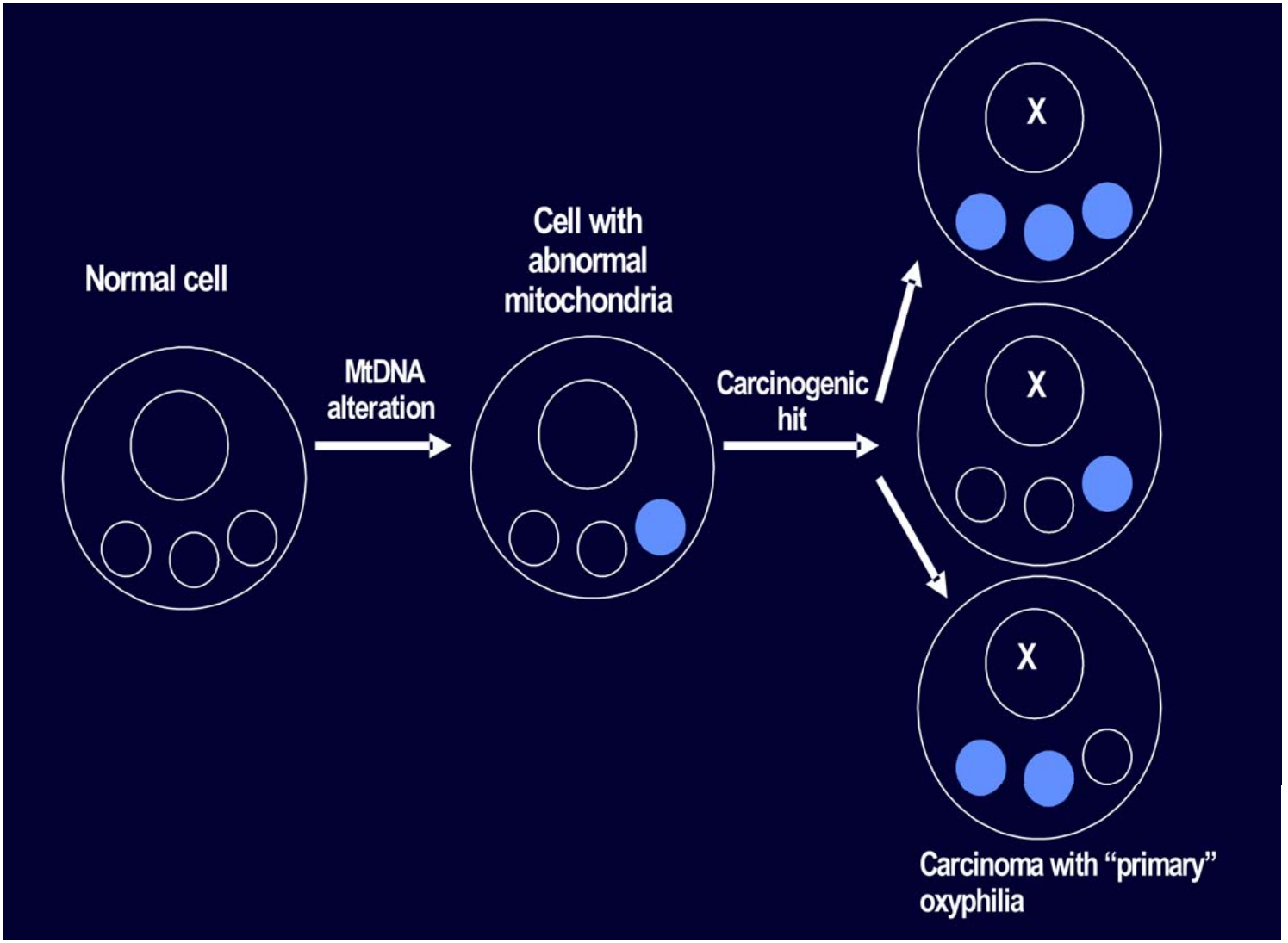
Manuel Sobrinho-Simões

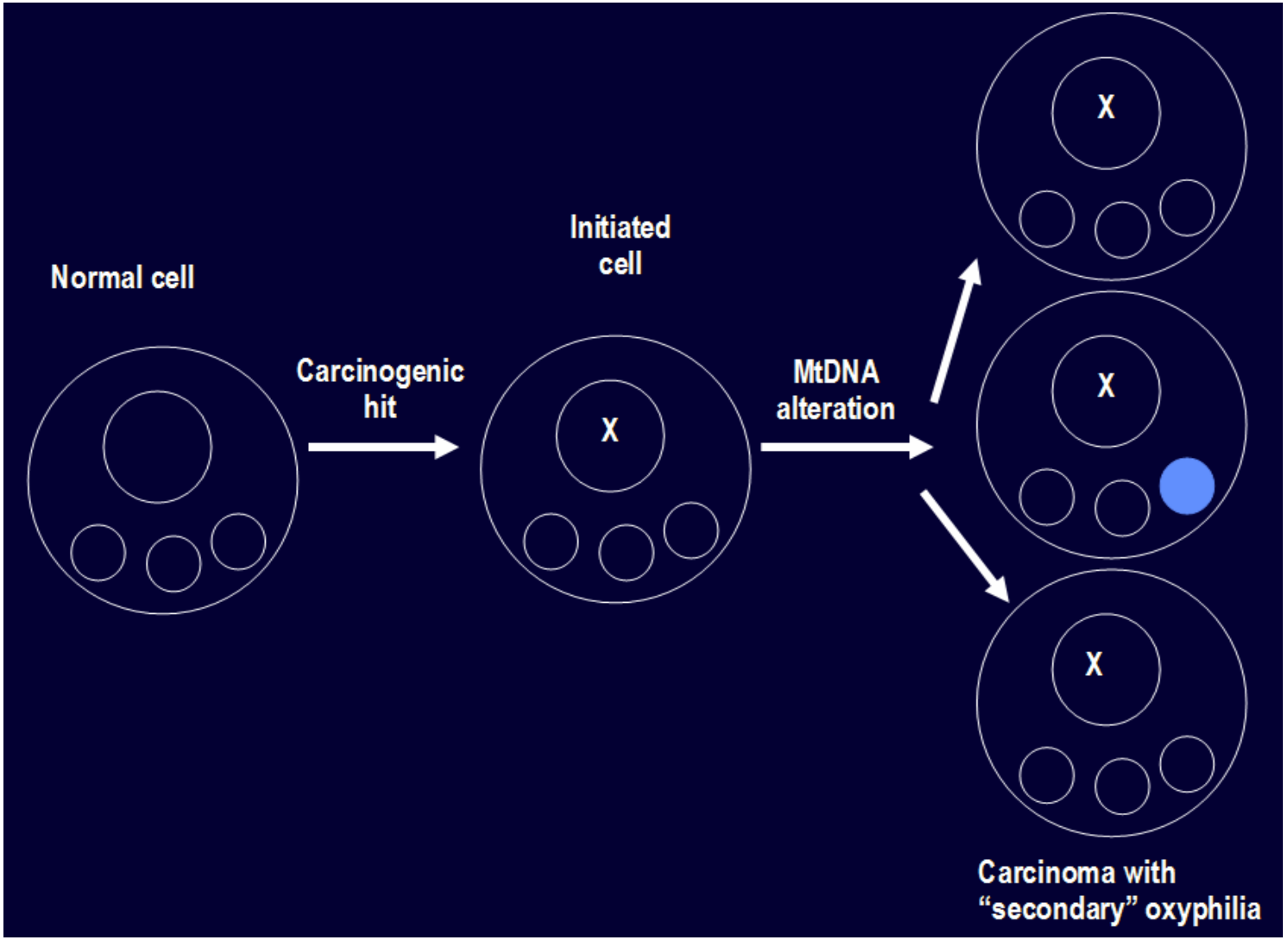
Medical Faculty & Institute of Molecular Pathology and Immunology of the University of Porto (IPATIMUP)

- Course on Thyroid Pathology

  Paris, June 15-16, 2006

Prof. Manuel Roberto Simoes


Normal cell
MtDNA alteration
Cell with abnormal mitochondria
Carcinogenic hit
X
X
X
Carcinoma with "primary" oxyphilia


Normal cell
Carcinogenic hit
Initiated cell
X
MtDNA alteration
X
X
X
Carcinoma with "secondary" oxyphilia

3.3 Follicular carcinoma

3.3 Follicular Ca

Arch Pathol Lab Med vol 130 july 2006 p 984

Vessel and/or capsular invasion.

- Vascular invasion within the tumor: not significant
- No capsule is no Fol. Ca!
  -(Cave Widely invasive FC)-
- A thin, fine capsule is (probably) not a Fol. Ca.
- CD 34 or an other vascular markers **are useless**
- Invasion of one vessel is very rare
- Cave torn of capsule (J. Rosai)
  Tumor herniation through a torn capsule simulating capsular invasion)
  Histopathology;2006,49,107-120

3.3 Carcinoma

- Is trabecular, solid, microfollicular (fetal) and NOT macrofollicular or normofollicular.
- Macrofollicular growth pattern is probably FV-PTC (Follicular Variant of Papillary Carcinoma).
- FTC peak : 60-70 year older age group.
- If there is any inflammation it is probably not FC but PTC. No lymphoid infiltrate in FC and near always in PTC

Arch Pathol Lab Med vol 130, july 2006

- **Vascular invasion**
- Should be assessed in vessels located within or beyond the capsule
- Plugs of tumor cells floating within vascular lumens unattached to the vessel wall do not qualify for vascular invasion.
- CAVE: Reactive vascular proliferation

J Rosai in Histopathology,49, 107-120, 2006: Pitfalls in thyroid tumour pathology

Arch Pathol Lab Med vol 130, july 2006

- **Vascular invasion, bis**.
- To qualify for vascular invasion the tumor cells should be covered by a partial or full layer of endothelium.
- Some authors will accept nonendothelialized tumor thrombi as evidence of vascular invasion if they are attached to the vessel wall.

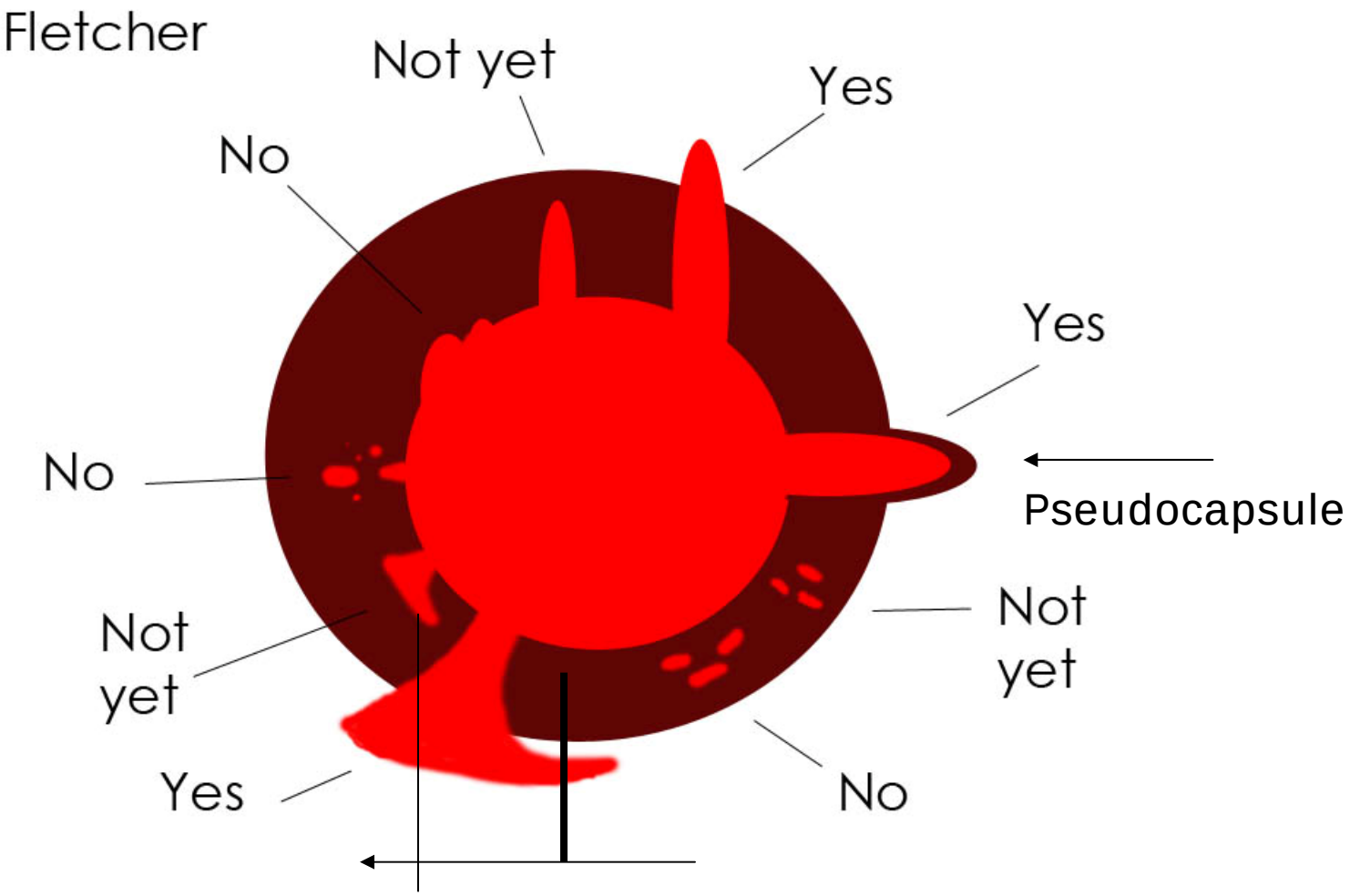
Virchows Arch (2006) 448; 385-393

- **Capsular breakthrough**
- Penetration of tumour through the whole capsule, deflecting the collagen fibres of the capsule.
- Contact of tumour with the surrounding non neoplastic thyroid tissue.
- A concomitant vascular invasion is not required even if metastasis are already present.
- Tumour foci within the capsule are not sufficient for the diagnosis. They represent, most likely, tumour trapping and distortion by fibrosis.

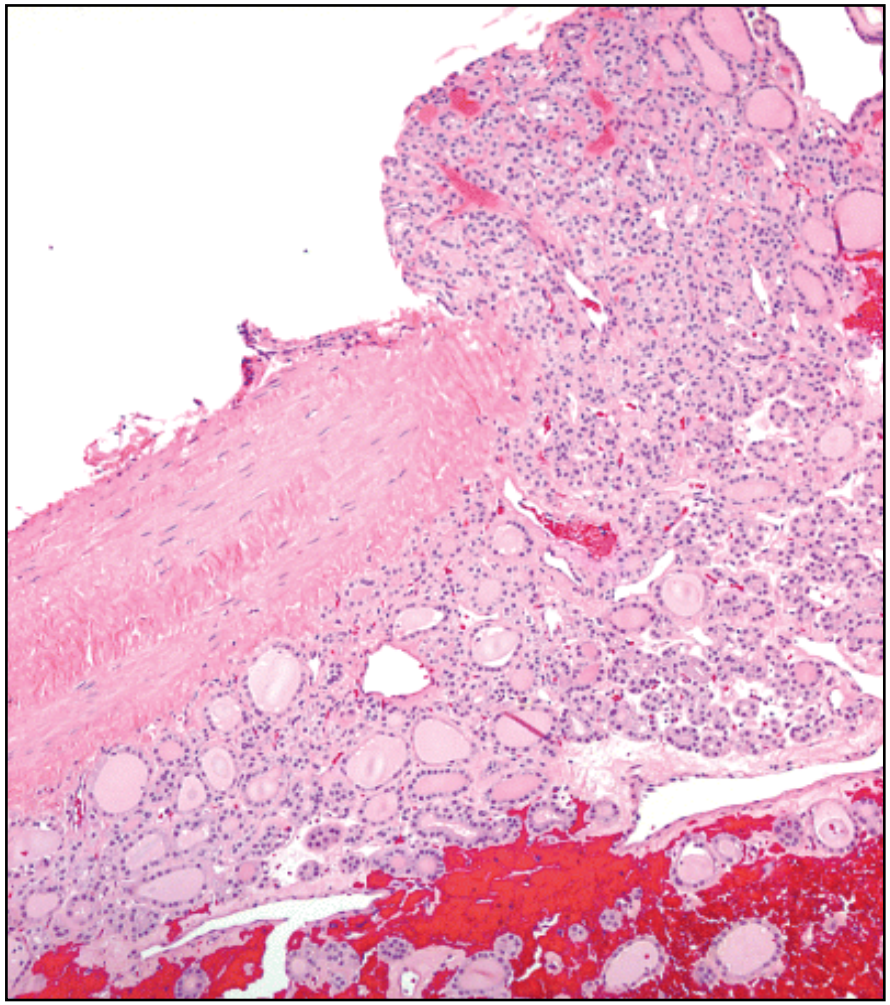
Arch Pathol Lab Med 130, july 2006 p984

- Small nodules found outside the tumour capsule showing a similar morphology to the main tumour mass should not be regarded as capsular invasion.
- Free floating islands of tumour cells present within the capsule without connection with the tumour mass should not be regarded as capsular invasion.

More sections to find the breaktrough

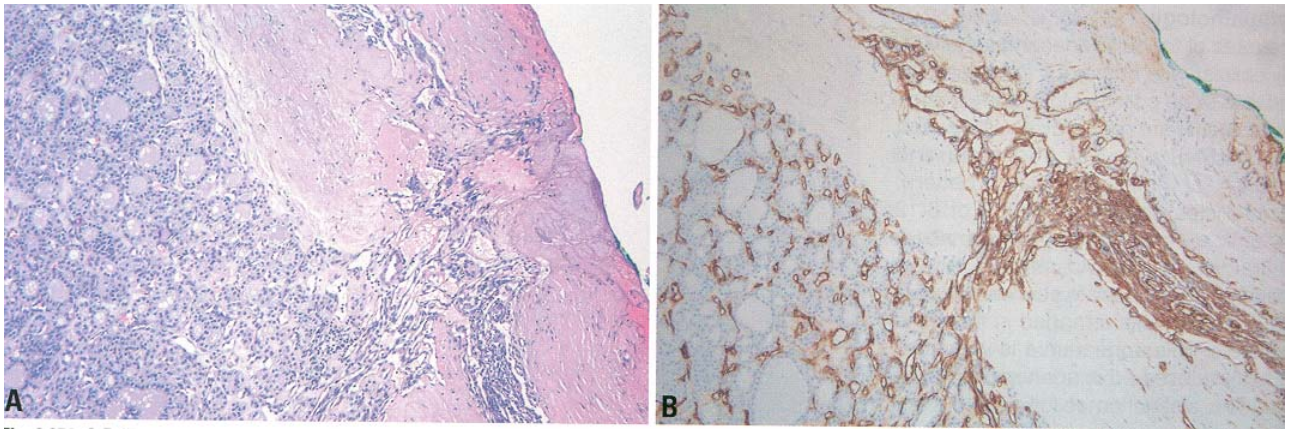


Torn capsule of a follicular adenoma with herniation of tumour tissue simulating capsular invasion. (J Rosai)



Histopathology, 2006,49,107-120

FNA in FA
WHAFF



Worrisome **H**istologic **A**lterations **F**ollowing **F**ine Needle Aspiration (Livolsi)

Ref. WHO

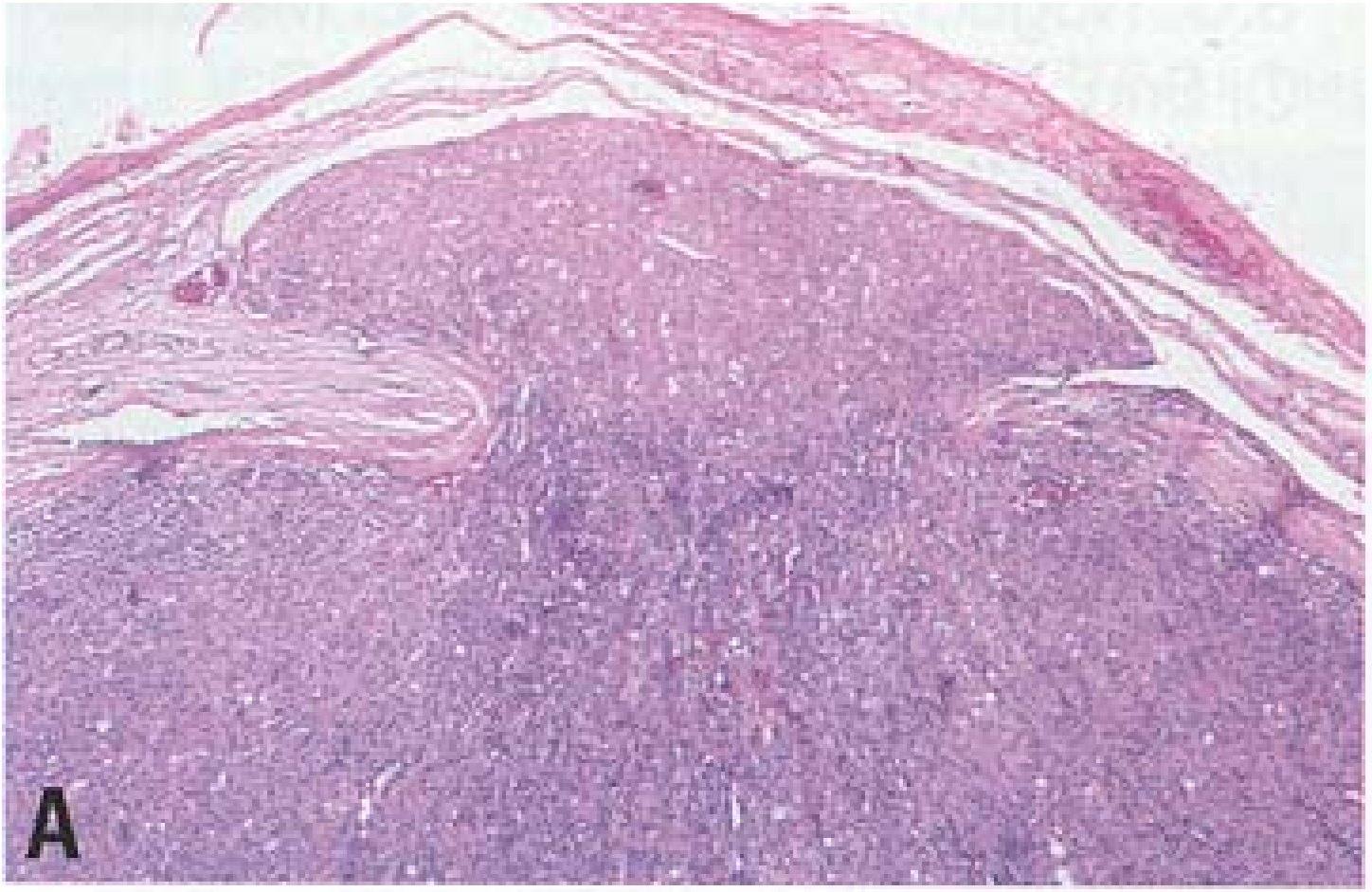
3.3 Anatomic forms of FC

- Minimally invasive MI-FC/ Low Grade
  - 1.With or without capsular invasion
  - 2.With limited vascular invasion (<4 Vessels involved)
- Widely invasive FC/ Intermediate Grade
- With extensive vascular invasion (>4 Vessels involved) No capsule anymore

3.3 Variants of FC

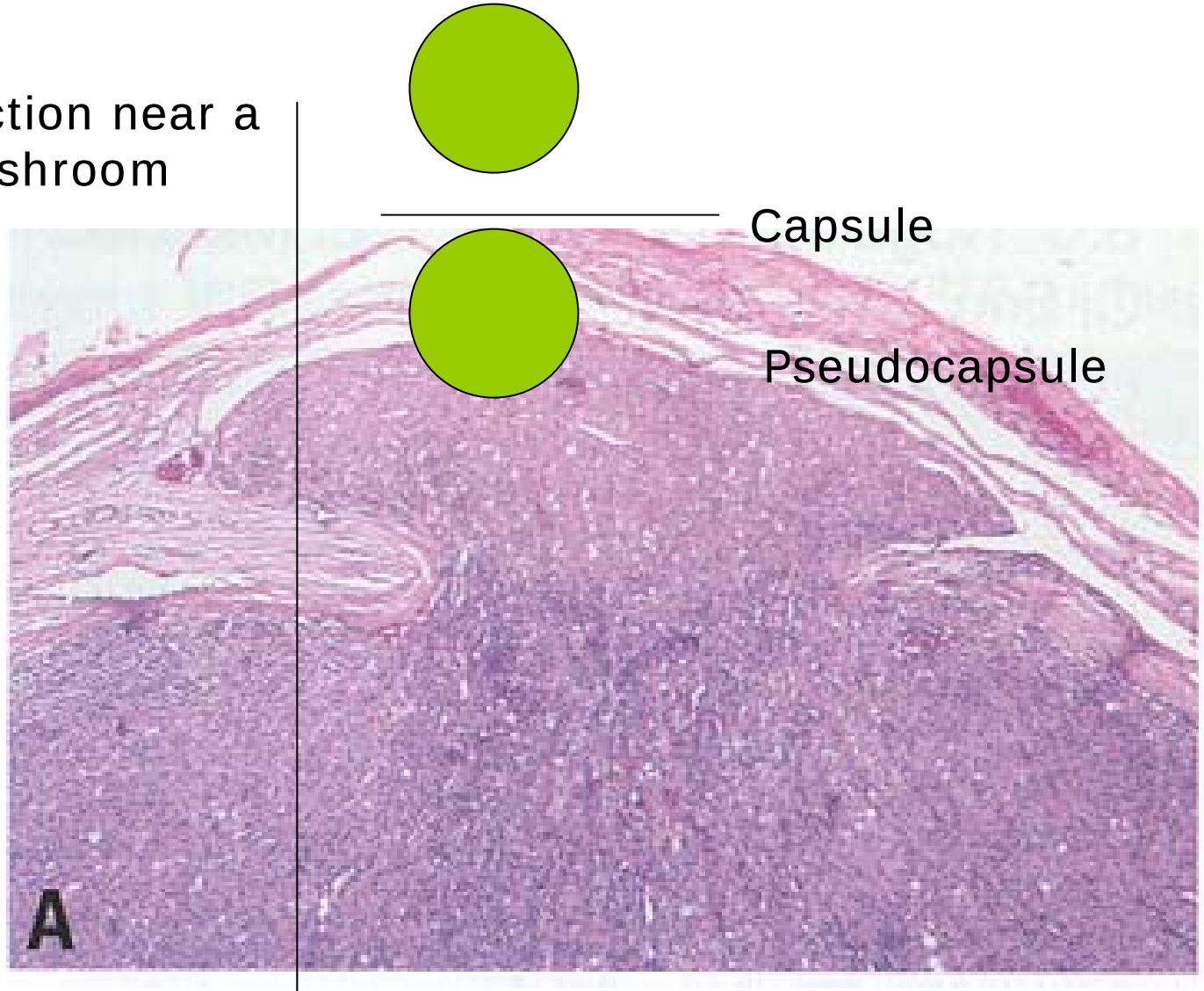
- Hurtle cell
- Clear cell
- Cave clear cell adenoma does also exist!

FC Mushroom



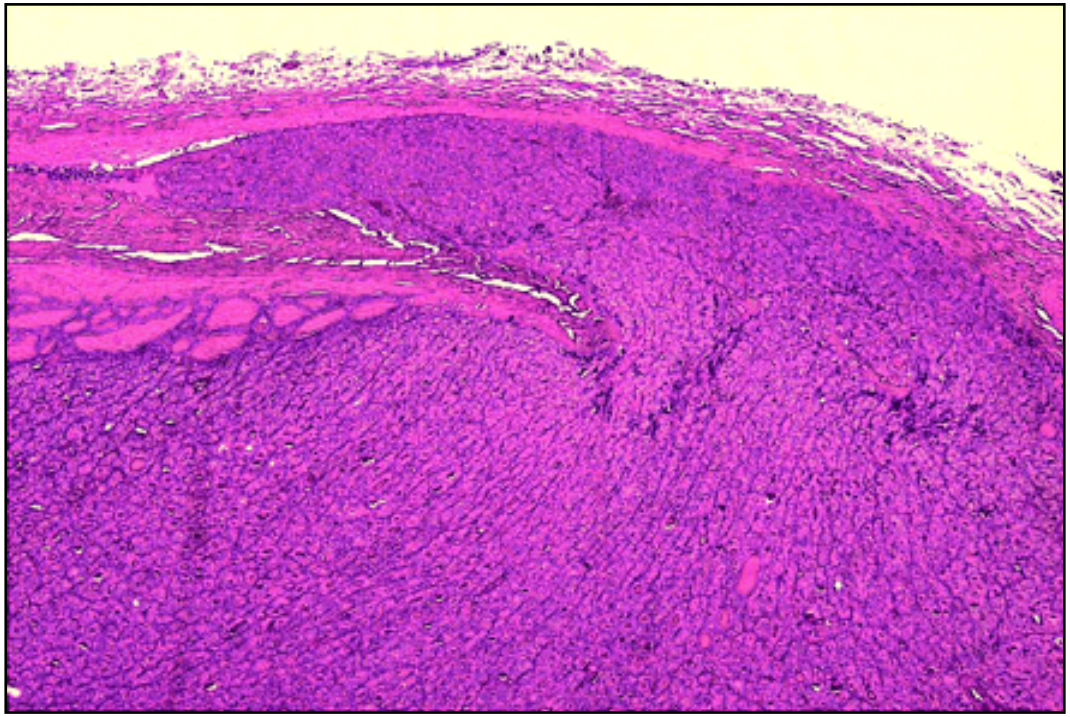
Paris 2006

Section near a mushroom



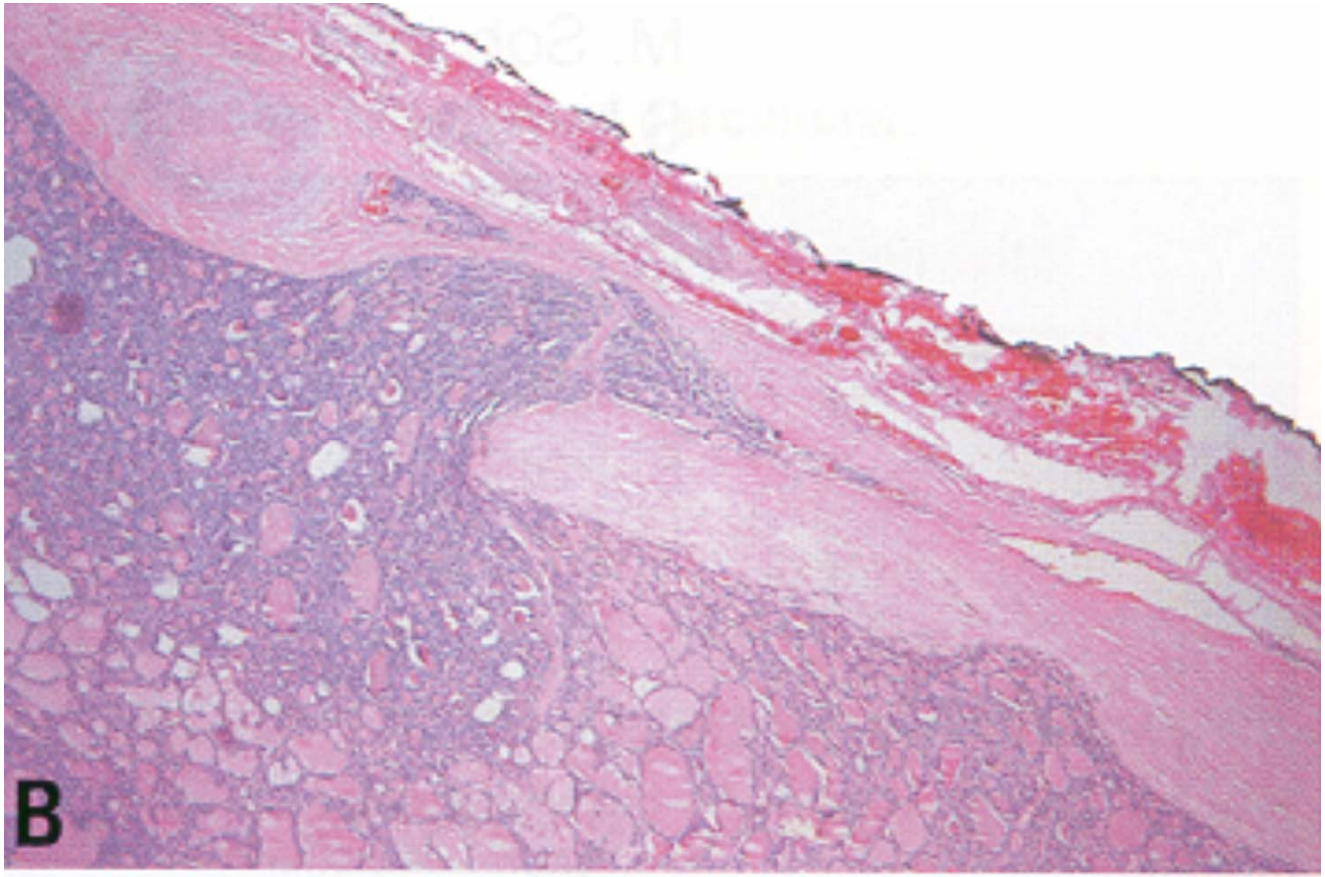
Minimally invasive follicular carcinoma—the invasive tongue of tumour has completely penetrated the capsule of the neoplasm

J Rosai: Vascular invasion is more important than capsular invasion



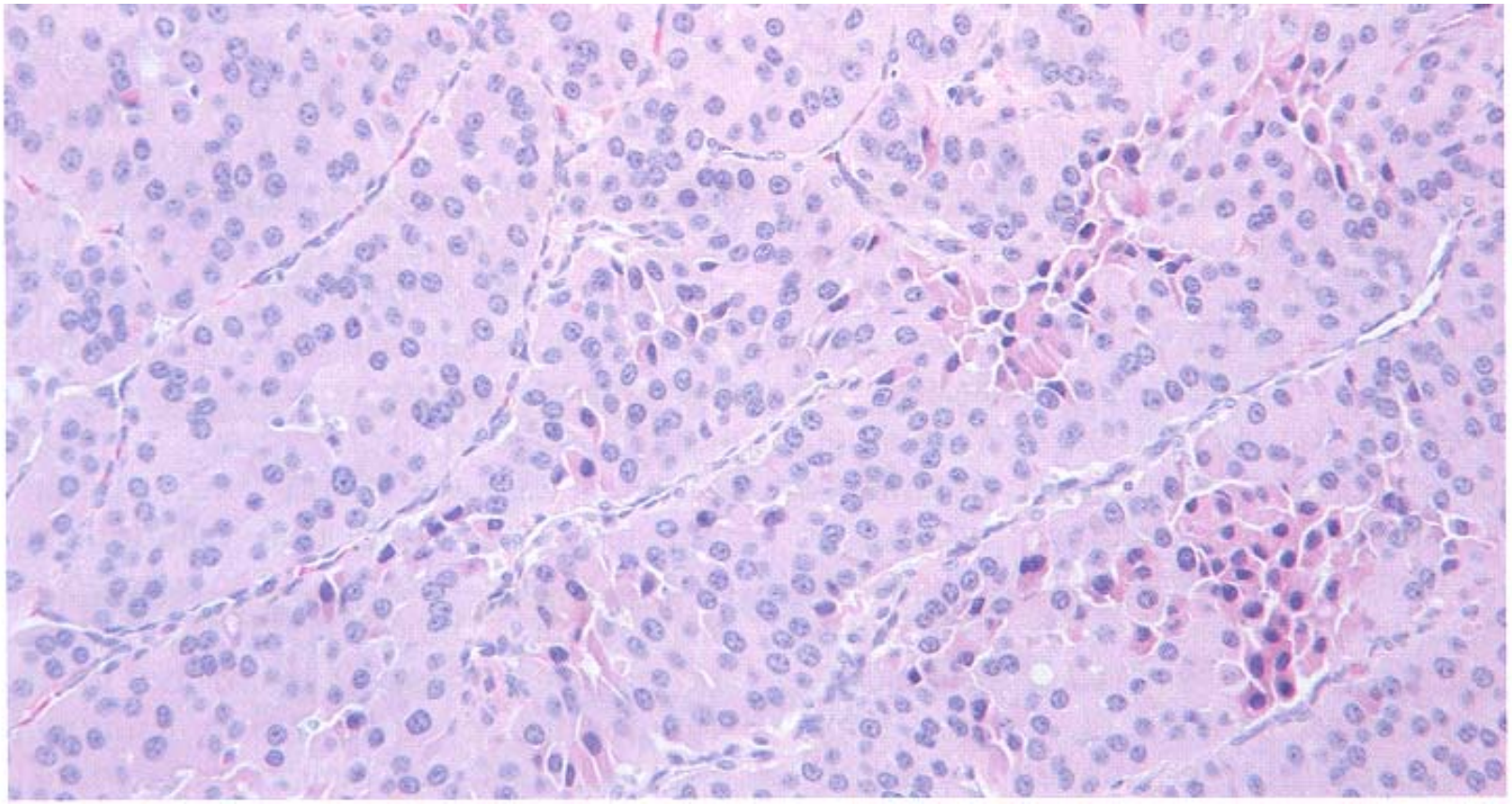
Paris 2006

FC Minimal capsular invasion



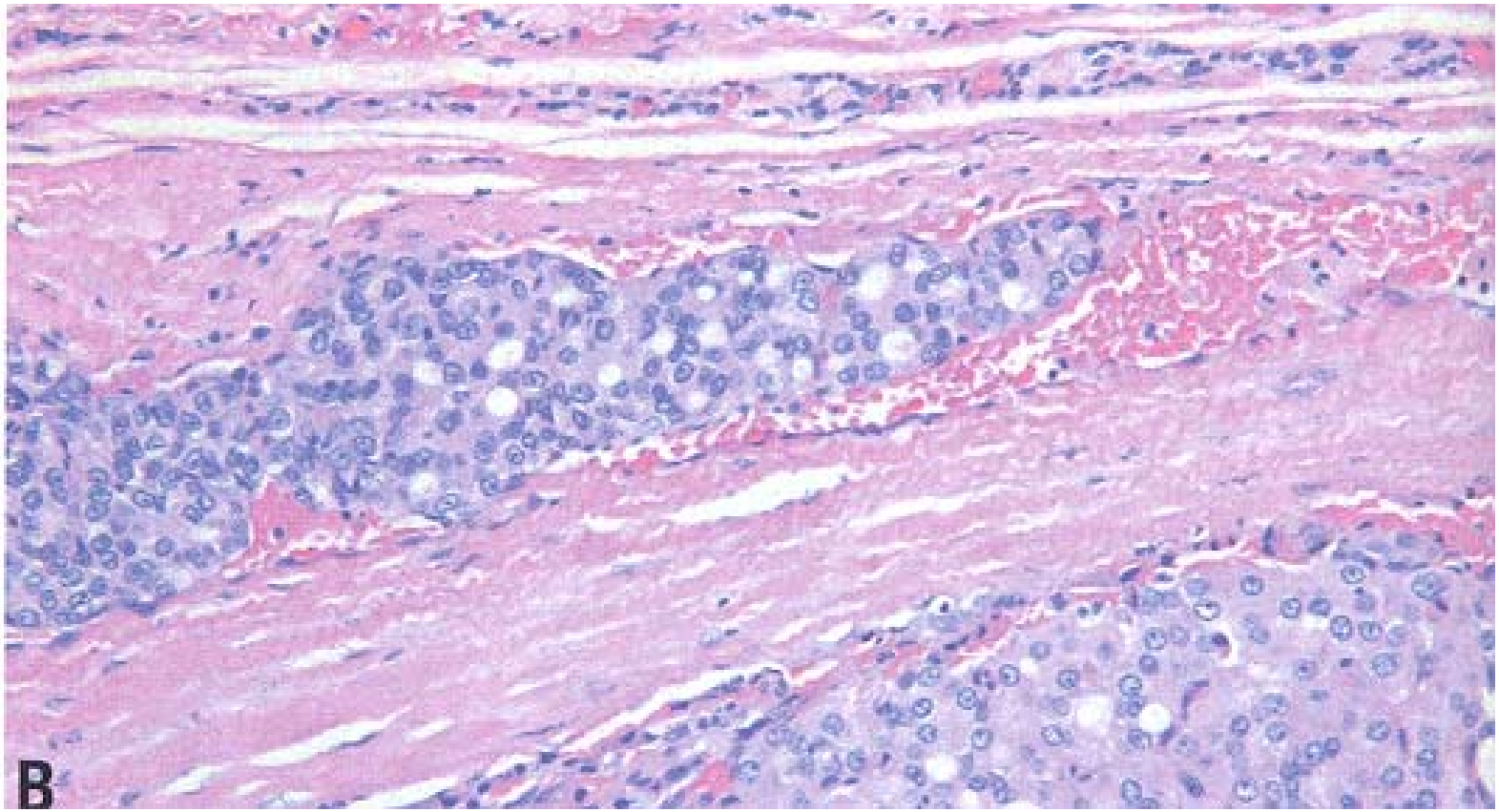
Ref. WHO

Hurtle cell variant of FC



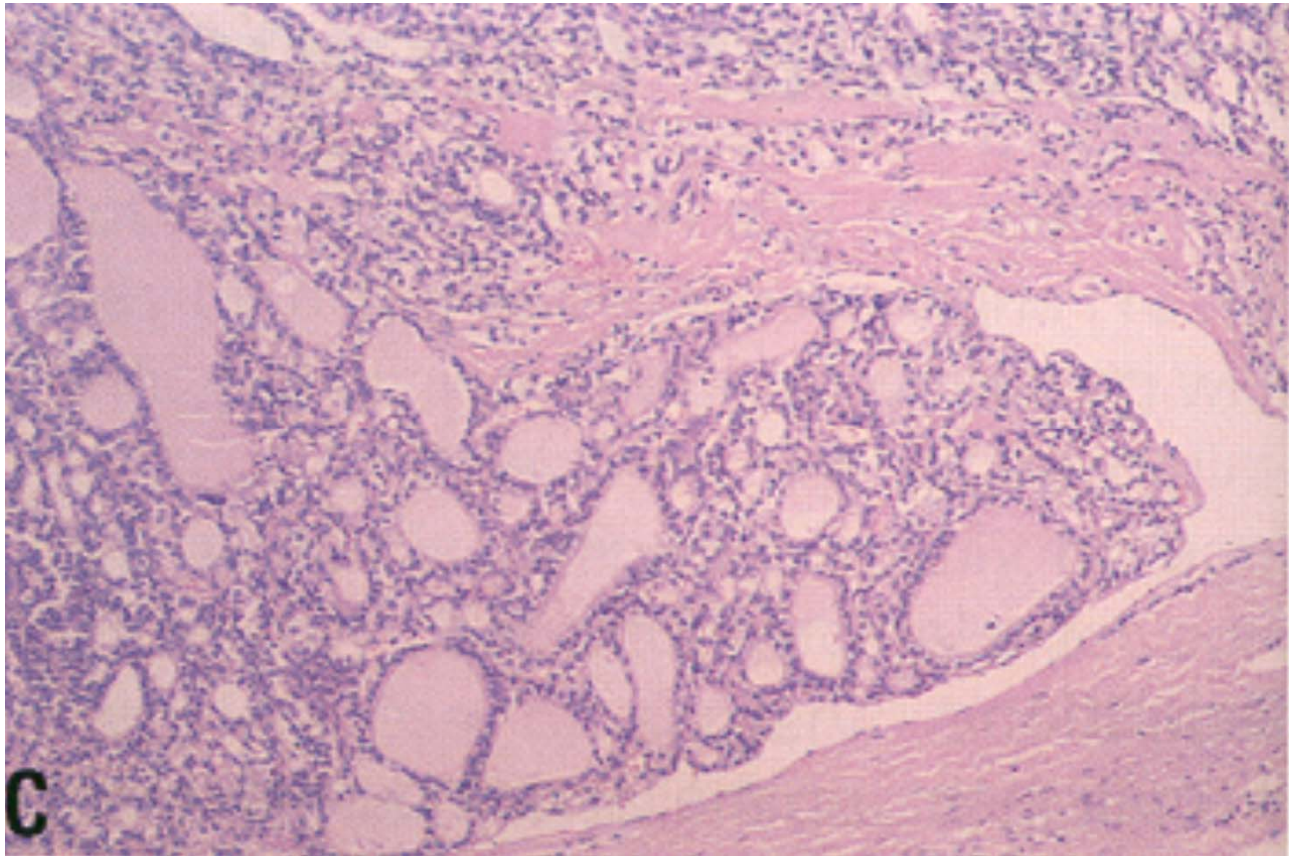
Ref. WHO

FC Vascular invasion



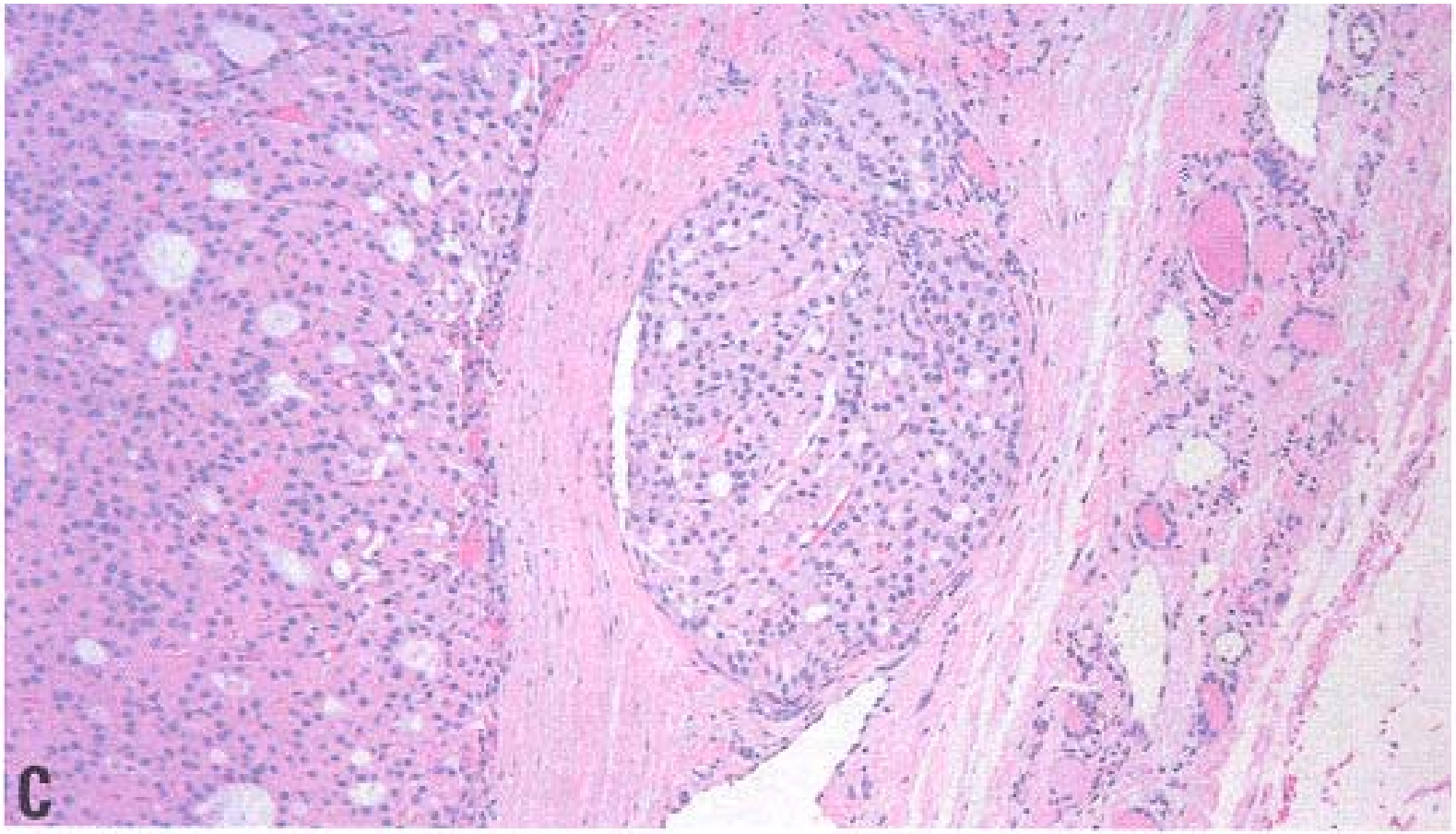
Ref. WHO

FC Vascular invasion



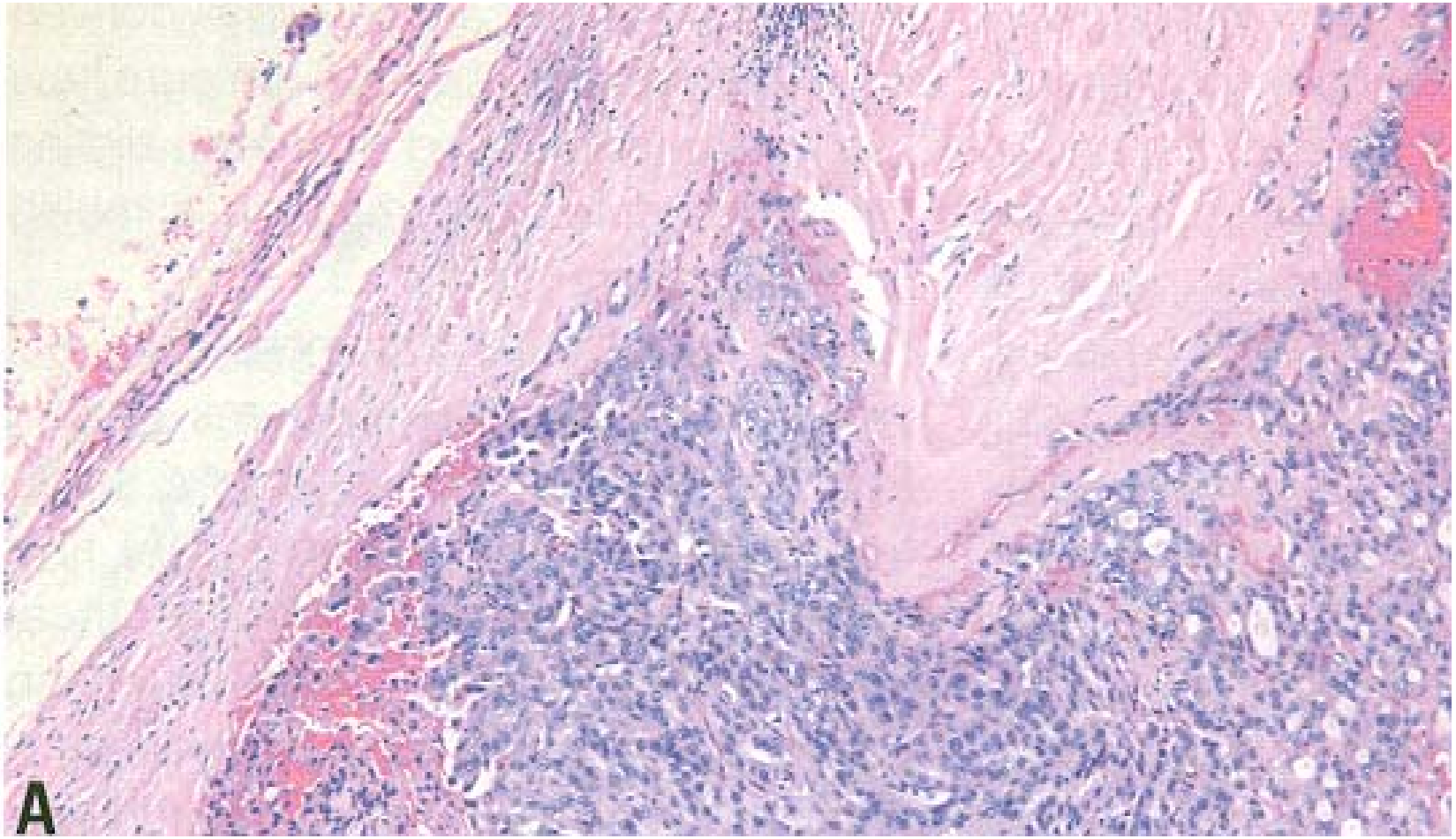
Ref. WHO

Vascular Invasion in FC



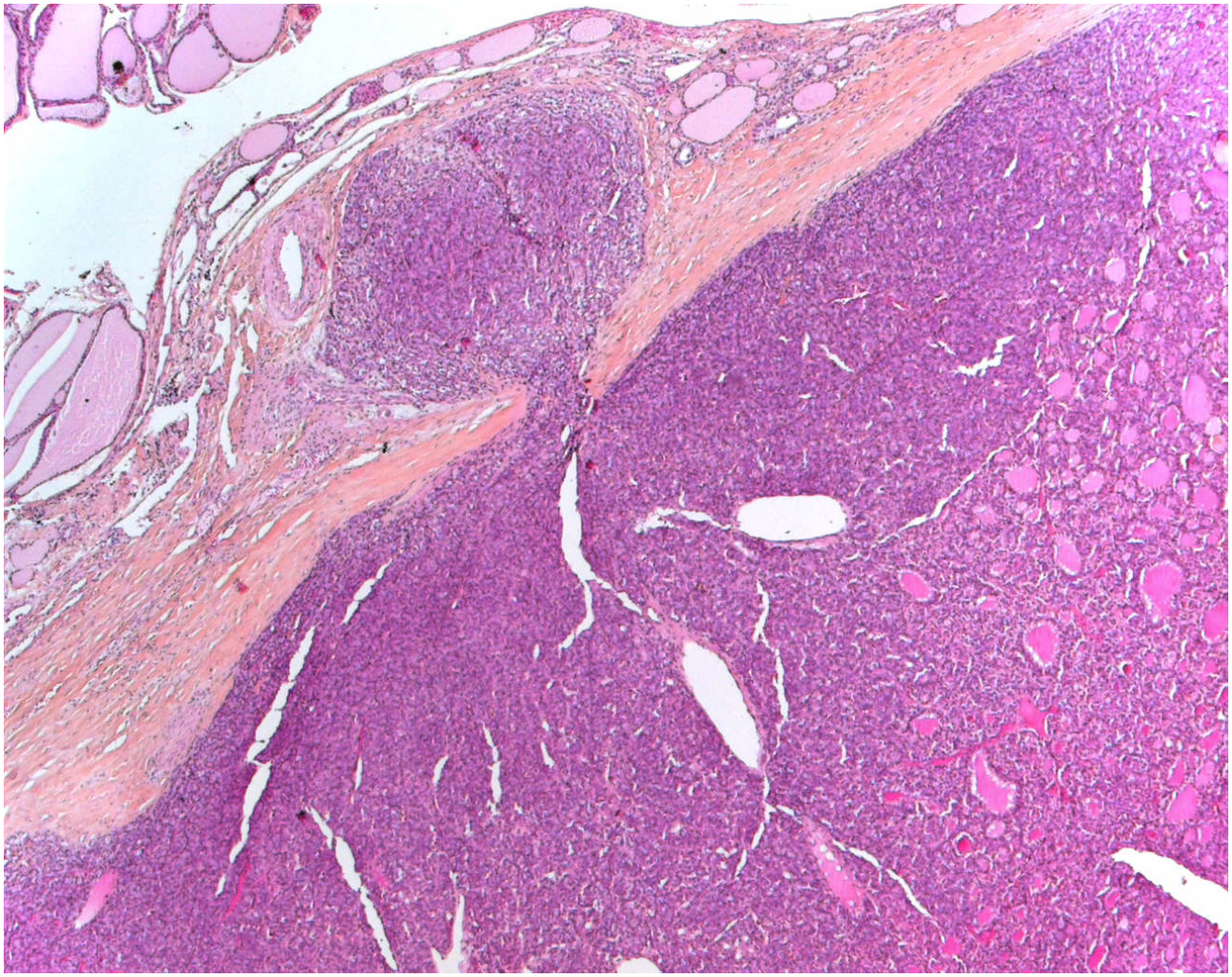
Ref. WHO

FC Capsular and vascular invasion



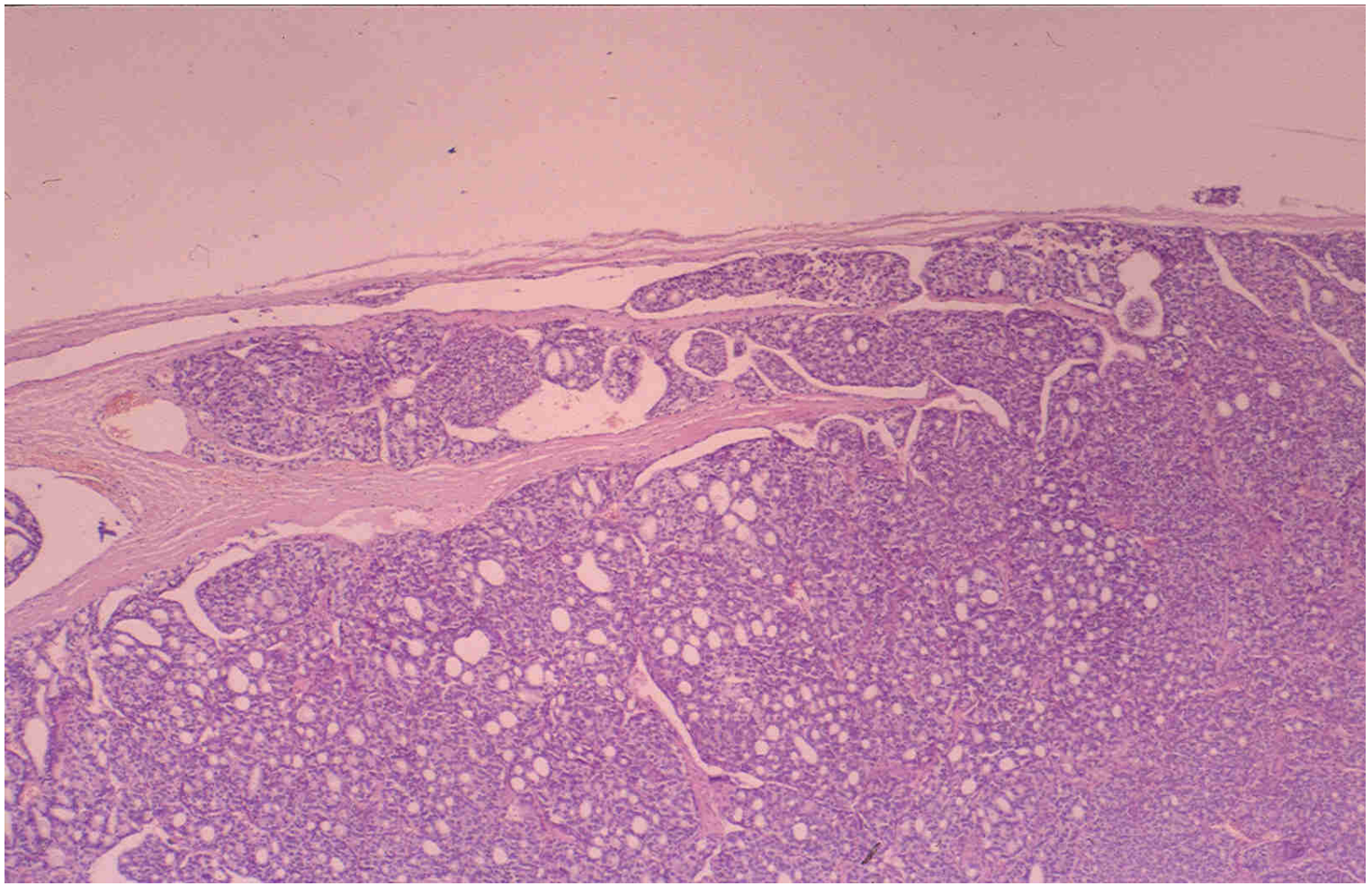
Ref. WHO

Paris 2006



Case nr. 19

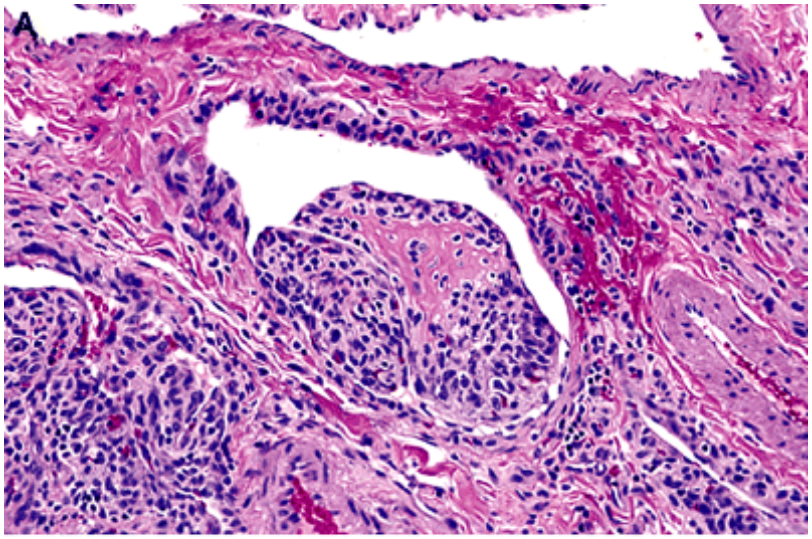
Widly invasive FC

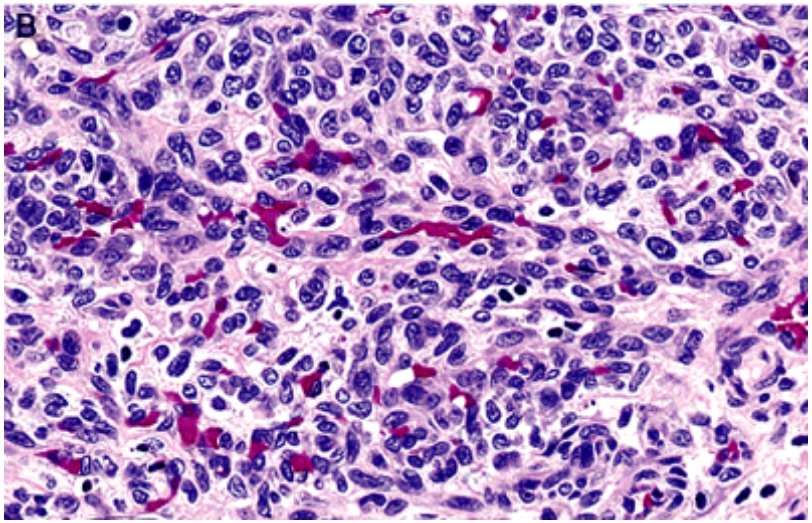


Paris 2006

Mimics of vascular invasion

Endothelial proliferation

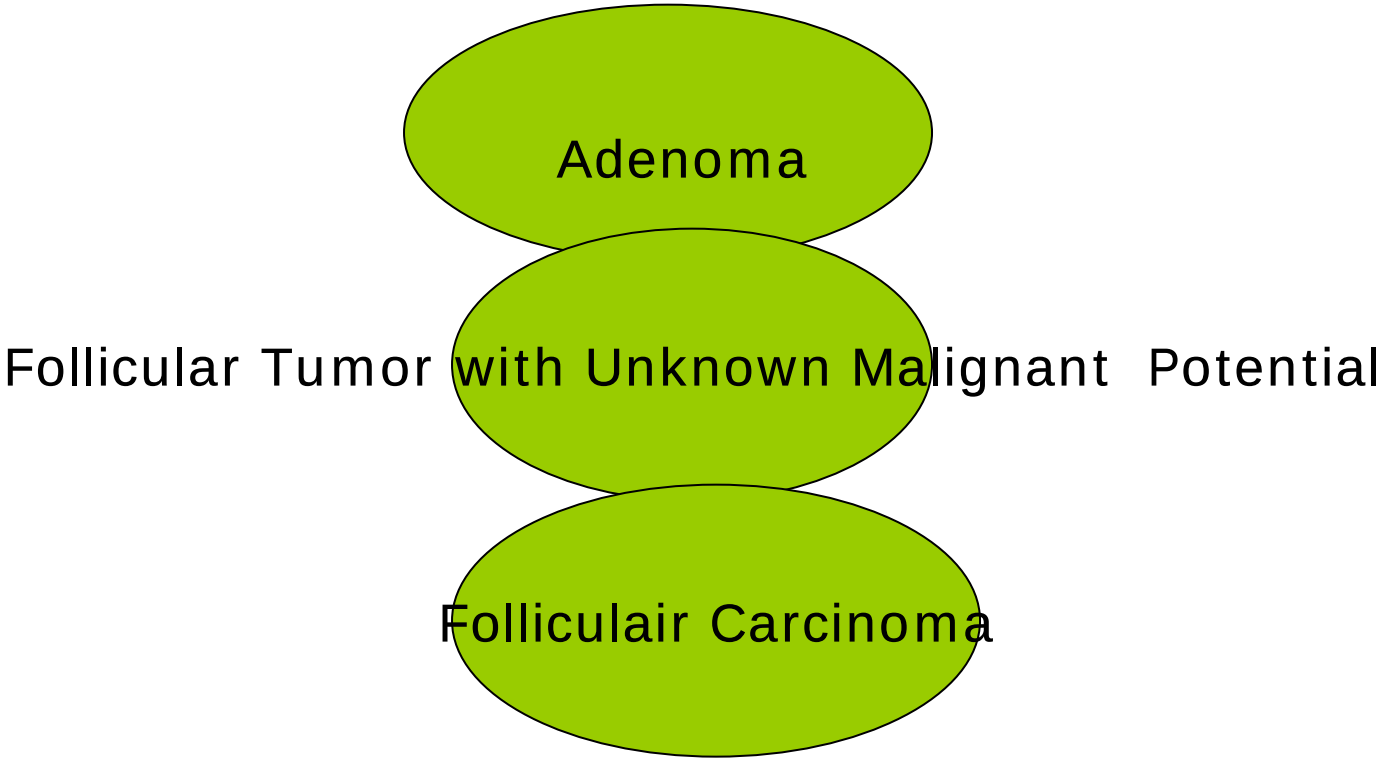




Kaposi sarcoma like

Histopathology 2006, 49,107-120

Benign vs Malignant
Adenoma versus Foll. Carcinoma



3.3 Follicular tumour of uncertain potential FT UMP

- Doubt about vascular invasion and/or capsular invasion.
- Take many blocks of the whole capsule.

3.4 PTC

Papillary Thyroid Carcinoma

Histopathology 2004, 44, p498 Stephenson

- PTC is the most common thyroid carcinoma. Its prognosis is extremely good.
  The most common single prognostic factor is age.

  Histopathology 2001, 39, p 536.
- PTC is not conventionally regarded as having any associated benign or premalignant lesion.
- PTC is a low grade tumour

3.4 PTC

- **Multicentric disease**
- This multicentricity is thought to be one cause of recurrences in patients treated by lobectomy
- If the lesion is found incidentally reoperation is not required
- Arch Pathol Lab Med vol 130 July 2006

3.4 PTC variants

- Microcarcinoma: smaller than 1 cm.
- Encapsulated (Lindsay tumour)
- FV PTC (Encapsulated or not)
- Solid (Most frequent in Childhood)
- Trabecular
- Diffuse sclerosing variant
- Tall cell variant
- Columnar cell variant (Separate entity?)
- Oncocytic variant with lymphoid stroma, Whartin like
- Hurtle cell variant / Clear cell variant

3.4 PTC variants bis

- Diffuse Follicular Variant
- Macrofollicular variant (more than 50 % macrofollicles)
- Cystic variant of PTC
- PTC with Exuberant nodular fasciitis like stroma
- Multifocal Pap T Ca
- Cribriform (morular) variant
- Multinodular variant
- PTC with focal insular component
- PTC with lipomatous stroma

3.4 PTCwith worse prognosis

- Tall cell variant (not in childhood!). If 30 % of cells are tall cells it is a tall cell variant
- Solid variant
- Diffuse sclerosing variant (Often with hughe squamous metaplasia) Children and young adults cave S100 positivity due to many FDC cells
- Columnar cell variant
- Diffuse follicular variant
- Oncocytic ? NO because no separate entitiy

3.4 PTC

- Follicles are frequently present
- Tubulo Papillar pattern also a frequent form of presentation
- Patterns: Less common: microglandular, guirlande, cribriform, anastomosing, tubular, trabecular.
- 50% contain multinucleate histiocytes (Fletcher)
- Psammoma bodies also in Hashimoto
- Often abundant sclerotic or fibrotic with calcification and/or ossification.

3.4 PTC Nuclei

- NOT Malignant:

  Dispersed cells with PTC nuclei: Hashimoto, Goiter.

  Intermingled with normal cells.

- Malignant:

  Clusters with PTC nuclei : PTC.

  All of the same family.

Classic Nuclear features of Papillary Thyroid Carcinoma (PTC)

- Nuclear optical clarity
- Nuclear grooves
- Sharply delineated nuclear membranes
- Intranuclear cytoplasmic protrusions
- Nuclear overlapping
- Elongated nuclei, oval nuclei (a normal nucleus is as big as an erythrocyte)
- Eccentric nucleoli
- ...

BUT

- Some PTC's may not exhibit all the charecteristic nuclear features while FA and FC exhibit focal clear or grooved nuclei.
- Scattered large hyperchromatic cells are very uncommon in PTC. No grooves, no oval nuclei, ...

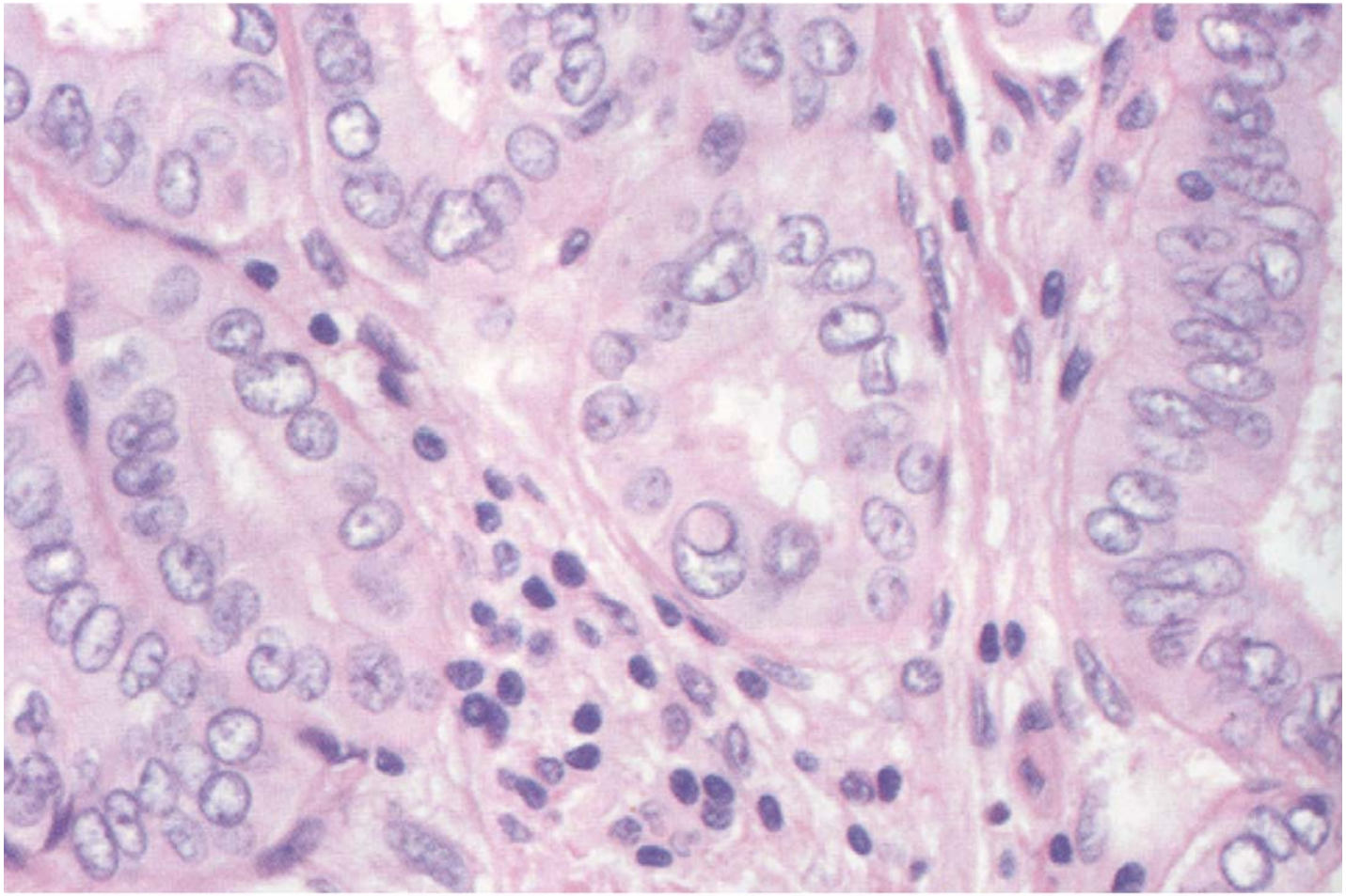
AJSP 28,10 oct. 2004. Most important criteria for the diagnosis of **FV** PTC, % = cases with this features

- Cytoplasmic invagination into nucleus 25%
- Abundant nuclear grooves 100%
- Ground glass nuclei 97%
- Psammoma bodies 16%
- Enlarged overlapping nuclei 98%
- Irregular shaped nuclei 100%

Less important criteria
% = cases with this features

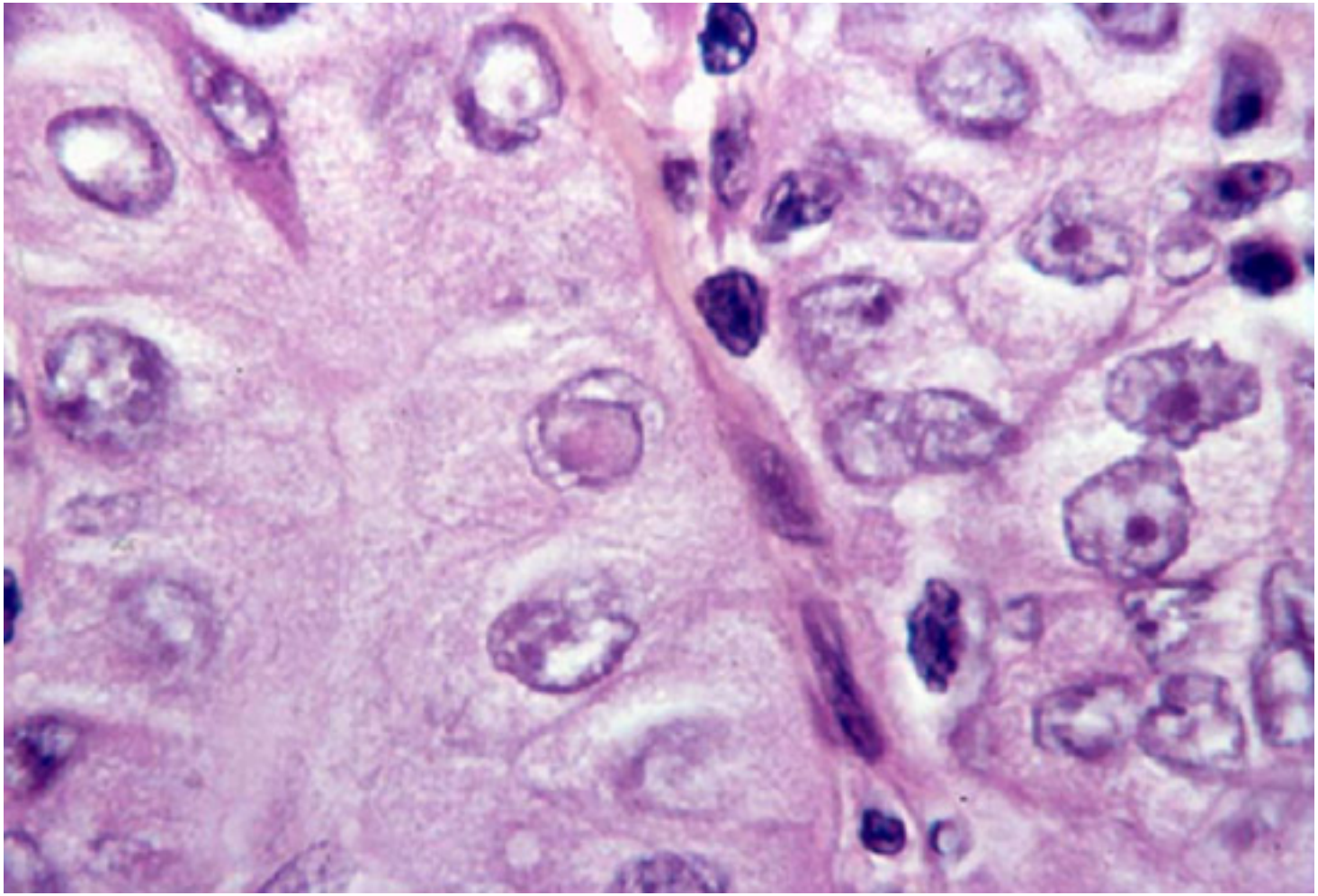
- Dark staining colloid 86%
- Irregular contours of follicles 64%
- Scalloping of colloid 58%
- Elongated follicles 80%
- Multinucleated macrophages in lumen of follicles 13%

PTC: Orphan Anny and overlap

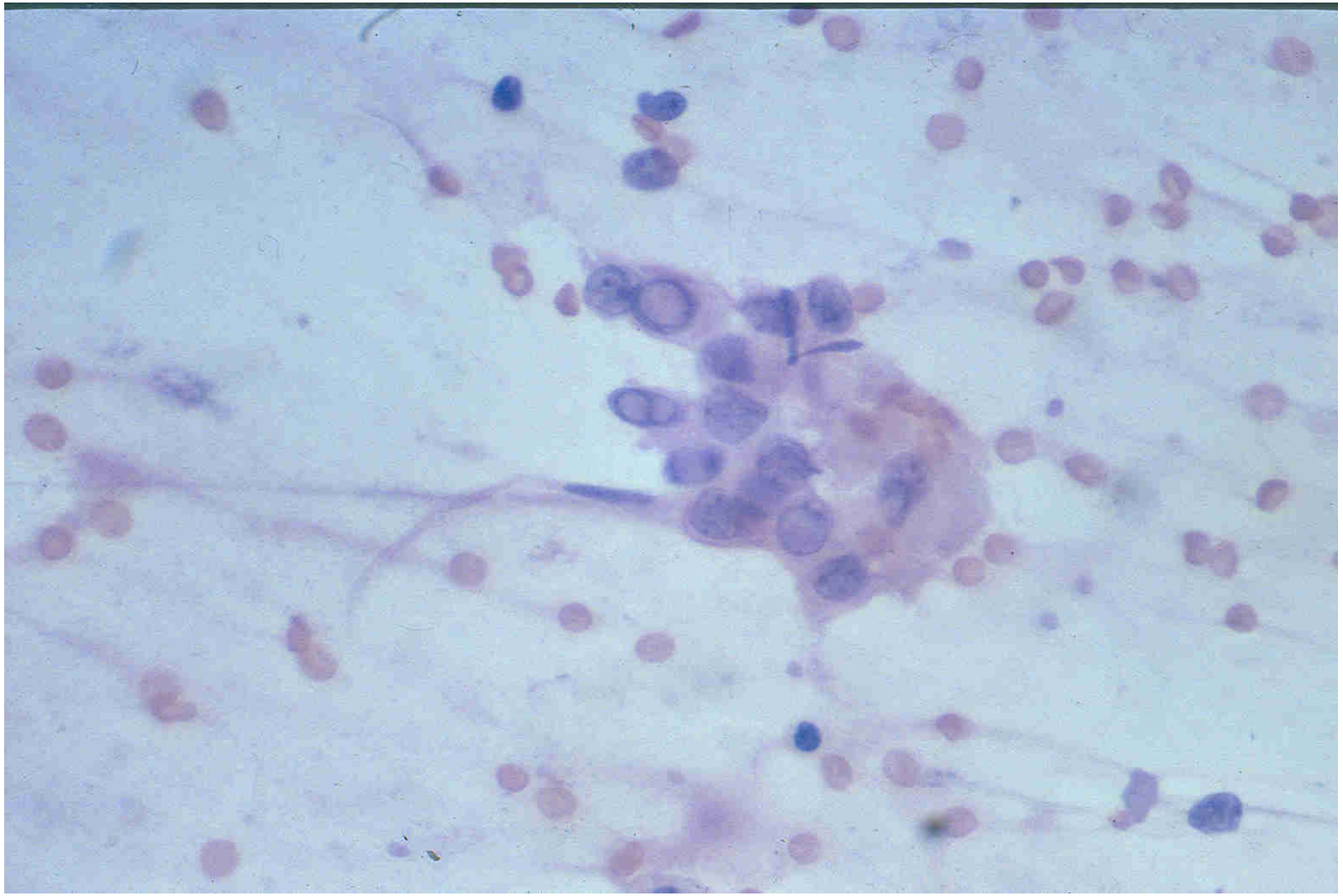


Paris 2006

Bubble artefacts lack a delimiting nuclear membrane

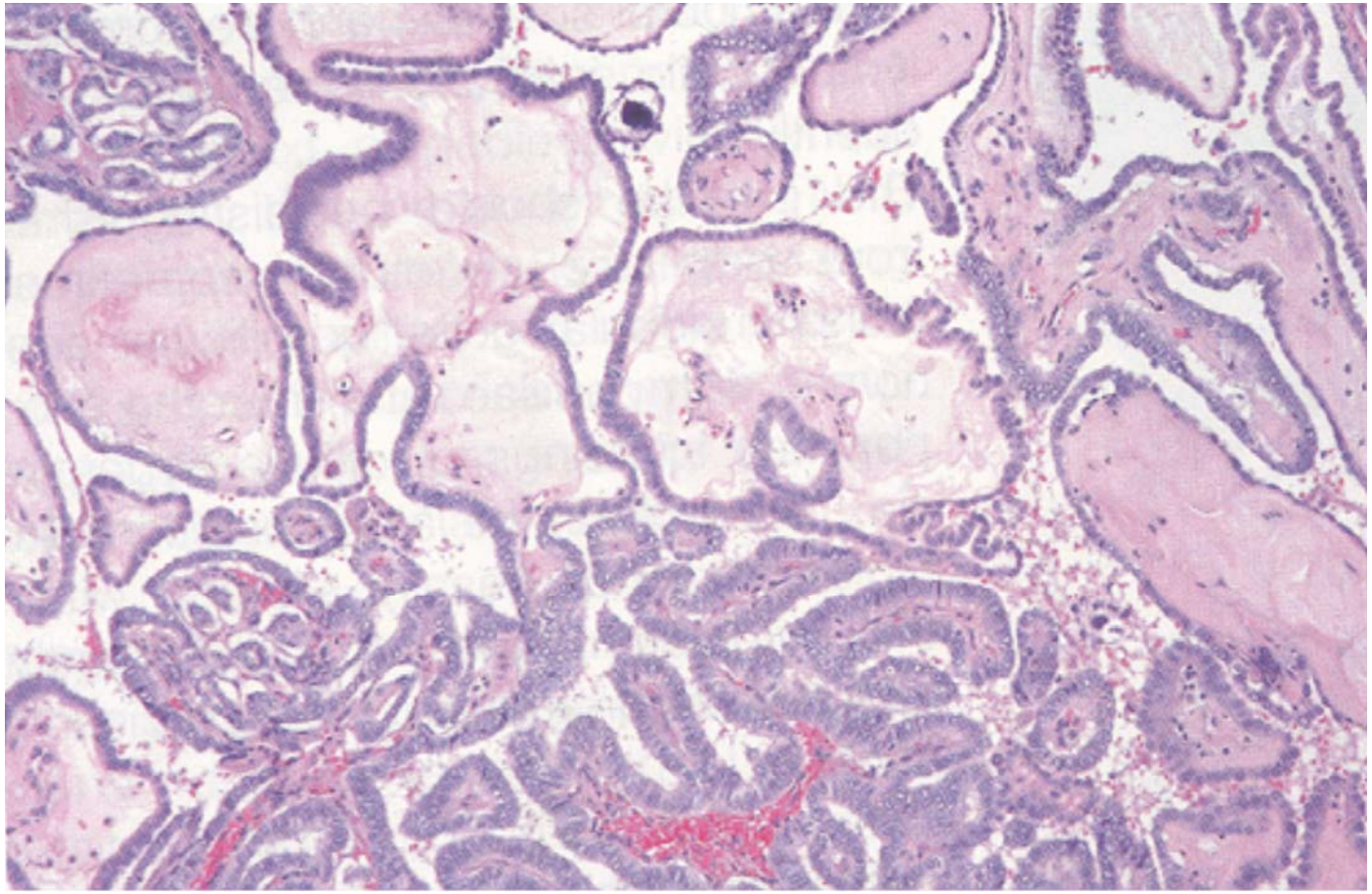


Paris 2006



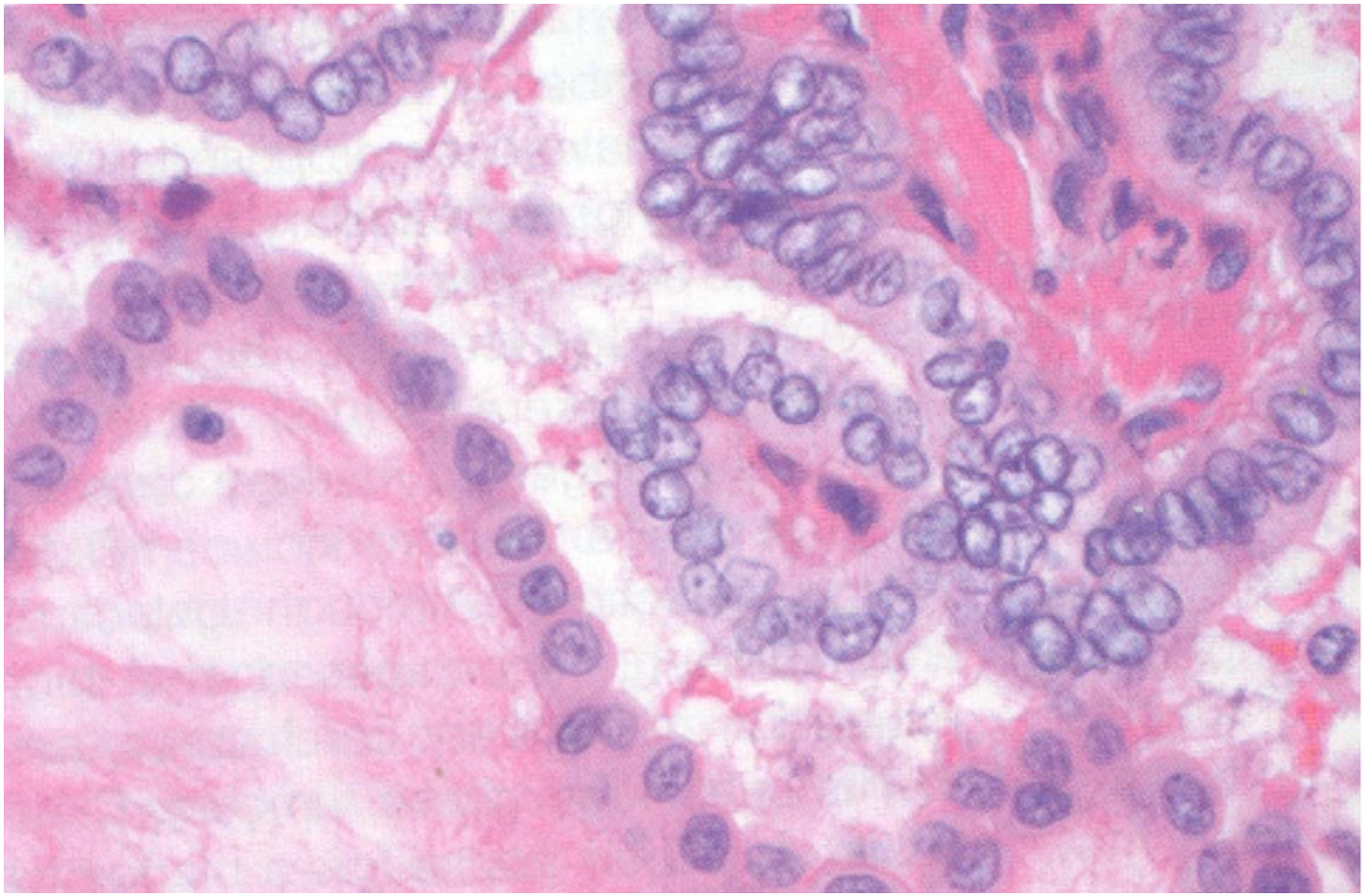
Paris 2006

PTC Papillarity



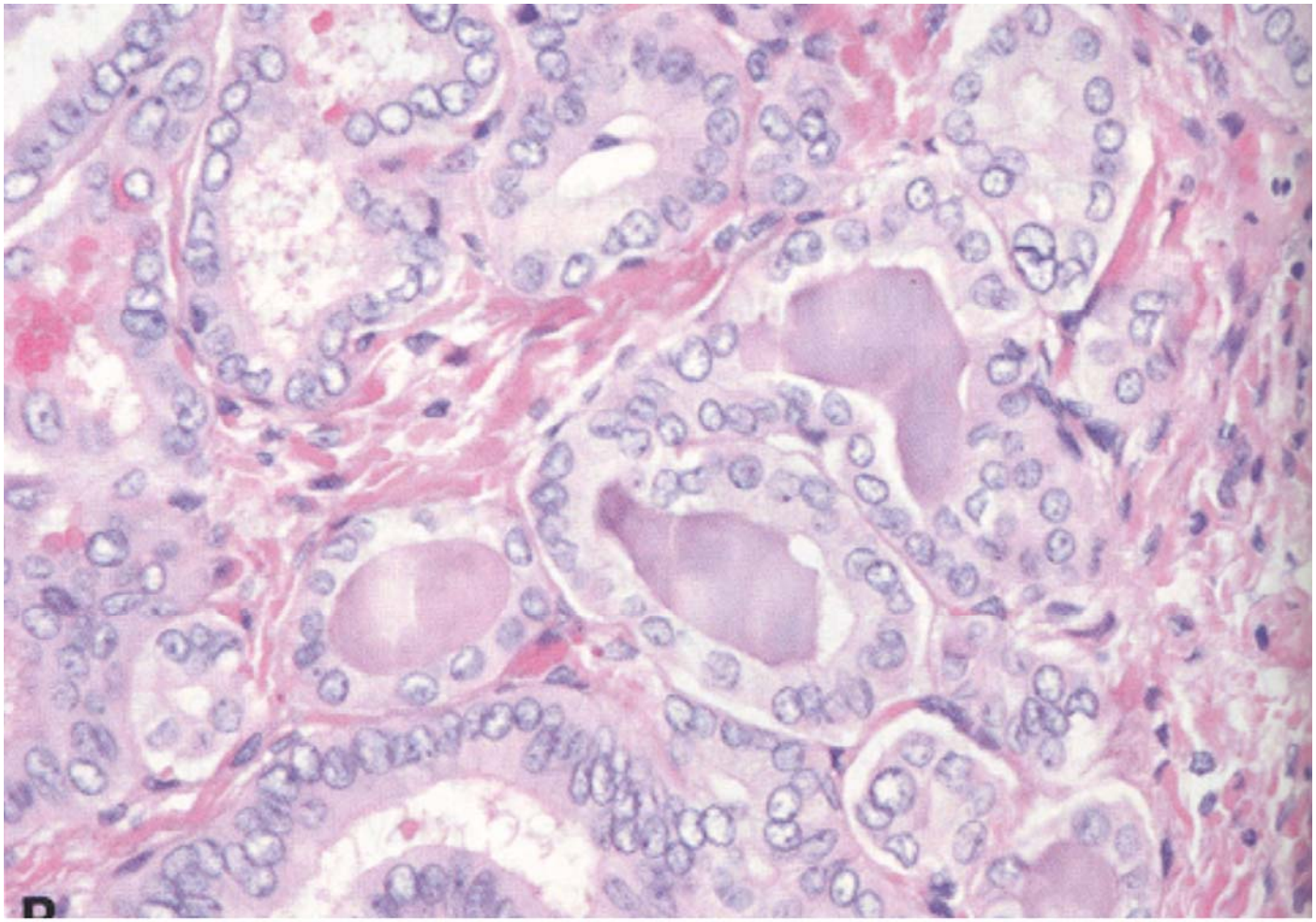
Ref.WHO

PTC: clear nuclei, grooves



Ref. WHO

PTC Basophilic colloid

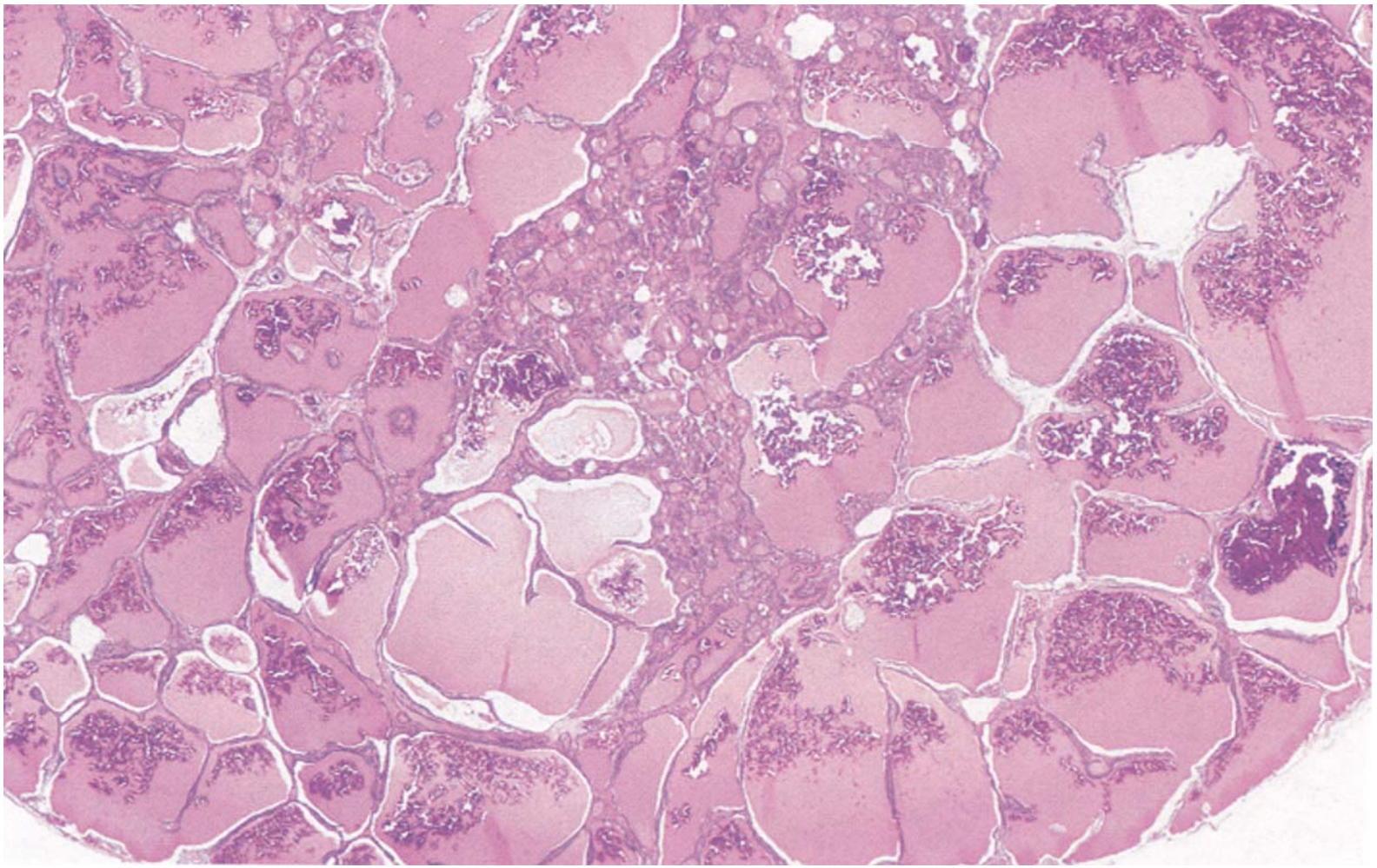


Ref. WHO

Macrofollicular variant of FV- PTC

- Only focal distribution of diagnostic nuclear features

Macrofollicular variant PTC

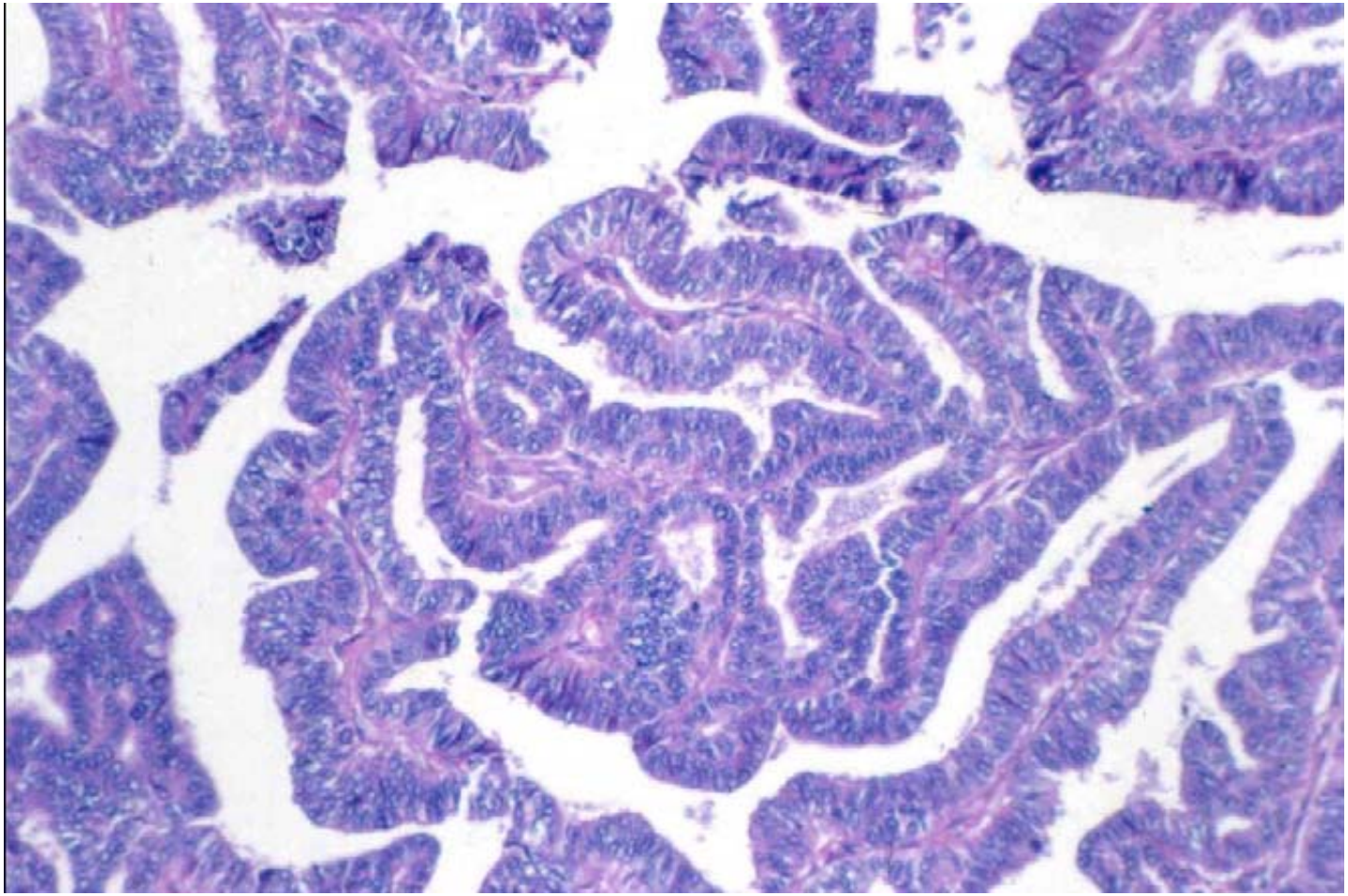


Ref. WHO

Columnar cell carcinoma: variant of PTC or separate entity ?

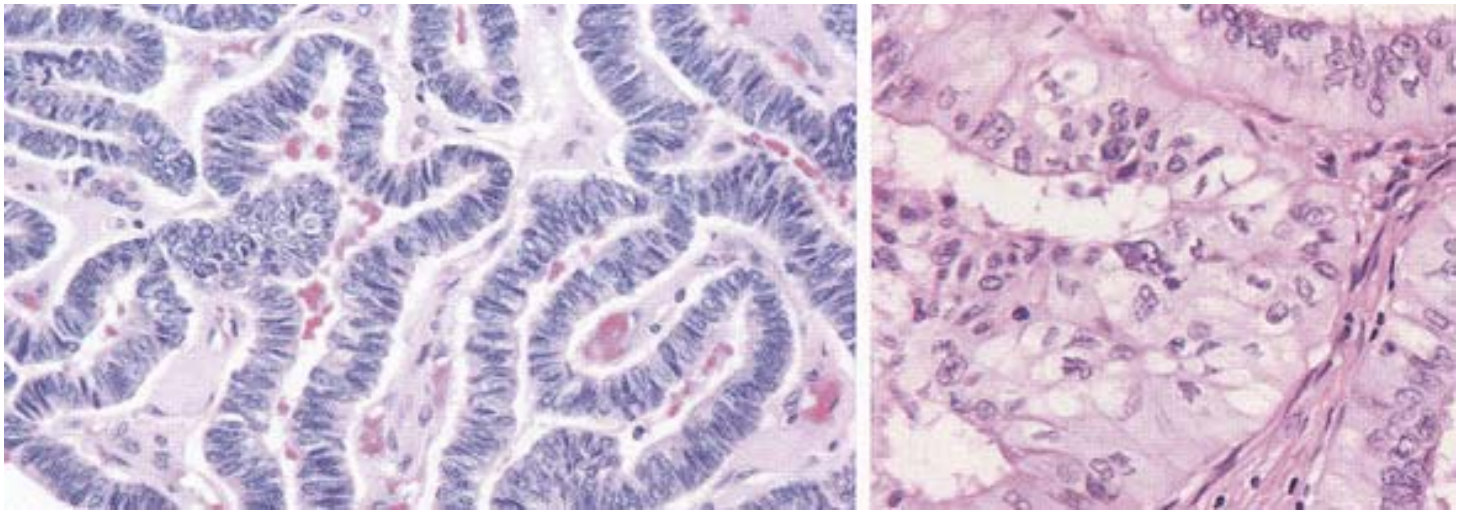
- Endometrial carcinoma or colonic carcinoma look
- DD Tall cell variant of PTC
- Striking nuclear pseudostratification
- Nuclear Hyperchromatism
- No PTC nuclei – Tall cell variant: PTC nuclei
- No oxyphilic change in cytoplasm

Columnar cell variant



Diagnostic histopathology 14:5,2008, p 236-243

PTC Columnar cell variant, subnuclear vacuolisation

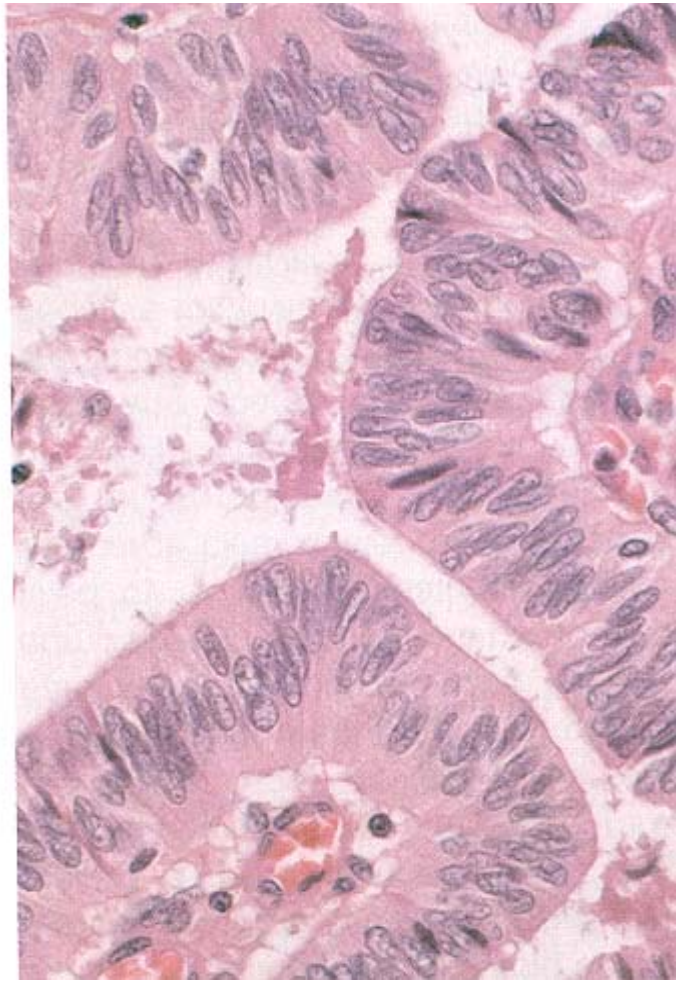


Ref. WHO

Tall cell variant Pap Ca

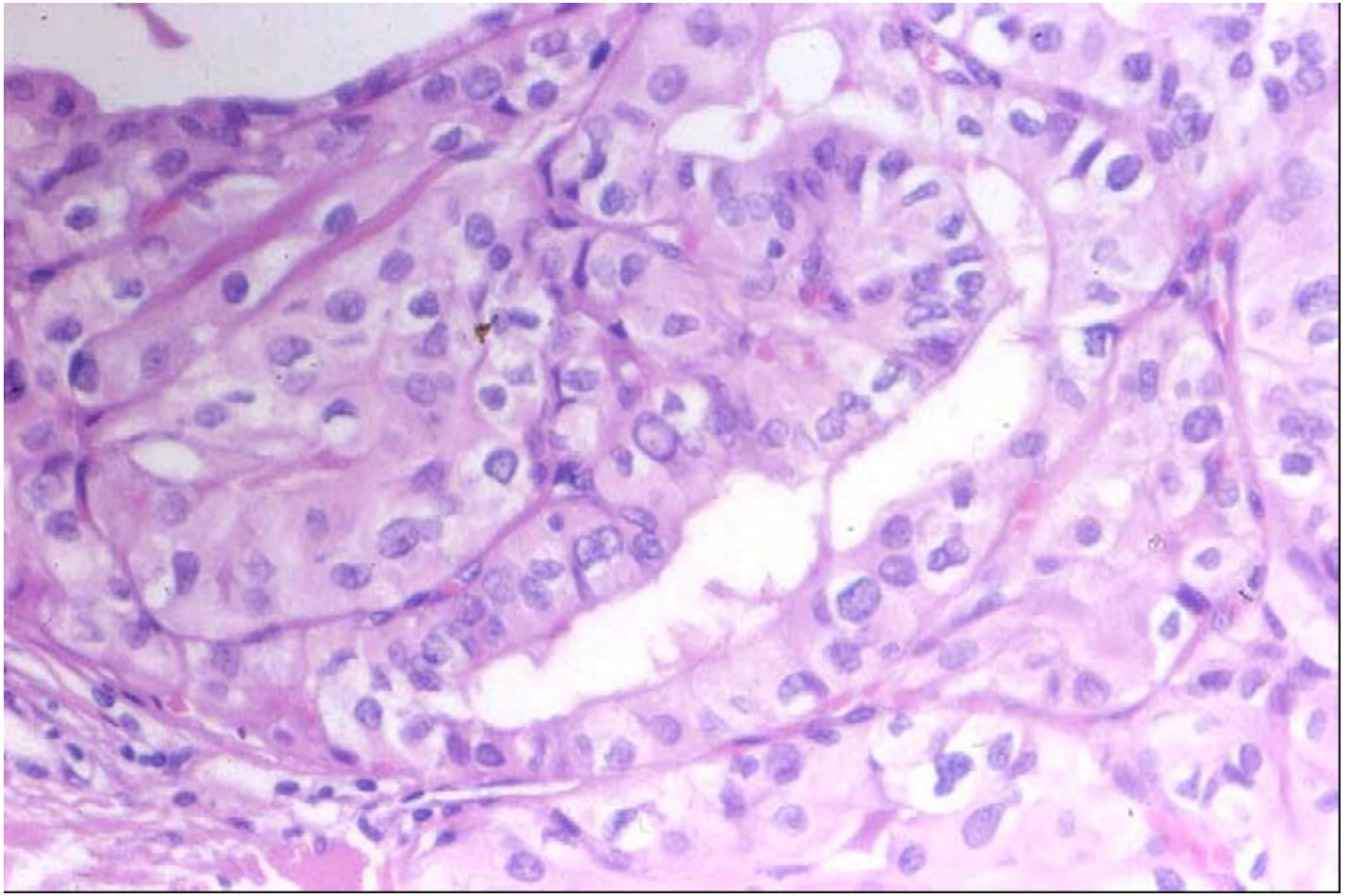
- Cells whose length is at least 3 times their width (for some autors 2 times)
- Abundant eosinophilic cytoplasm (DD with Columnar cell variant)
- Higher incidence of extra thyroid disease
- CD 15 pos, EMA positive
- Dedifferentiate like conventional PTC into Spindle ca, Squamous ca or Undifferentiated ca (Anaplastic ca)

Tall cell variant PTC



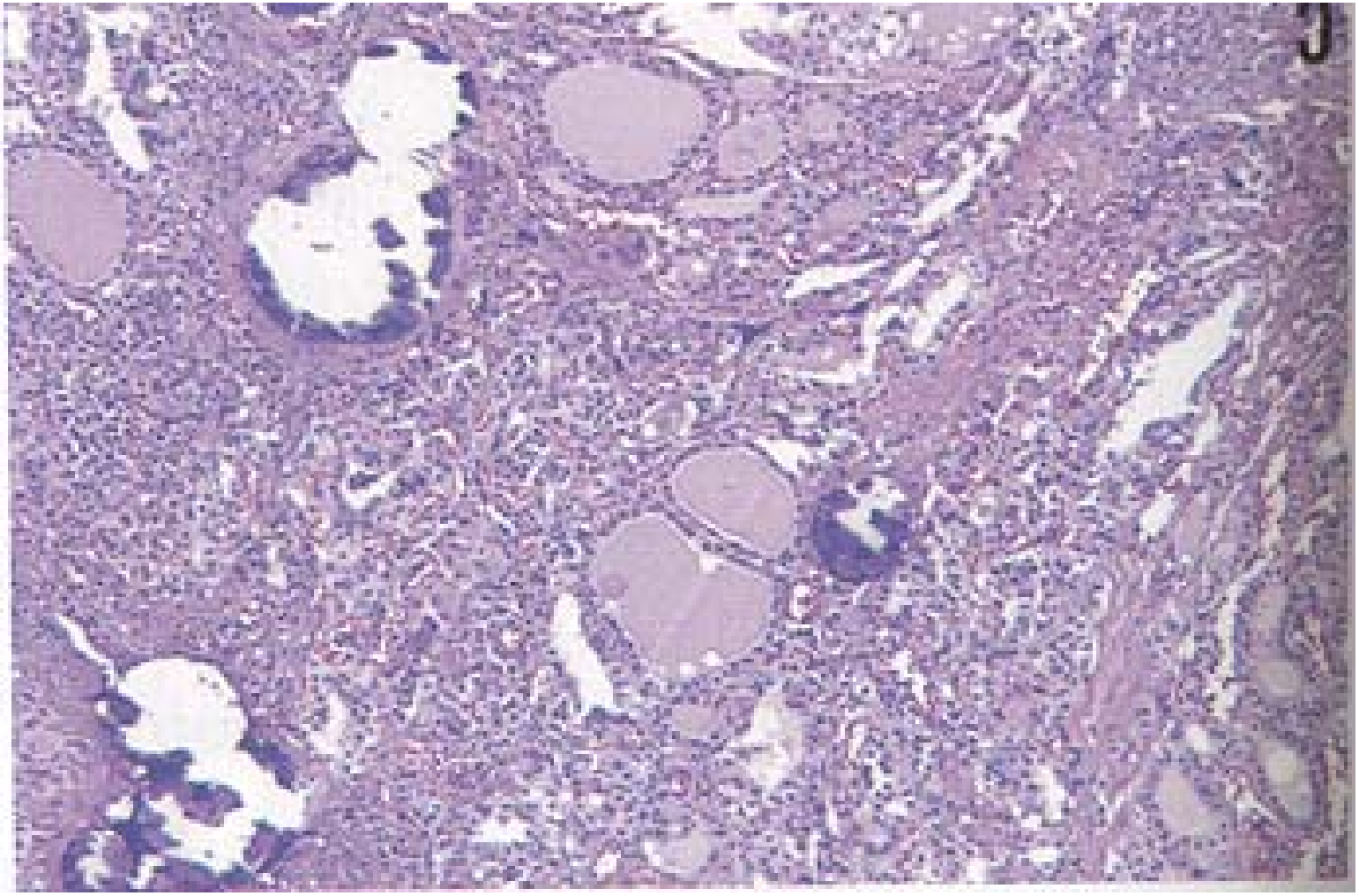
Ref. WHO

Tall cell variant



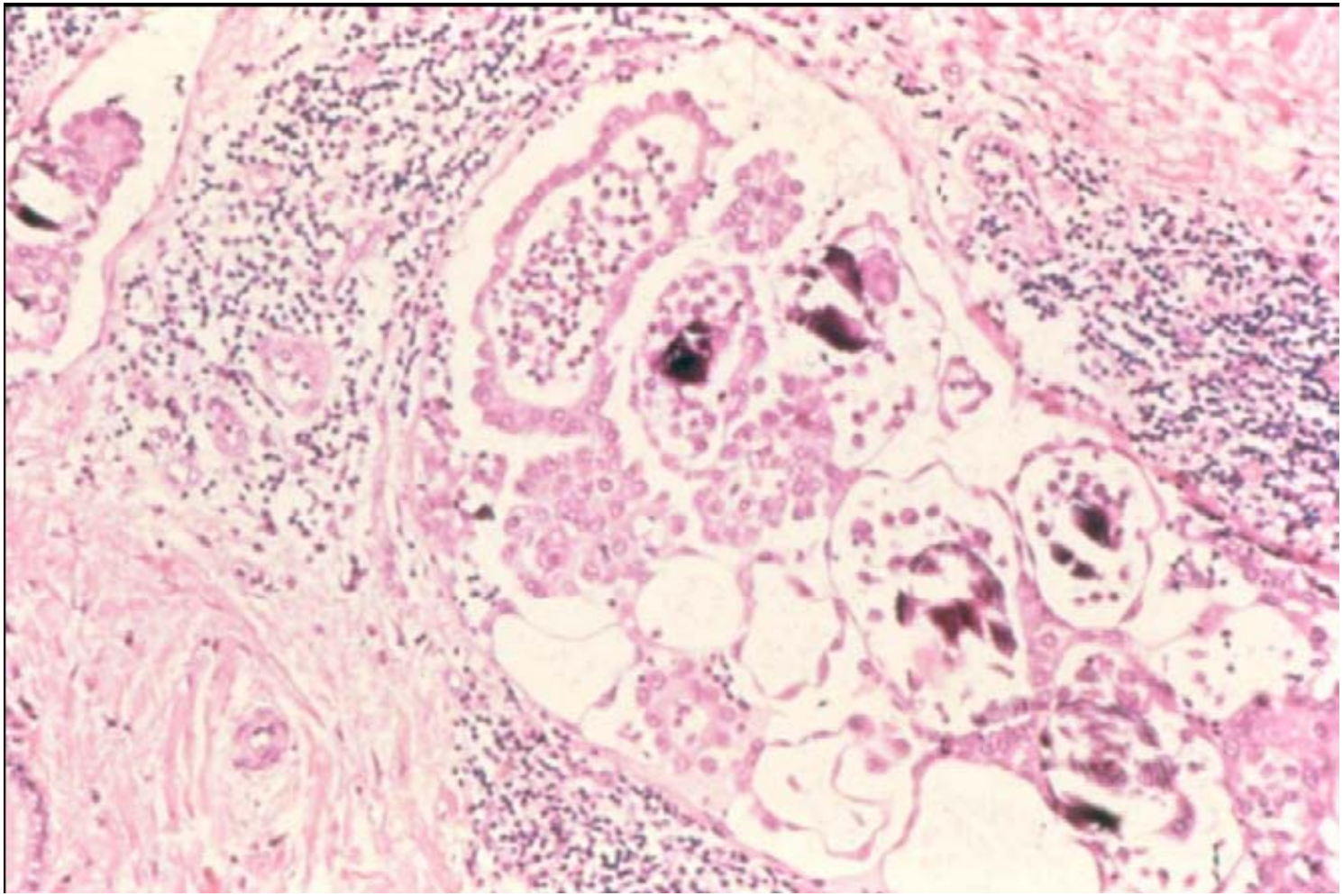
Diagnostic histopathology 14:5,2008, p 236-243

Diffuse sclerosing variant with microcalcificatios



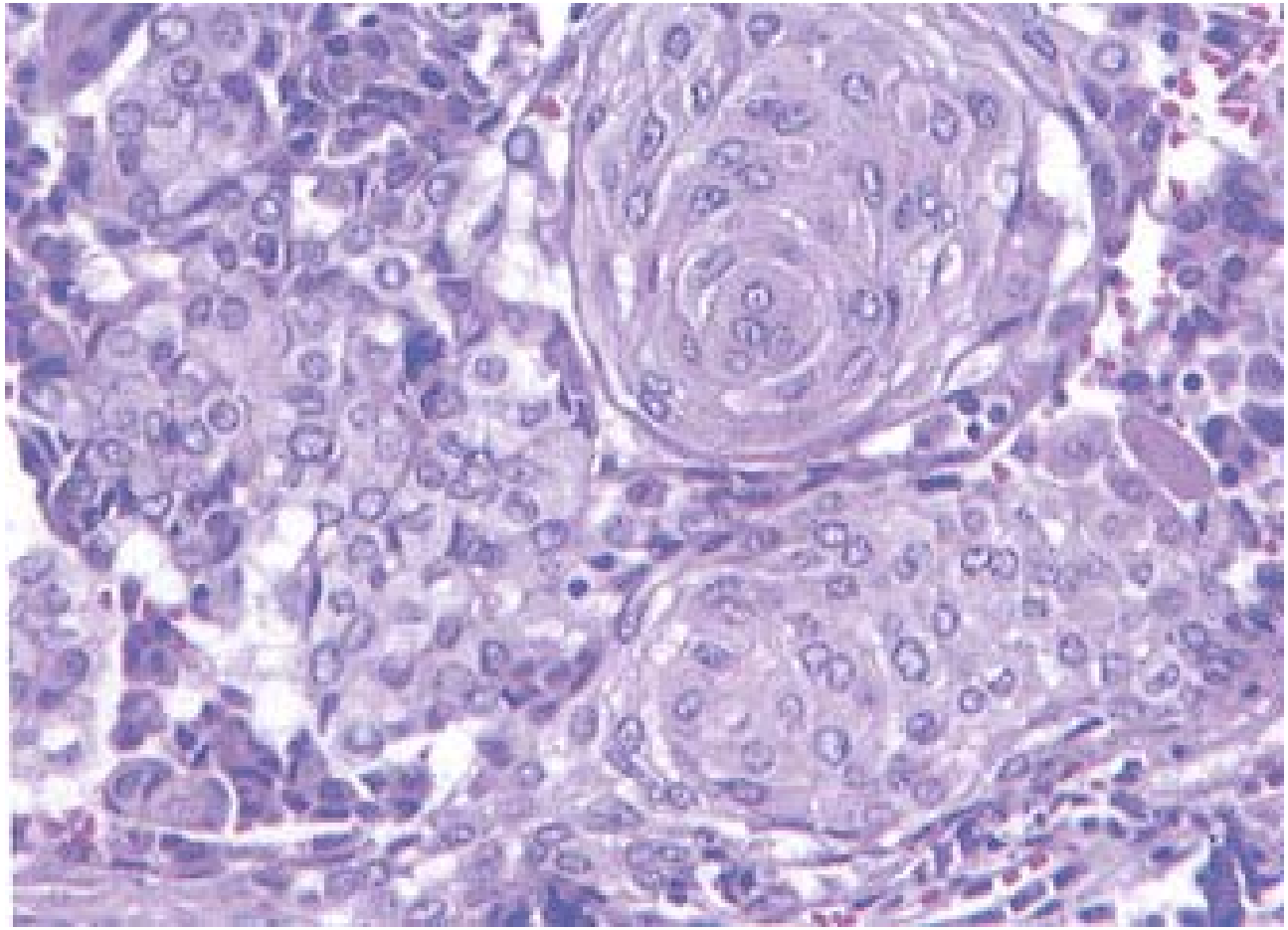
Ref. WHO

Diffuse sclerosing variant of PTC



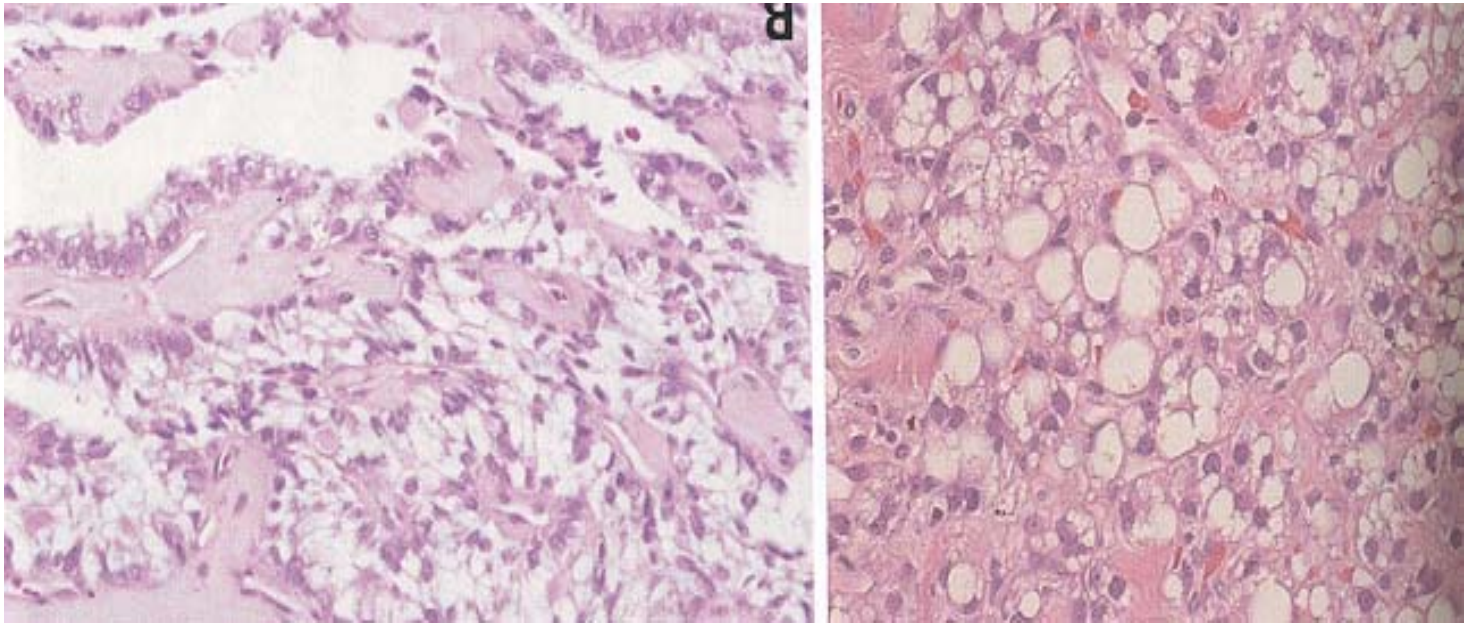
Diagnostic histopathology 14:5,2008, p 236-243

PTC with squamous metaplasia



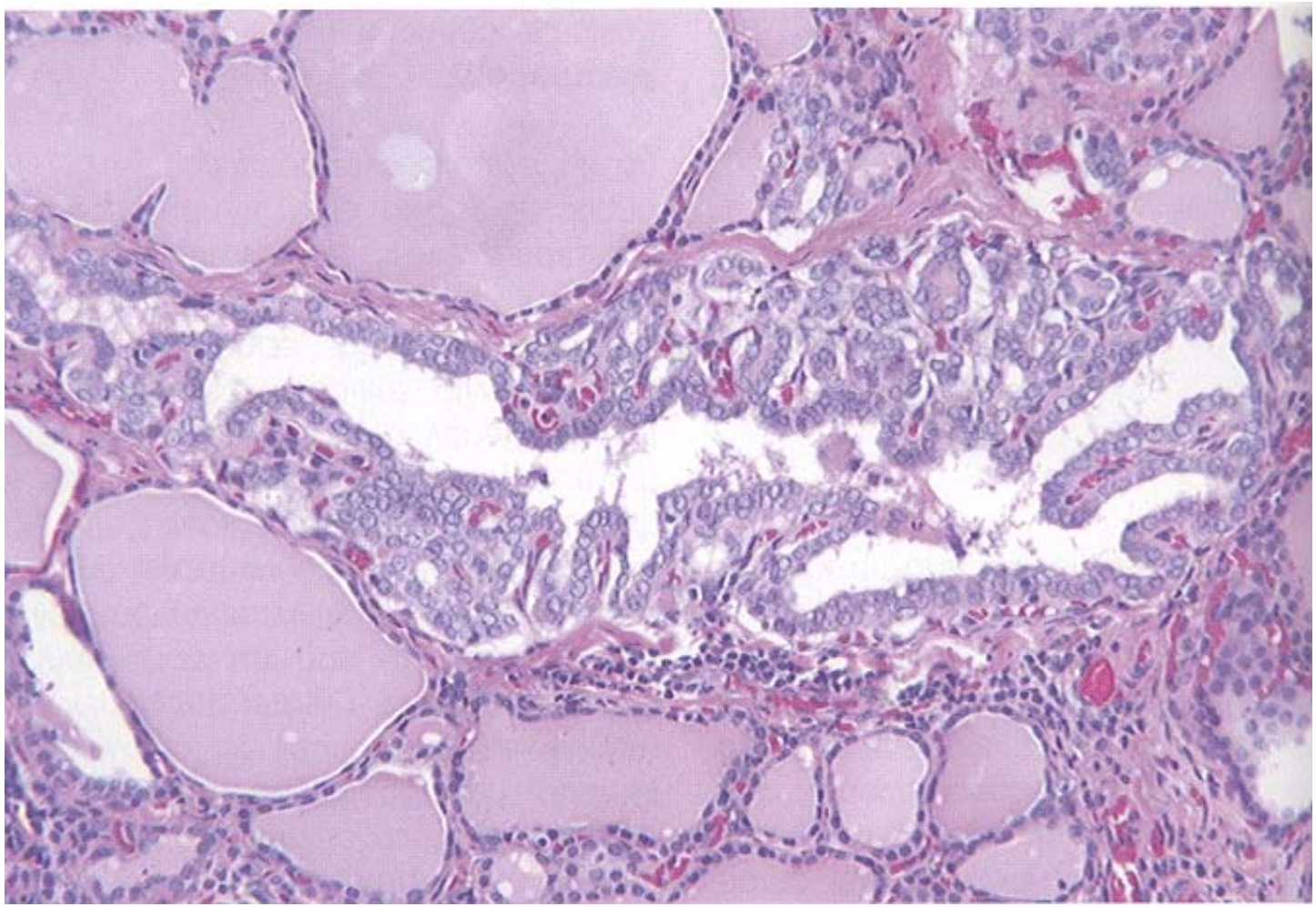
Ref. WHO

PTC Clear cell variant

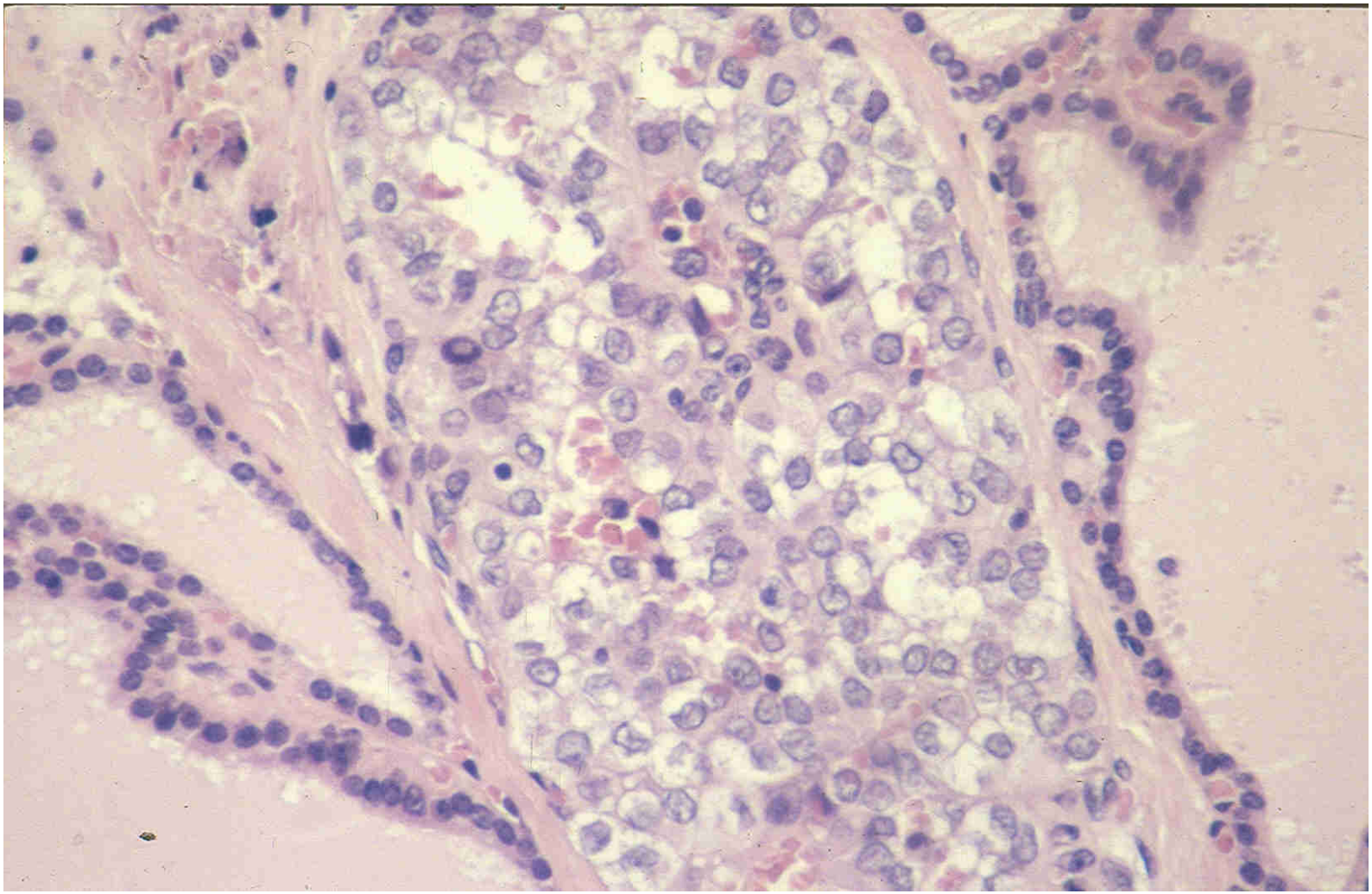


Ref. WHO

Micro PTC

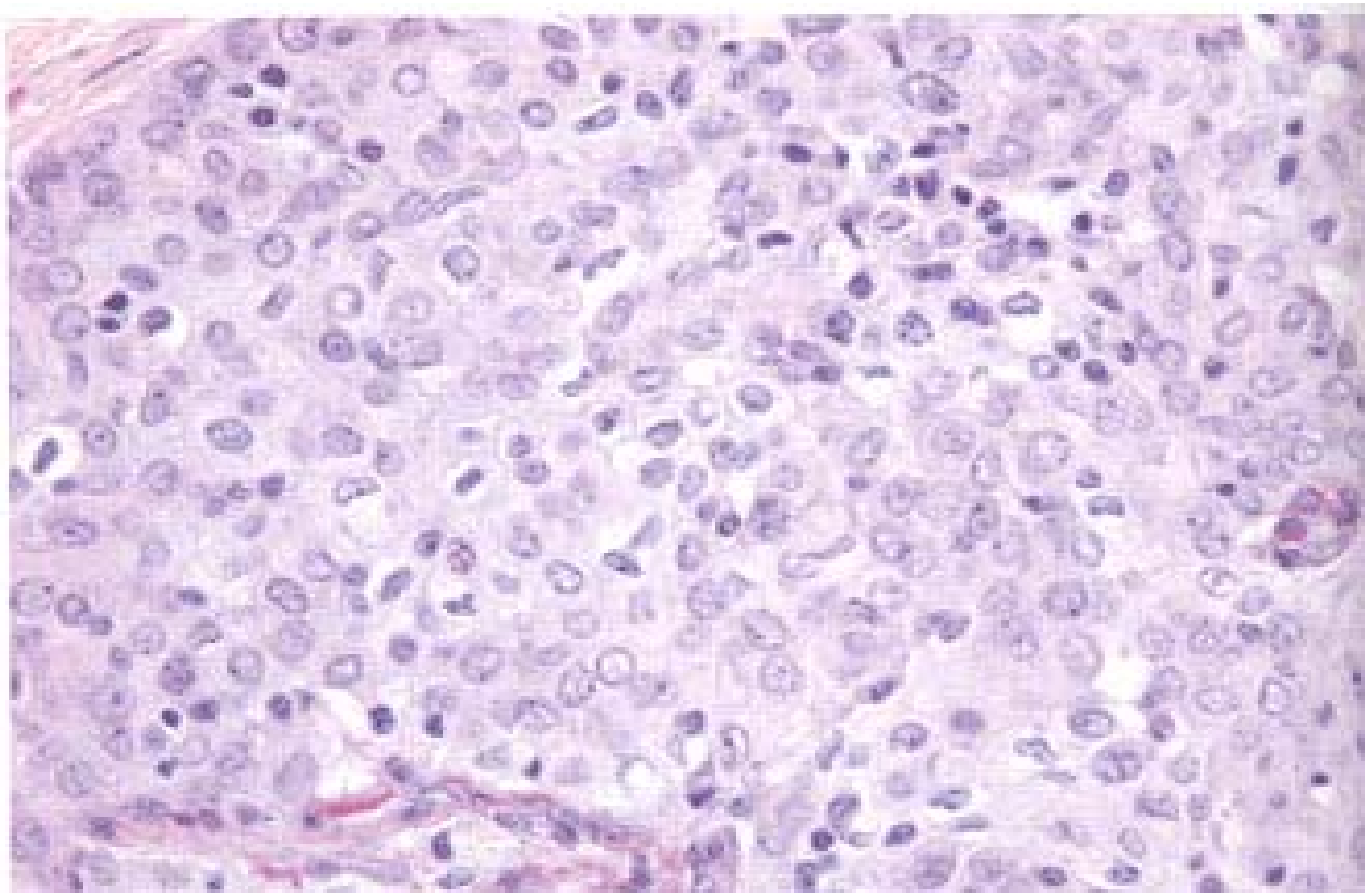


Ref. WHO



Paris 2006

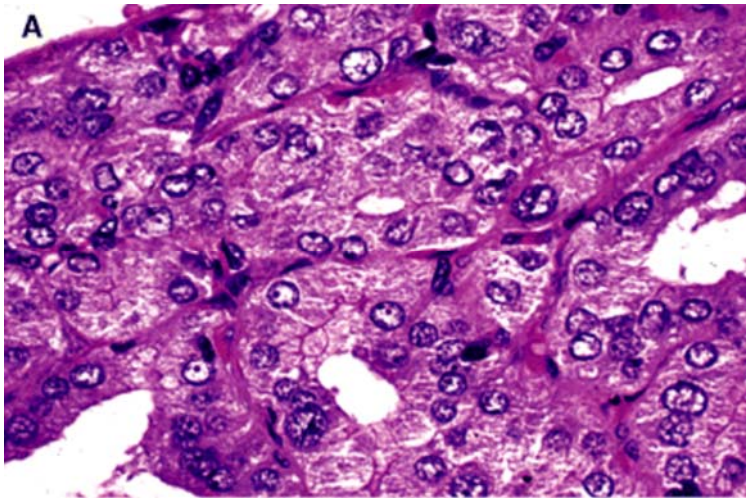
Solid PTC



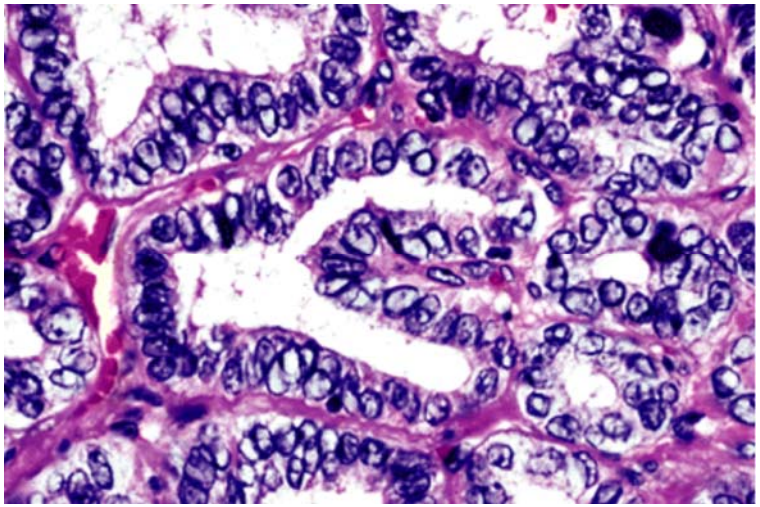
Ref. WHO

DD Solid growth

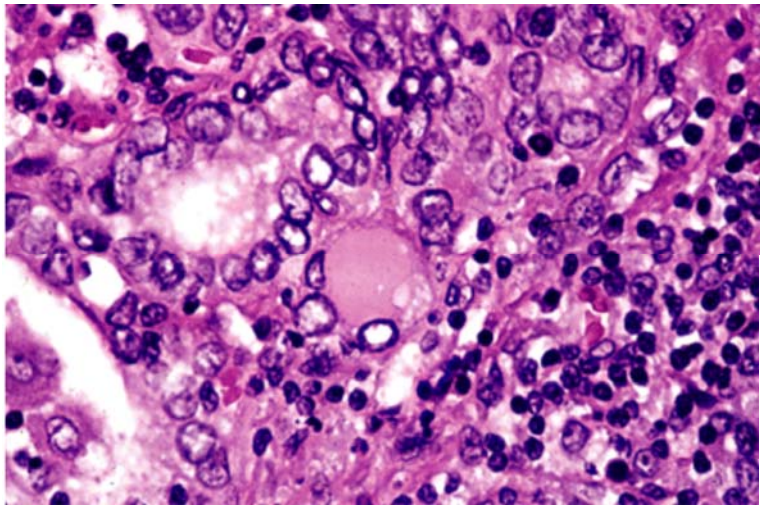
- FC
- PDC
- UC
- Med Ca
- CASTLE (with thymus like elements)
- Parathyroid Carcinoma
- Lymfoma
- Metastatic carcinoma
- MucoEpidermoid Carcinoma
- Solid PTC



Graves



PTC



Hashimoto

Histopathology 2006, 49, 107-120.

Seminars 12, 1, 1995 p 45-63

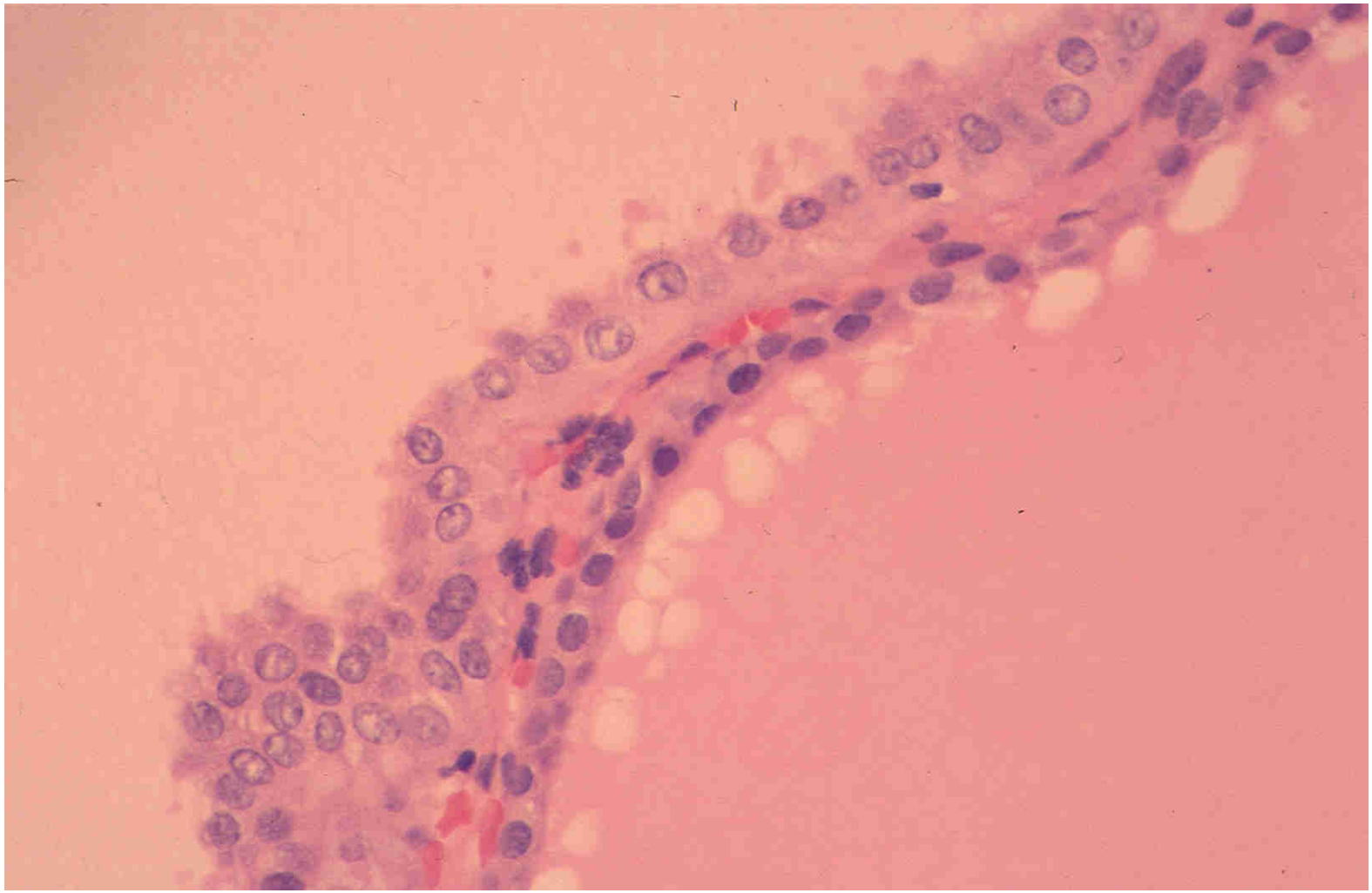
- Follicular adenoma's can exhibit clear or even grooved nuclei!
- Encapsulated PTC : prognosis is so good with lobectomy effecting cure in almost all cases. There is little consequence of mistaking it for a benign lesion

CDP: 2005, 11, p 52 - 59

- If PTC nuclei are concentrated in one of the nodules and tend to form one or several “microcarcinoma’s” then we make the diagnosis of FV PTC for the whole nodule
- Take home lesson: Even if one is seeing a lesion resembling a “fetal” follicular adenoma one should look carefully for the nuclear features

Nuclear Bubbles - Clearing

- Artefact due to underfixation



Paris 2006

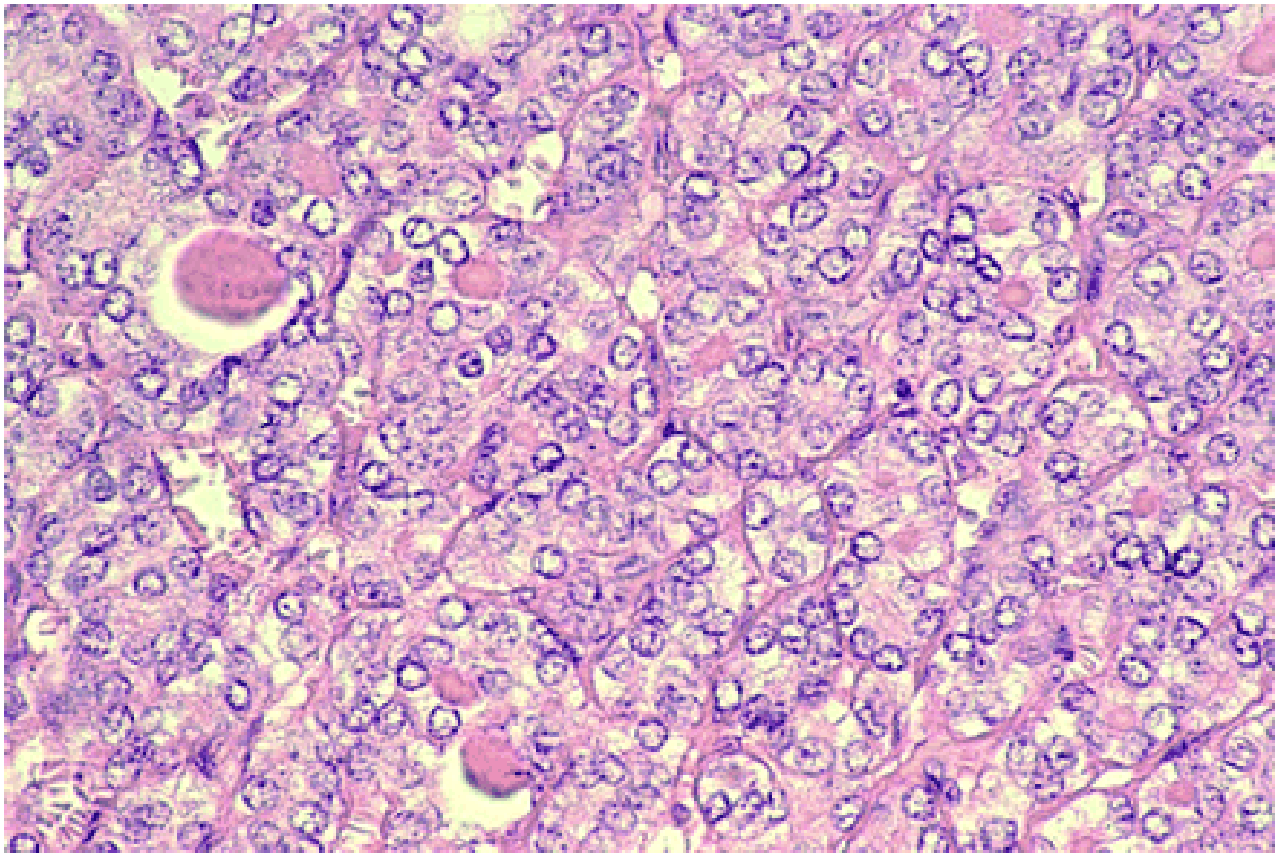
Tissue reaction PTC

- Exuberant nodular fasciitis-like stromal reaction to PTC obscuring the neoplastic nature of the process

FV-PTC “The real problem “

- Nodule with a single zone of PTC nuclei is a FV PTC
- There is an abrupt change in nuclear morphology compared with the surrounding benign portion.
- Sometimes very difficult to recognize

Follicular Variant of Papillary Carcinoma, FV PTC



Ref. WHO

FV PTC: three subtypes

- Encapsulated
- Poorly circumscribed
- Diffuse, multinodular

FV PTC

- 1.Nuclear clearing in it may be very focal
- 2.Nuclear clearing is clonal and subcapsular
- 3.Follicular neoplasm: nuclei are round, smaller often centrally located clearing due to poor fixation, and change has a diffuse edge.

Histopathology 48 , 6 May 2006 p 629

Diffuse variant of FV PTC "A trap"

- Replaces the whole thyroid
- No edge to the tumor
- No normal thyroid to compare with

Calcification

- Calcificated nodule: always decalcification because there are often small PT CA.

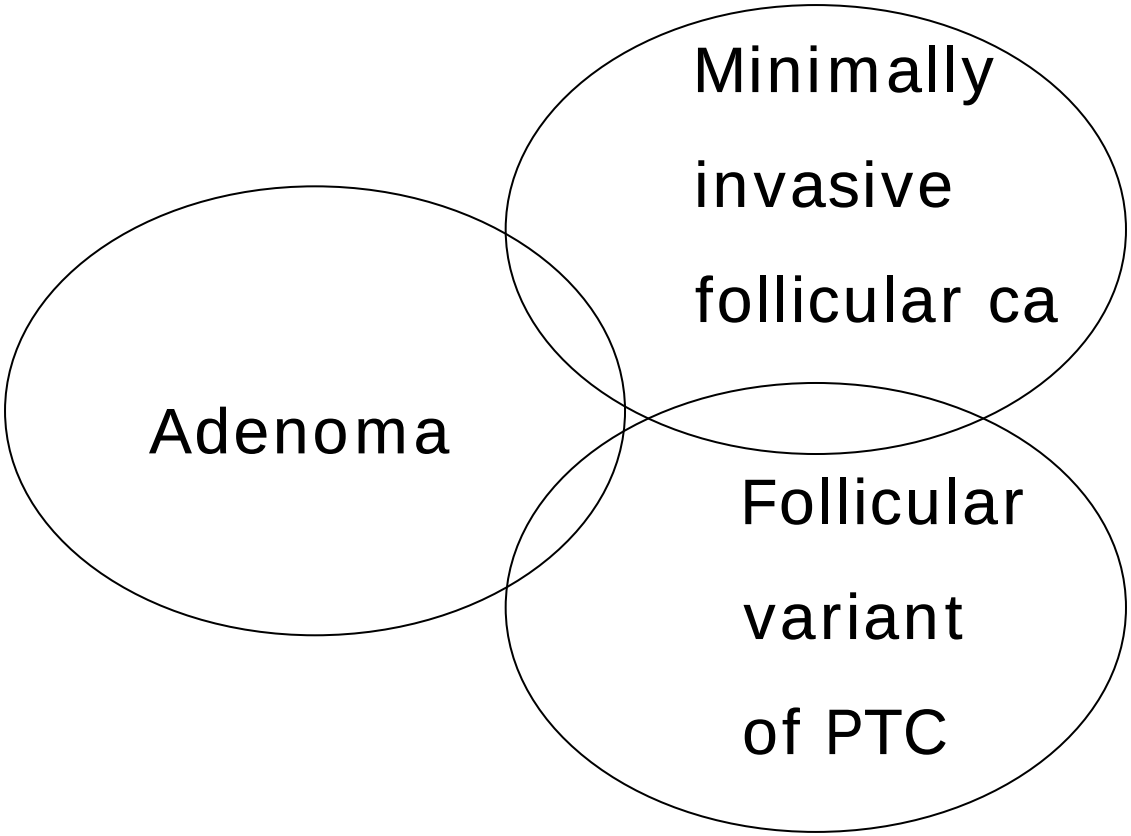
Psammoma bodies

- Typical of PTC
- Often when Hurtle cell differentiation: psammoma like bodies
- Hashimoto thyroiditis
- Many in diffuse sclerosing variant of PTC

CDP 2005 11 p52 59

- Small foci of PTC nuclei in benign lesions is not restricted to follicular adenoma's.
- Also Hashimoto's thyroiditis and nodular (adenomatous) goiter.
- If large, clear, irregular nuclei are rare and do not form clusters we do not go beyond the diagnosis of goiter

Follicular patterned, encapsulated neoplasms



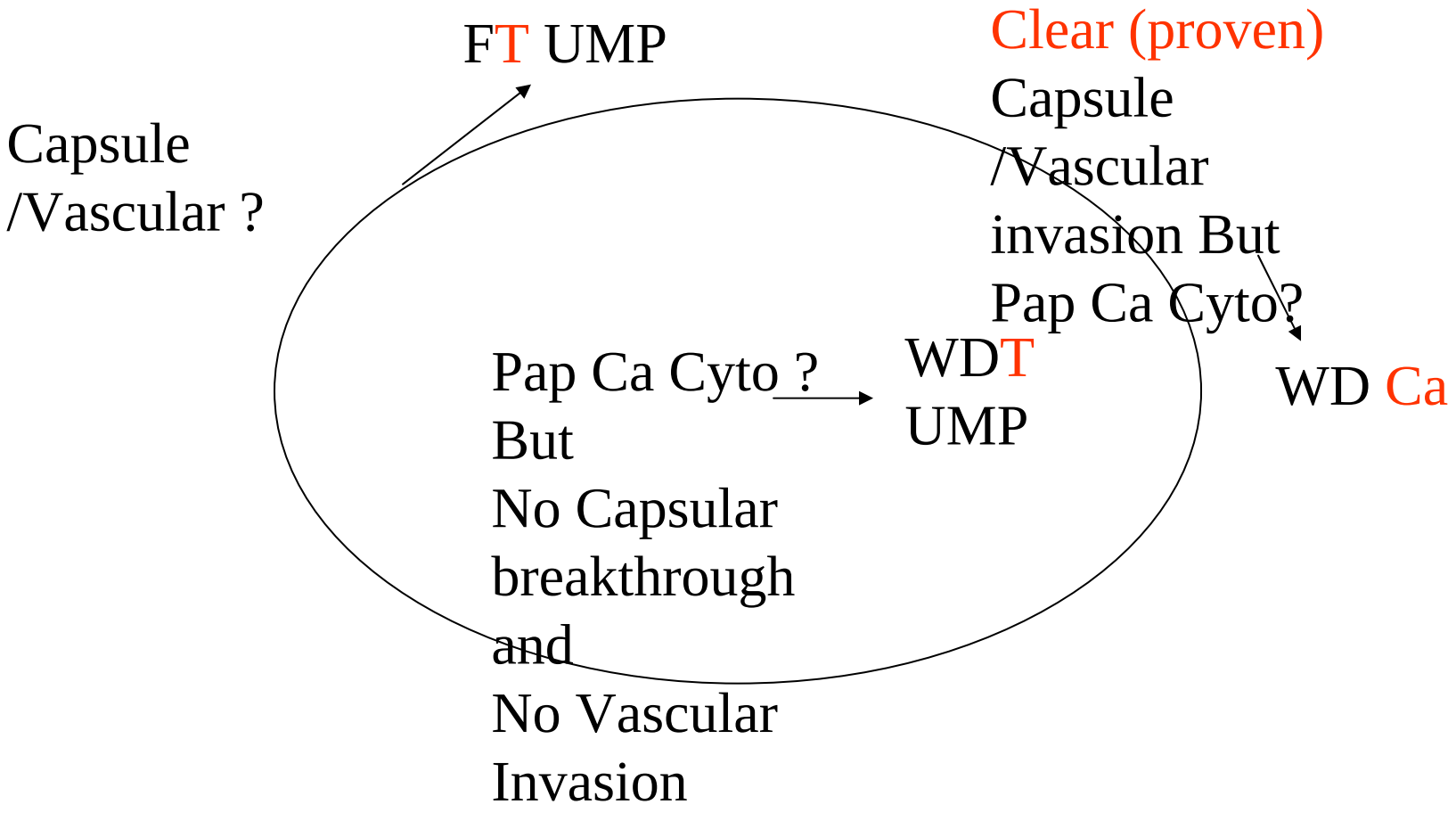
3.5 Well differentiated tumour of uncertain malignant potential

- Follicular architecture and cytology suspicious for papillary carcinoma
- **No** capsule and/or vascular invasion. **Not** suspicous for vascular and/or capsular invasion.

Well differentiated carcinoma

- Capsular and/or vascular invasion
- Cytology is unclear for Pap CA but suspicious for Pap Ca
- Fol. Ca has no lymphocytic infiltrate what so ever . PTC has always more or less lymphocytic infiltrate

Doubt


FT UMP
Clear (proven)
Capsule
/Vascular
invasion But
Pap Ca Cyto?
Capsule
/Vascular ?
Pap Ca Cyto ?
But
No Capsular
breakthrough
and
No Vascular
Invasion
WDT
UMP
WD Ca

Unknown malignant potential UMP

- Follicular Tumour (FT) UMP Capsular breakthrough and/or vascular invasion?
- Well Differentiated Tumour (WDT) UMP

  PTC cytology in doubt and no capsular or vascular doubt
- Well differentiated carcinoma if there is clear vascular invasion and/or capsular breakthrough but there is doubt about the PTC cytology

WD Carcinoma

- Well differentiated carcinoma if there is clear vascular invasion and/or capsular breakthrough but there is doubt about the PTC cytology

3.6 Pitfalls
Histopathology 49, 107-120

- Tumour herniation through a capsule
- Reactive vascular proliferation simulating vascular invasion
- Pseudo infiltration of skeletal muscle
- Parasitic noduli simulating metastatic thyroid ca

3.7 Prognosis PTC and FC

- Women have a better prognosis
- With age prognosis get worse
- Before 45 year prognosis is much much better (Man 40 years, Women 50 years)
- Every 10 year prognosis decreases significantly
- Extrathyroid extension or more than 5 cm diameter make them high risk

Prognostic factors in papillary and follicular thyroid carcinoma

- Completeness of surgery and responsiveness to radioactive iodine

A – Age
M – Distant metastases
E – Extrathyroid extension
S – Size of the tumours

Still debatable: aneuploidy (D...AMES), vascular invasion and molecular features (MIB1, p53)

3.8 Medullary Carcinoma: Intermediate grade

- 80% have amyloid, 20% have no amyloid
- Small proportion is calcitonin negative
- Chromo and Synapto and CEA are usually positive
- C cell Hyperplasia is not Med ca
- C cells are most frequent in the lateral regions of the upper poles of the thyroid
- In young and old persons there are C cell aggregates
- Neuroendocrine nuclei instead of PTC nuclei or small nuclei of FC

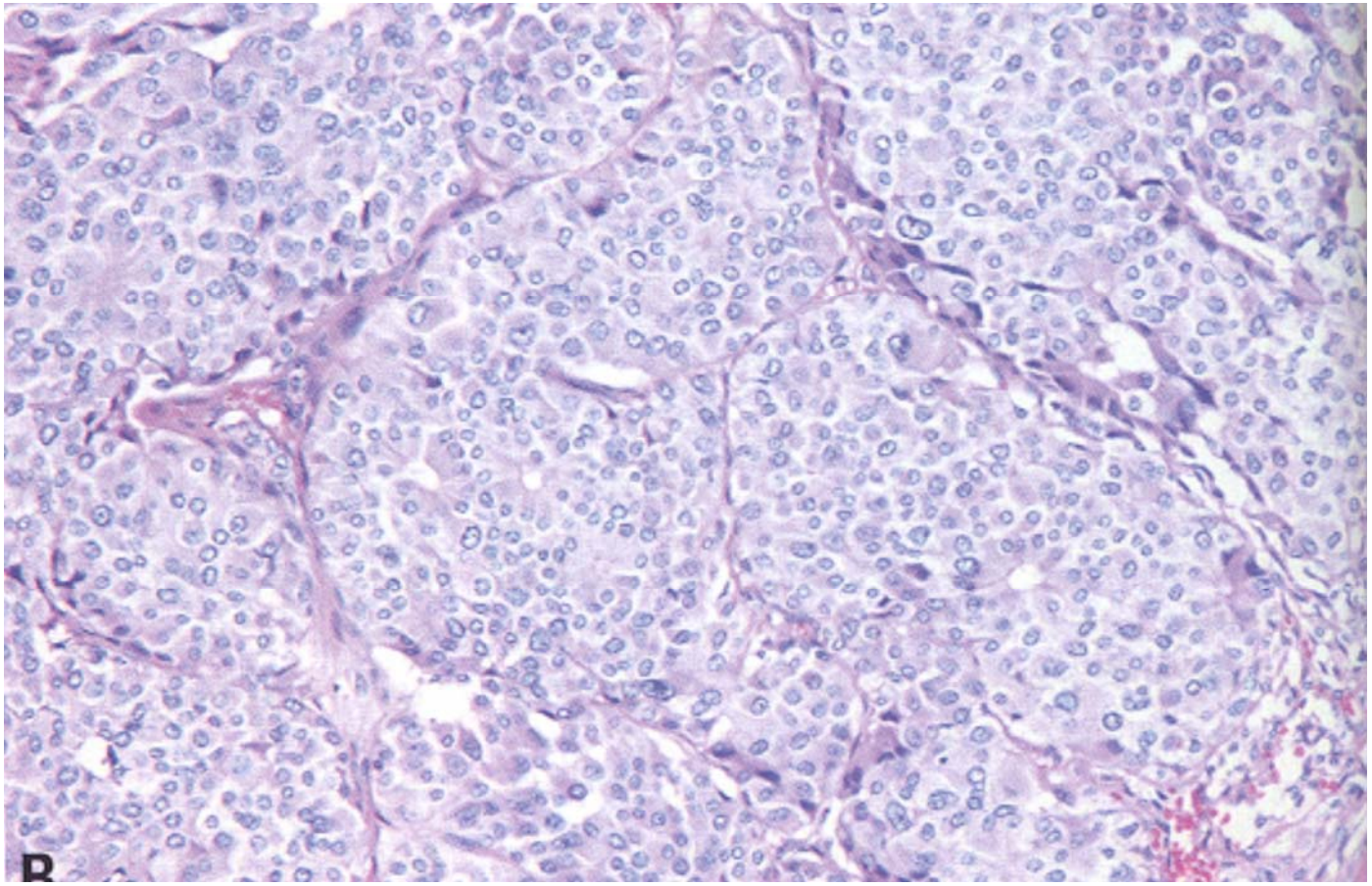
Med. Ca

- Familial form versus occasional form
- Always genetic counseling
- There is no anaplastic med. Ca. (Undifferentiated)
- DD Meta carcinoid lung

Histological Patterns of Medullary Carcinoma (Uscap Short Courses 2004)

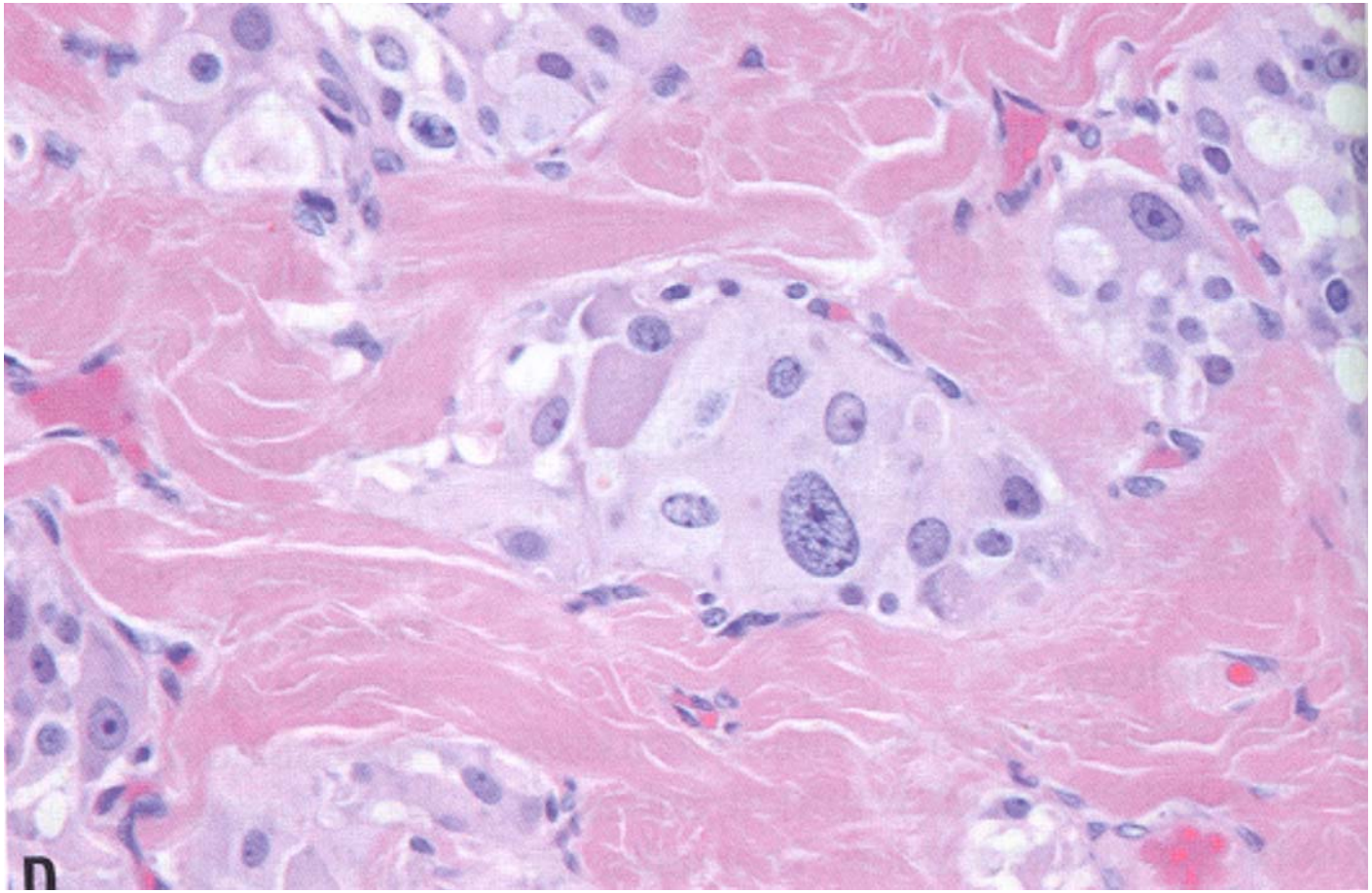
- Epithelial (nested)
- Spindled
- Mixed spindle and epithelial
- Papillary
- **Follicular**
- Glandular
- Giant cell
- Small cell
- Clear cell
- Oncocytic
- Squamous
- HTT like
- Carcinoid like
- Pseudo angiosarcoma
- Pigmented
- Neuroblastoma like
- Paraganglion like
- ...

Med. Ca



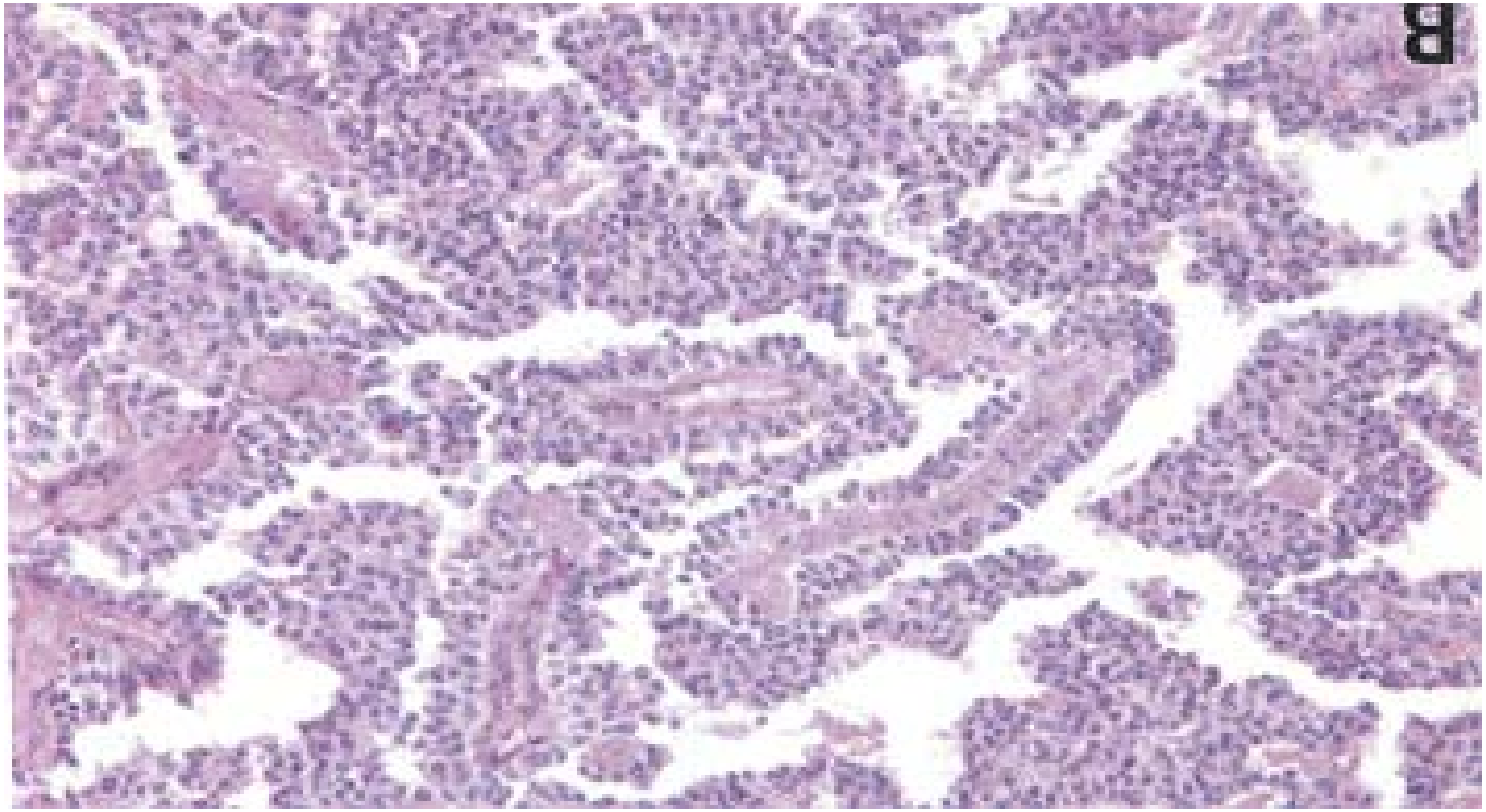
Ref. WHO

Med. CA insular pattern



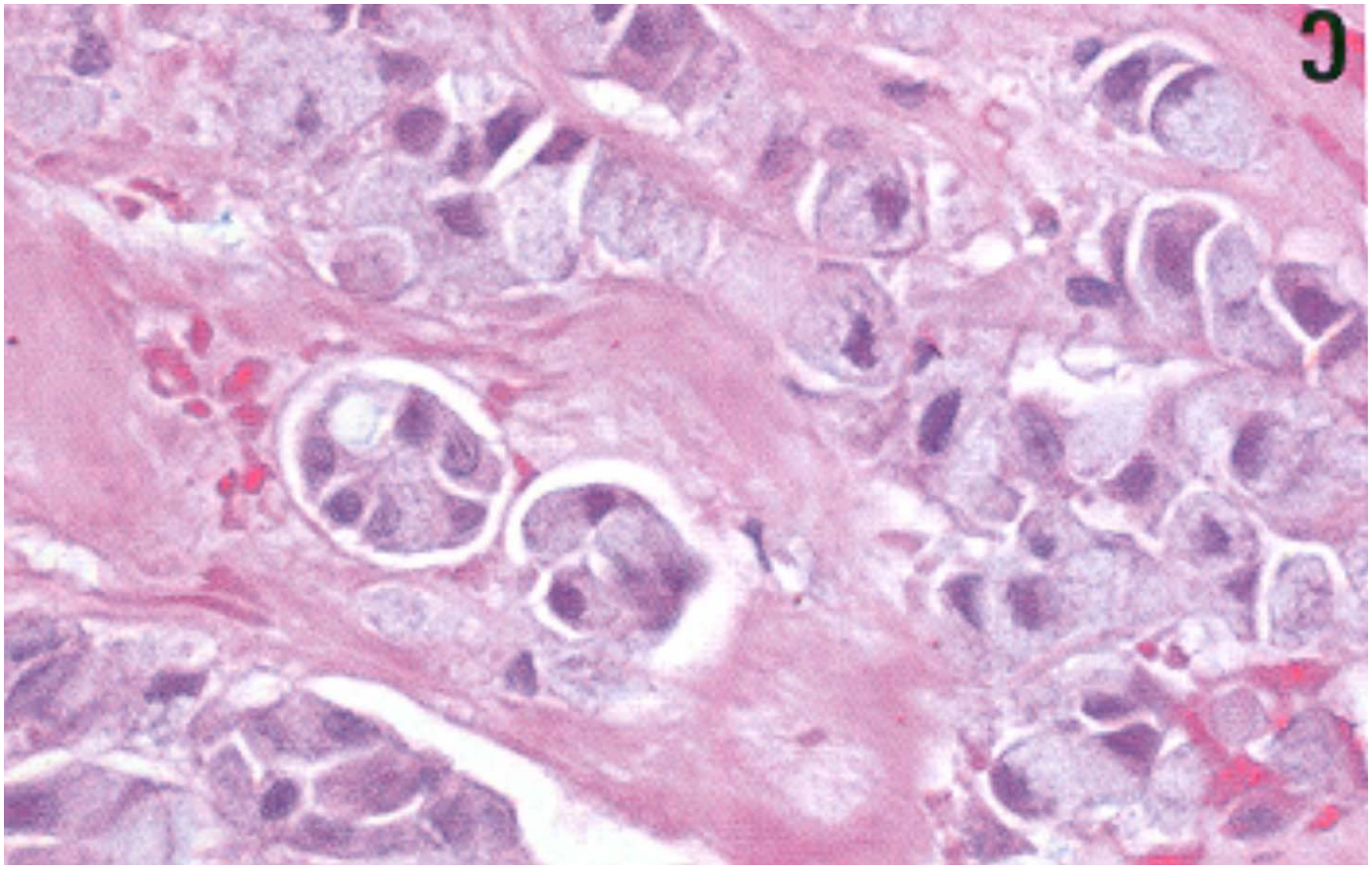
Ref. WHO

Med. Ca Pseudopapillary pattern



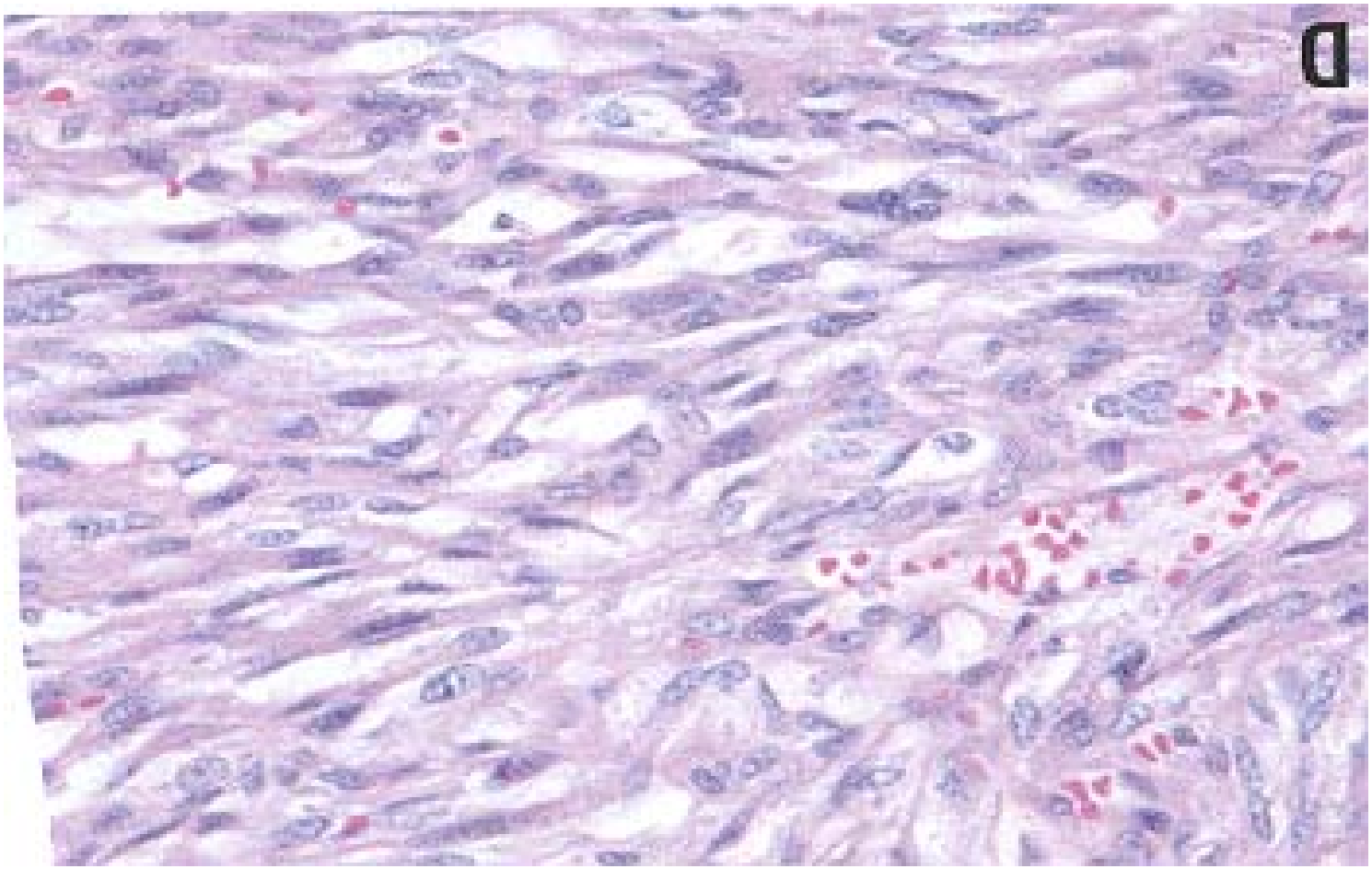
Ref. WHO

Med. Ca vacuolated cells



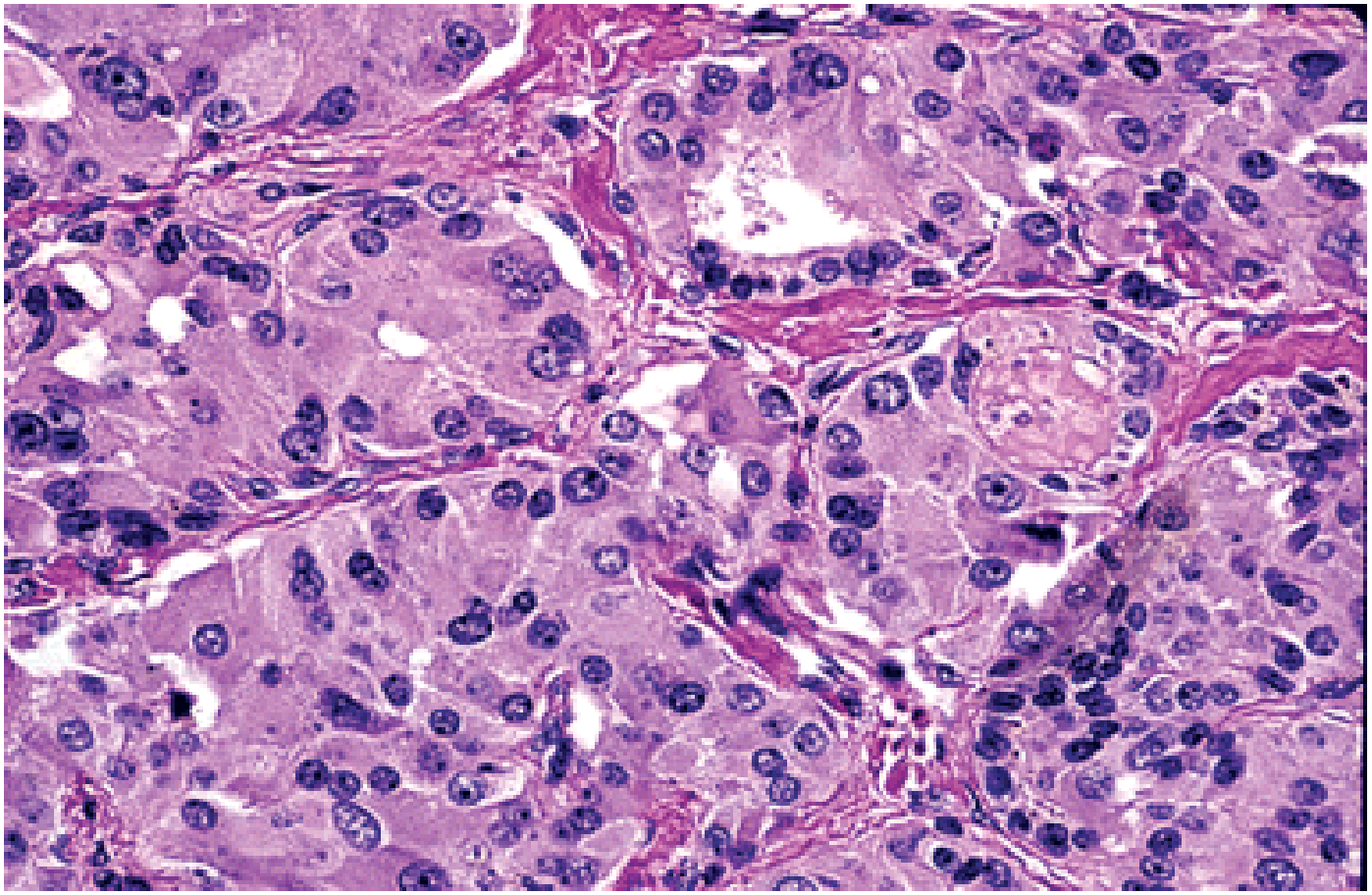
Ref. WHO

Spindled cell growth pattern of Med. Ca



Ref. WHO

Oncocytic variant of medullary carcinoma.
Note the amphophilic staining quality of the cytoplasm and the fibrohyaline bands

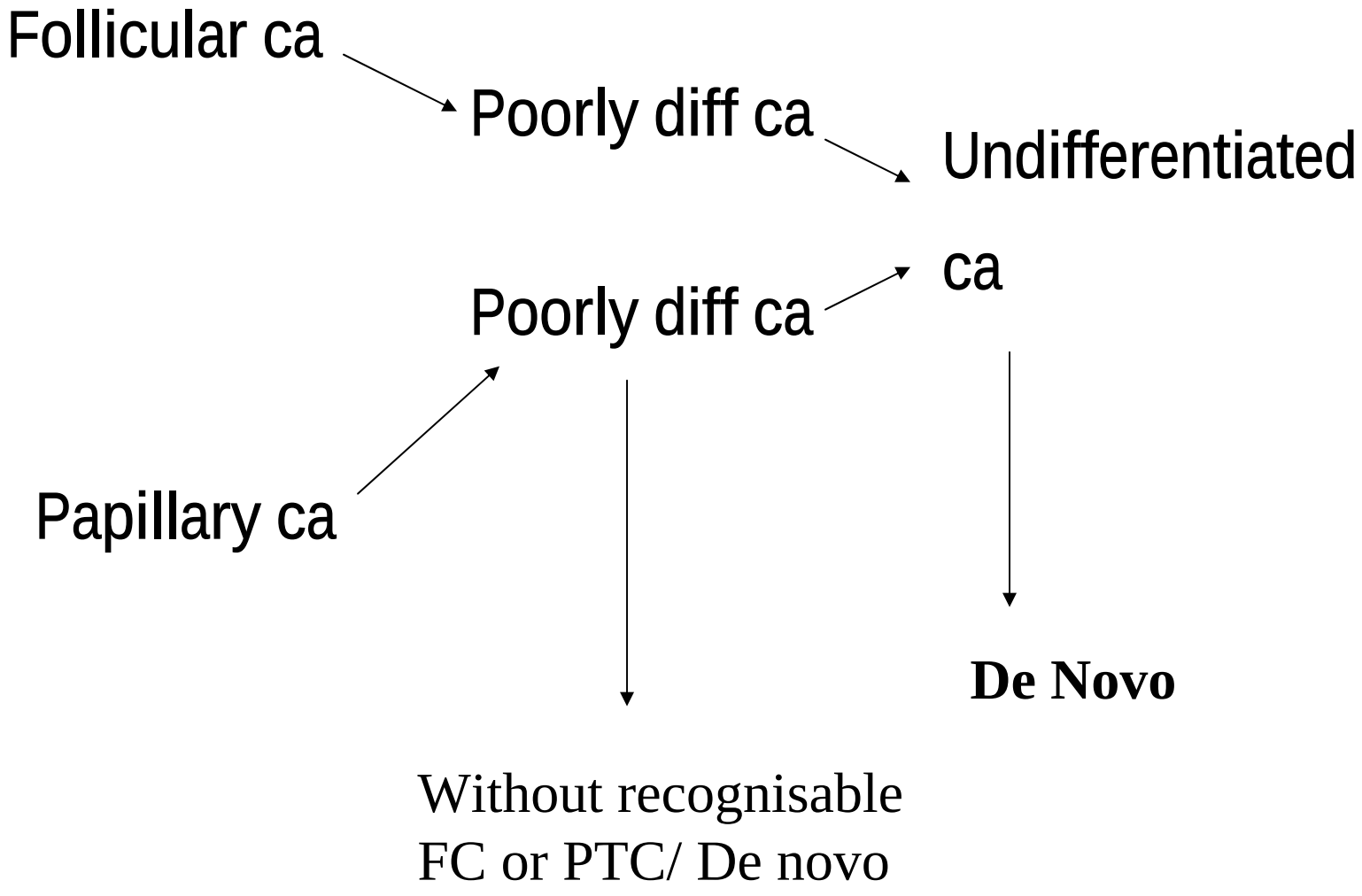


Ref. WHO

IHC Med Ca

- Calcitonin
- CEA
- Serotonin
- Bombesin
- Synaptophysin
- Chromogranin (Cave parathyroid adenoma)
- ACTH
- Some are calcitonin negative

Soares et al, Virchows Arch 444:572, 2004



3.9 PDC

Poorly Differentiated Thyroid Carcinoma

Intermediate grade

Poorly Differentiated Carcinoma of thyroid

- Reviews of large numbers of thyroid carcinomas have often included examples of carcinomas that are recognizable as originating from follicular epithelium (often with evidence of coexistent papillary or follicular carcinoma), but with some notable differences: moderate to high rates of mitotic activity, composed of solid masses or trabeculae of relatively uniform epithelial cells, tiny follicles present in varying numbers, regions of acute necrosis, and more aggressive than the usual well-differentiated carcinomas.

PDC

- These tumors generally lack the usual histologic features and exceptional aggressiveness of anaplastic carcinomas, but they are neither typical follicular nor papillary carcinomas

The Turin proposal
AJSP(31),8, aug 2007

- Criteria for PDC (majority of the tumor)
- -All three-
- 1.Presence of solid/trabecular/insular growth pattern, alone or in combination
- 2.Absence of the conventional nuclear features of PTC even if criterium 1 is met!
- 3.Presence of at least one of the following features: convoluted nuclei/mitotic activity more than 3/10 HPF, tumour necrosis

AJSP(31), 8, aug 2007 (bis)

- Convoluted nuclei: small round hyperchromatic nuclei with convolutions of the nuclear membrane (raisin like contour, occasional grooves)
- Weaker positivity for TG and TTF1, sometimes dotlike paranuclear
- If PTC nuclei: PTC with necrosis, PTC with trabecular growth pattern, …
- De novo or from PTC or FC

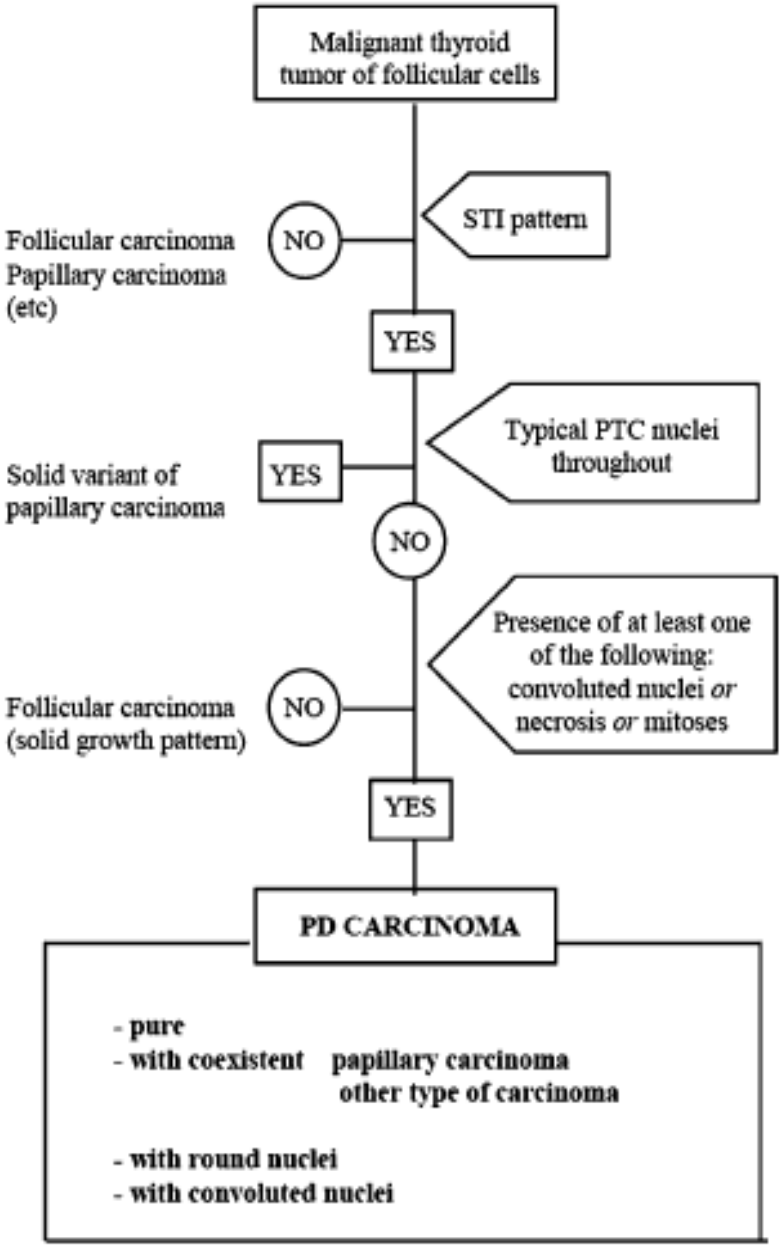
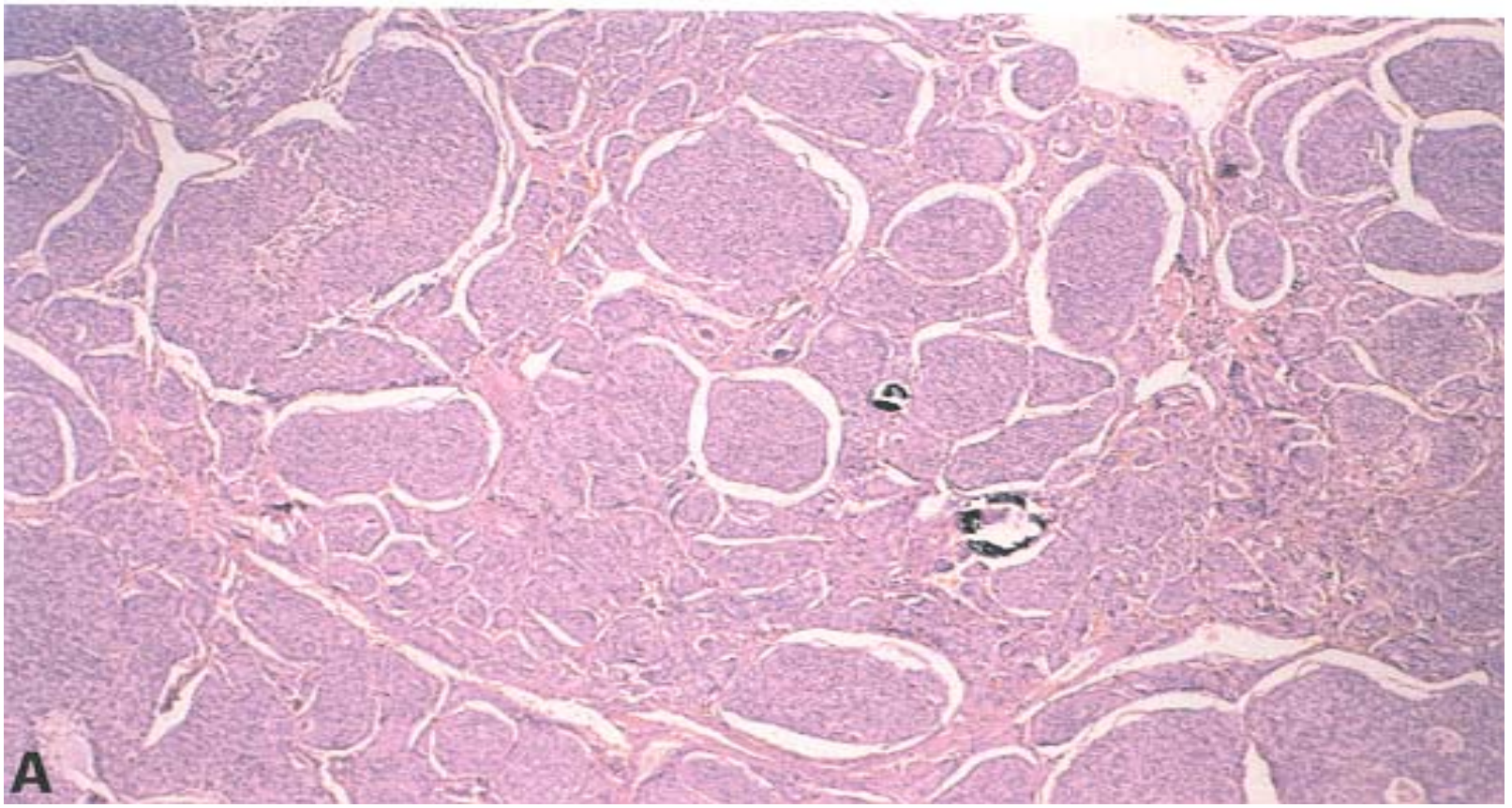


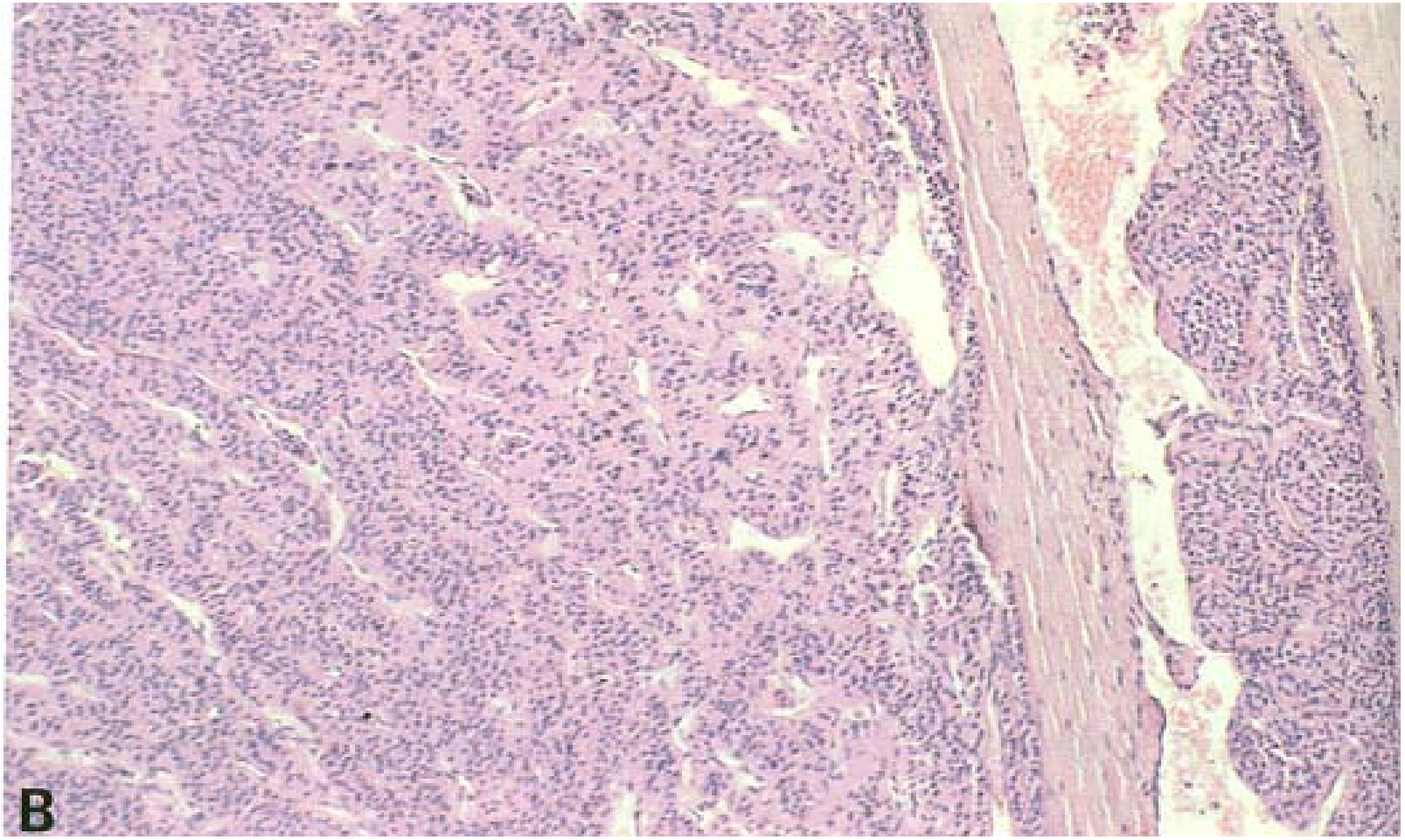
FIGURE 1. Diagnostic criteria for poorly differentiated thyroid carcinomas.

Insular PDC



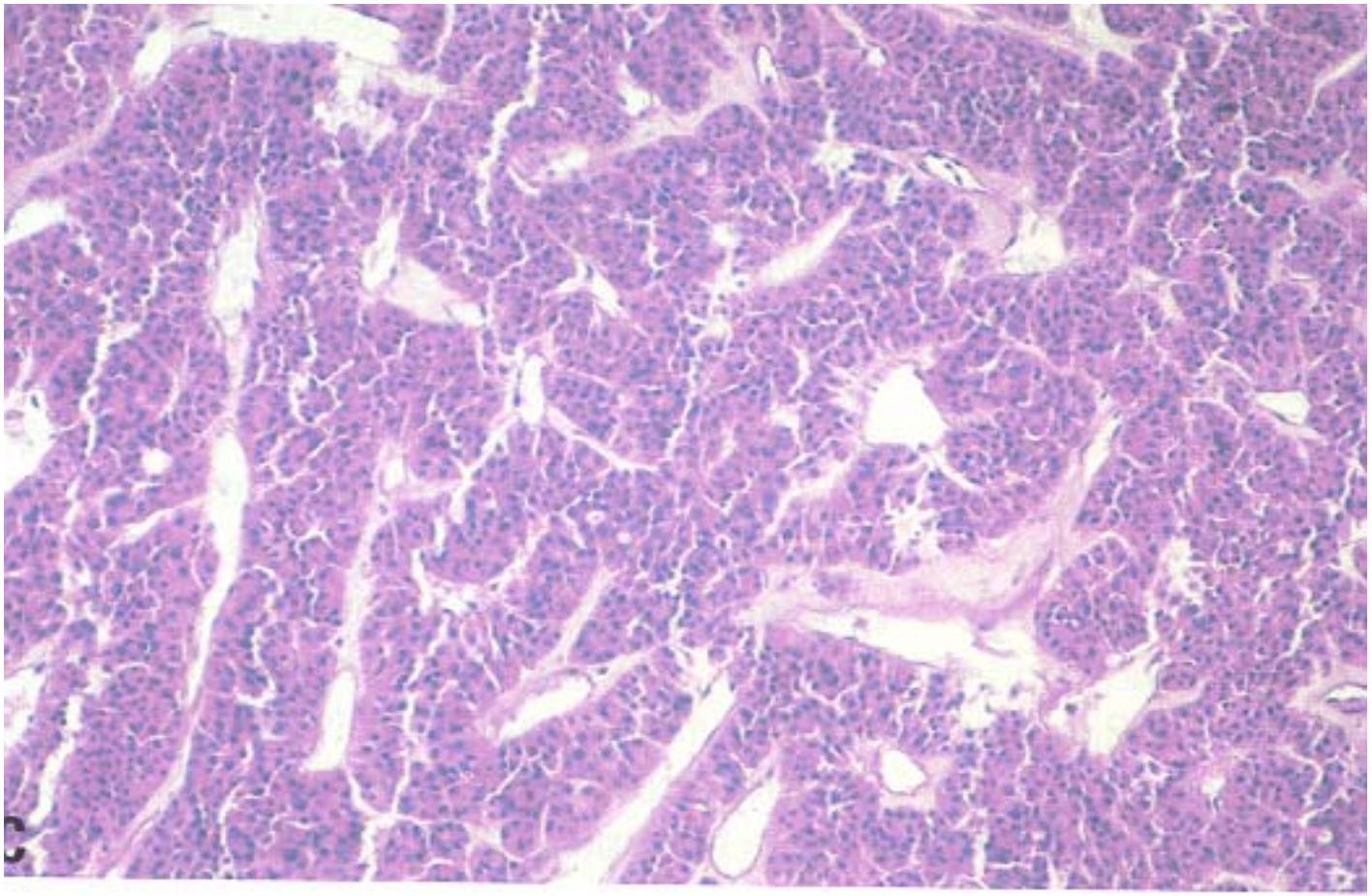
Ref. WHO

PDC trabecular with vascular invasion



Ref. WHO

PDC Trabecular

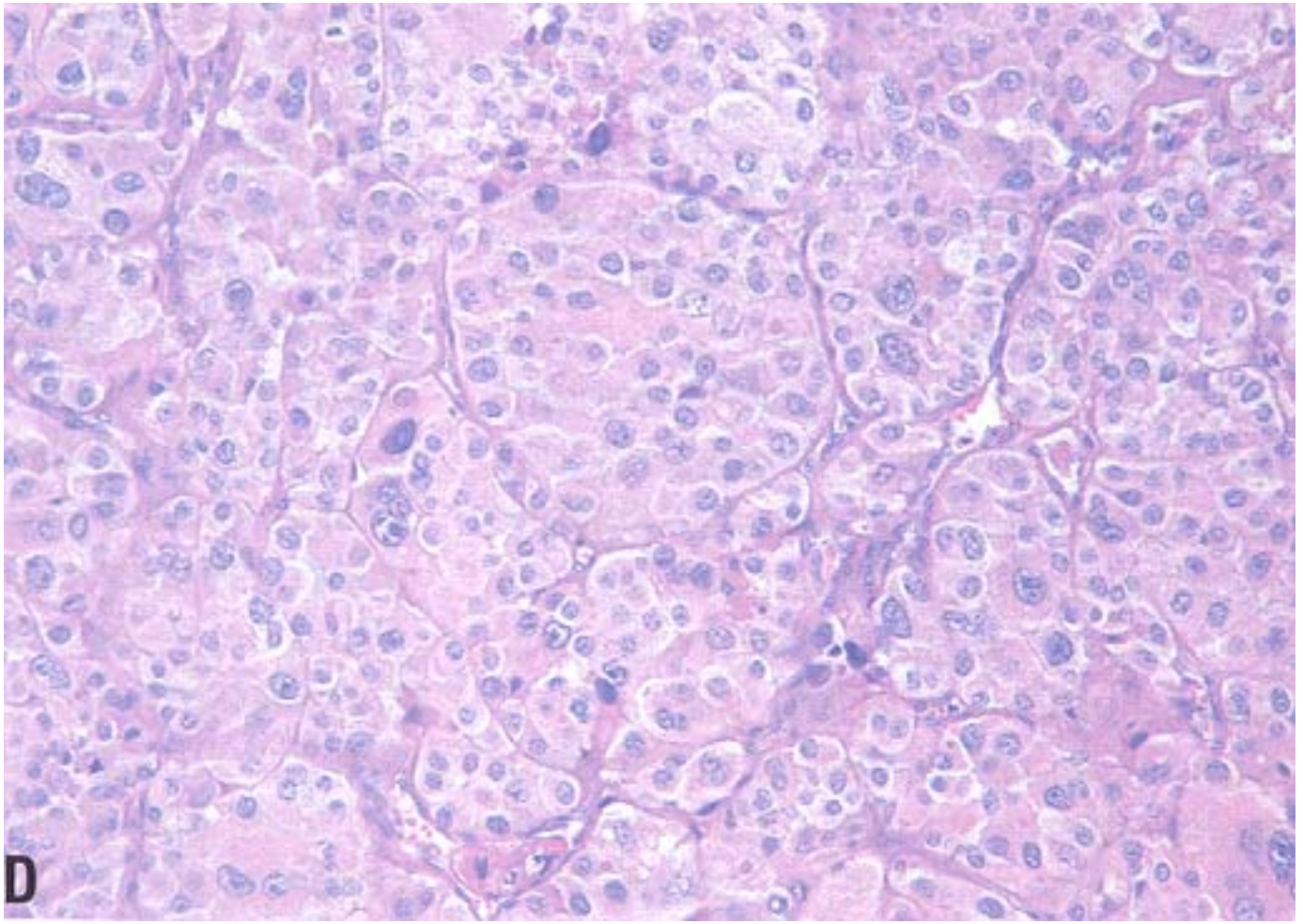


Ref. WHO

Trabecular Growth

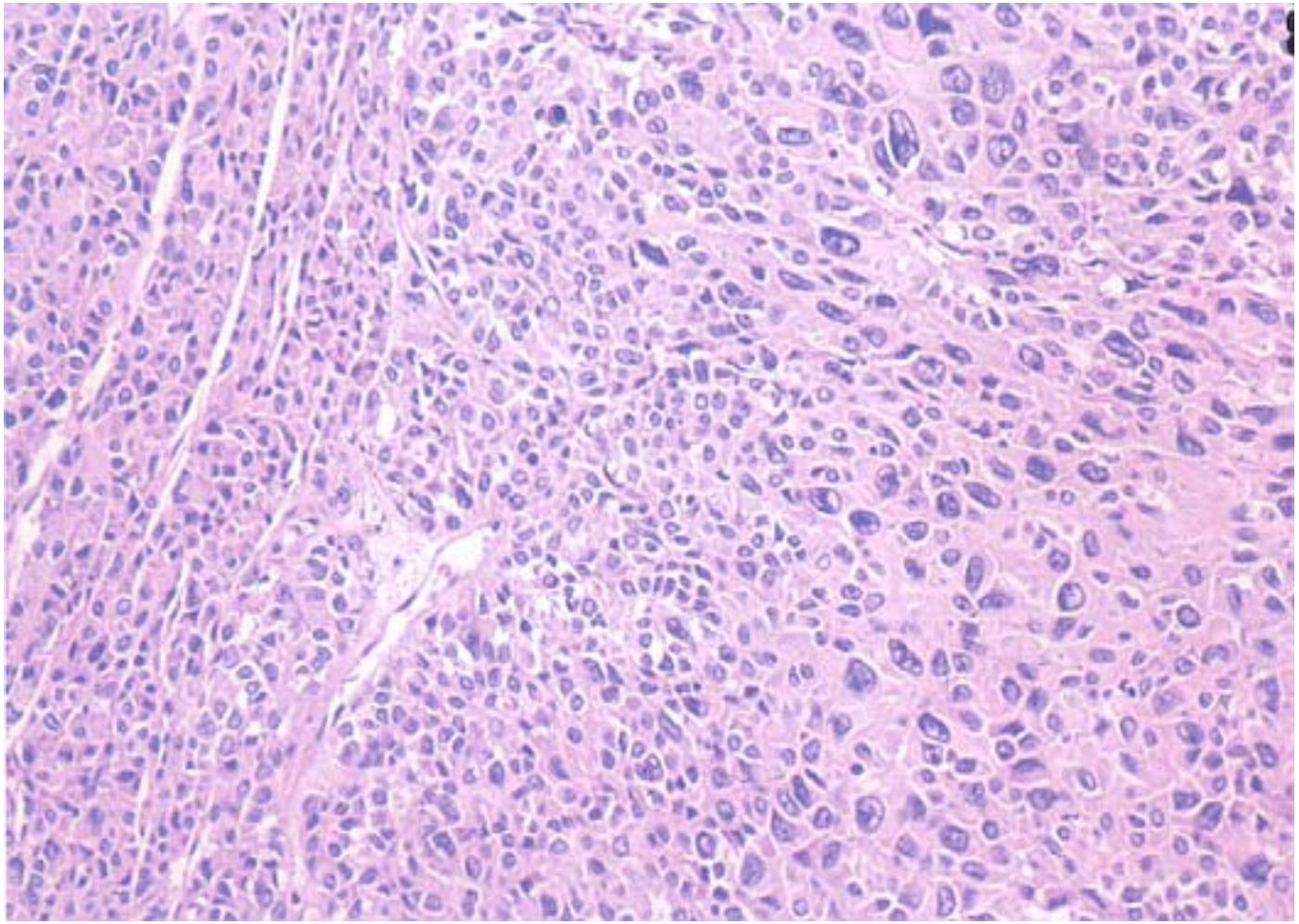
- HTT
- Med ca
- FC
- PTC

Solid pDC

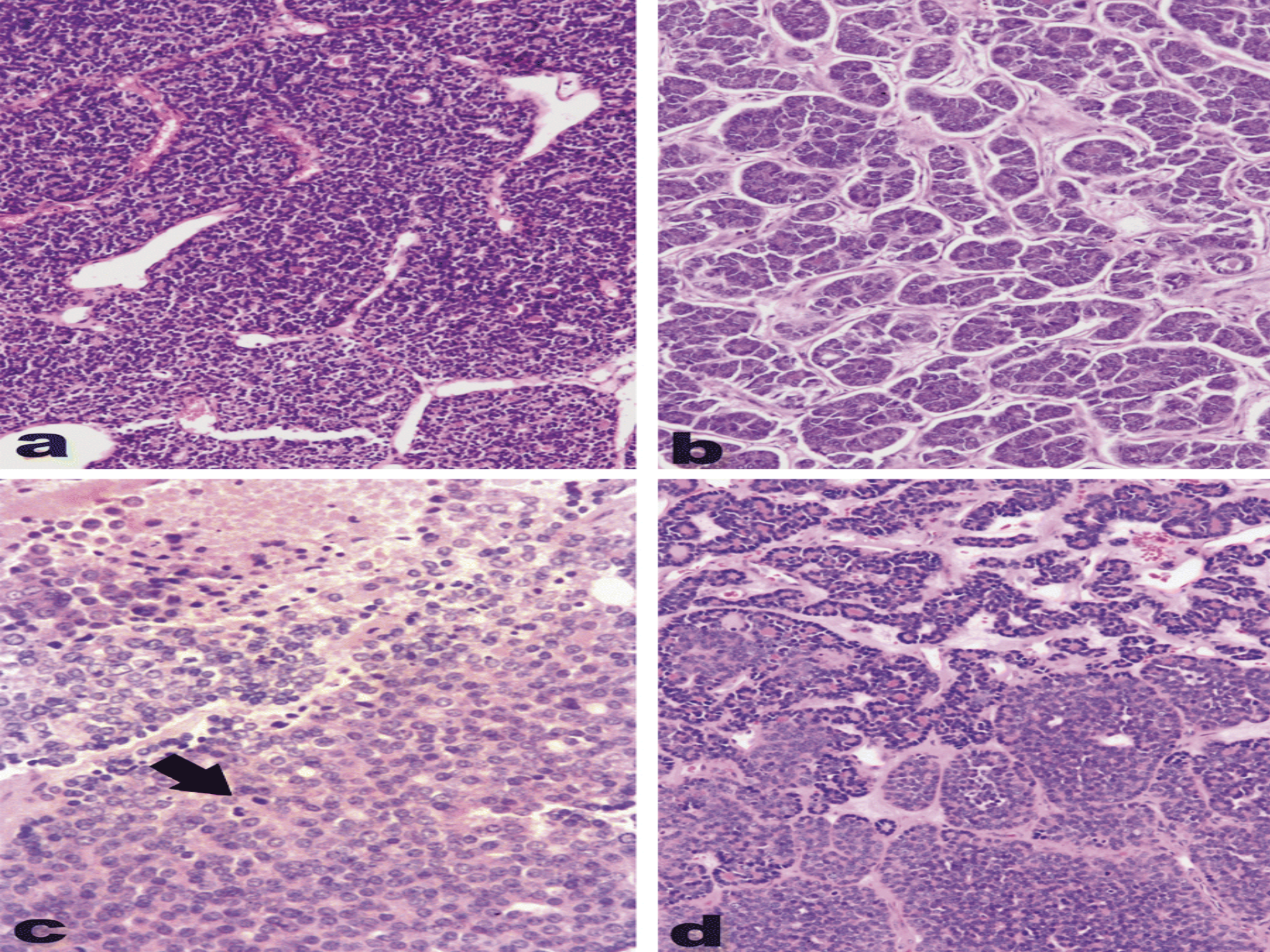


Ref. WHO

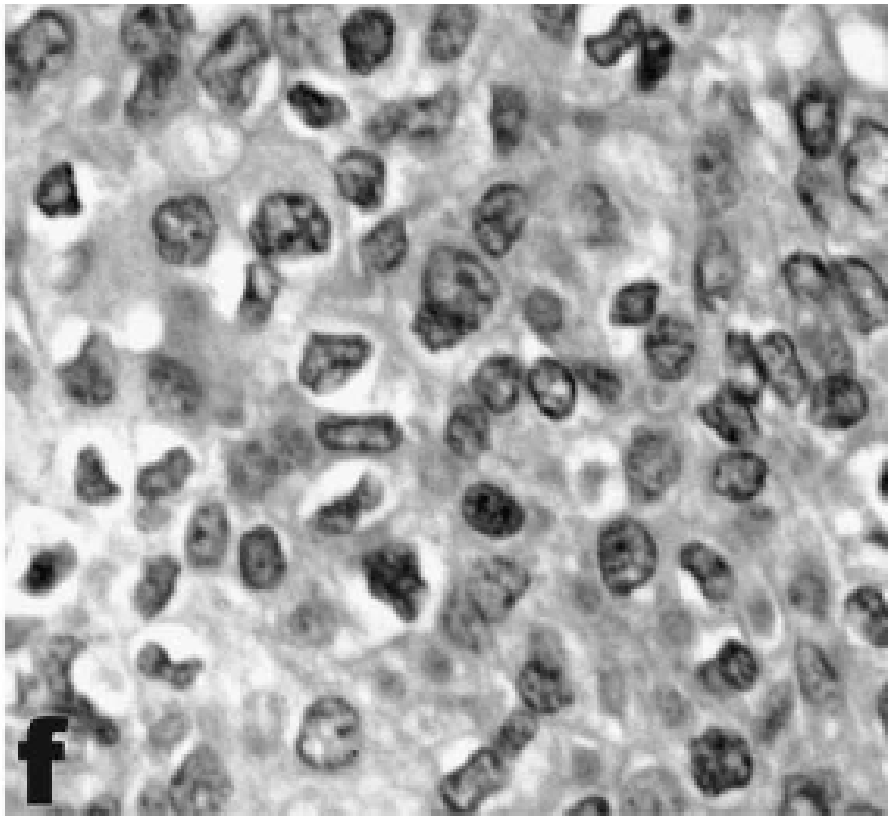
PDC transformation to UDC



Ref. WHO


a
b
c
d

Convoluted nuclei



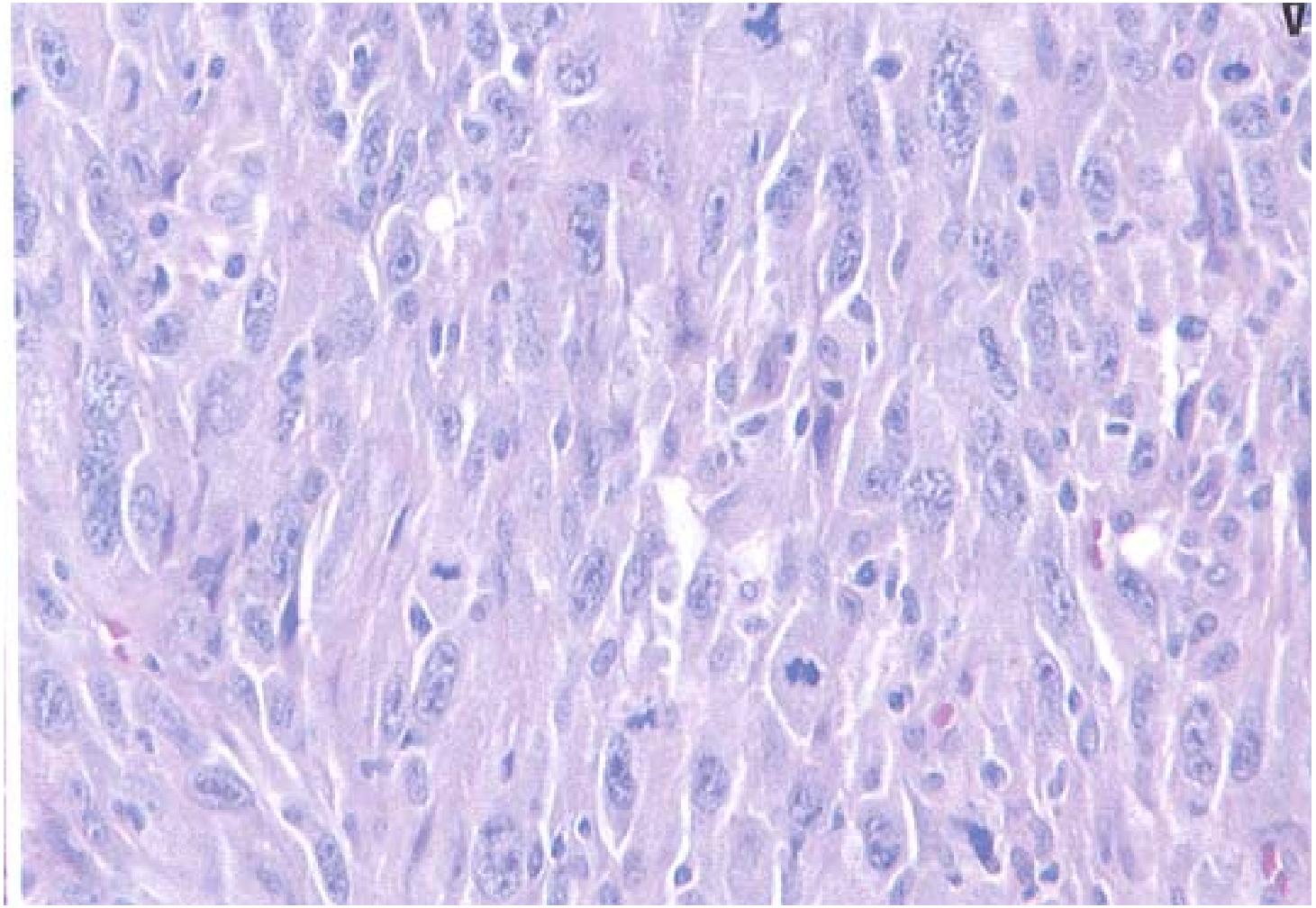
The Turin proposal

3.10. Undifferentiated (Anaplastic) Ca High grade

- 1.Large pleomorphic giant cells resembling osteoclasts with cellular tissue septae, may have cavernous blood filled sinuses (Osteoclasts are CD 68 pos)
- 2.Spindle cells resembling sarcoma (Vim pos)
- 3.Squamoid
- 4.Paucicellular variant EMA pos, Ker pos.

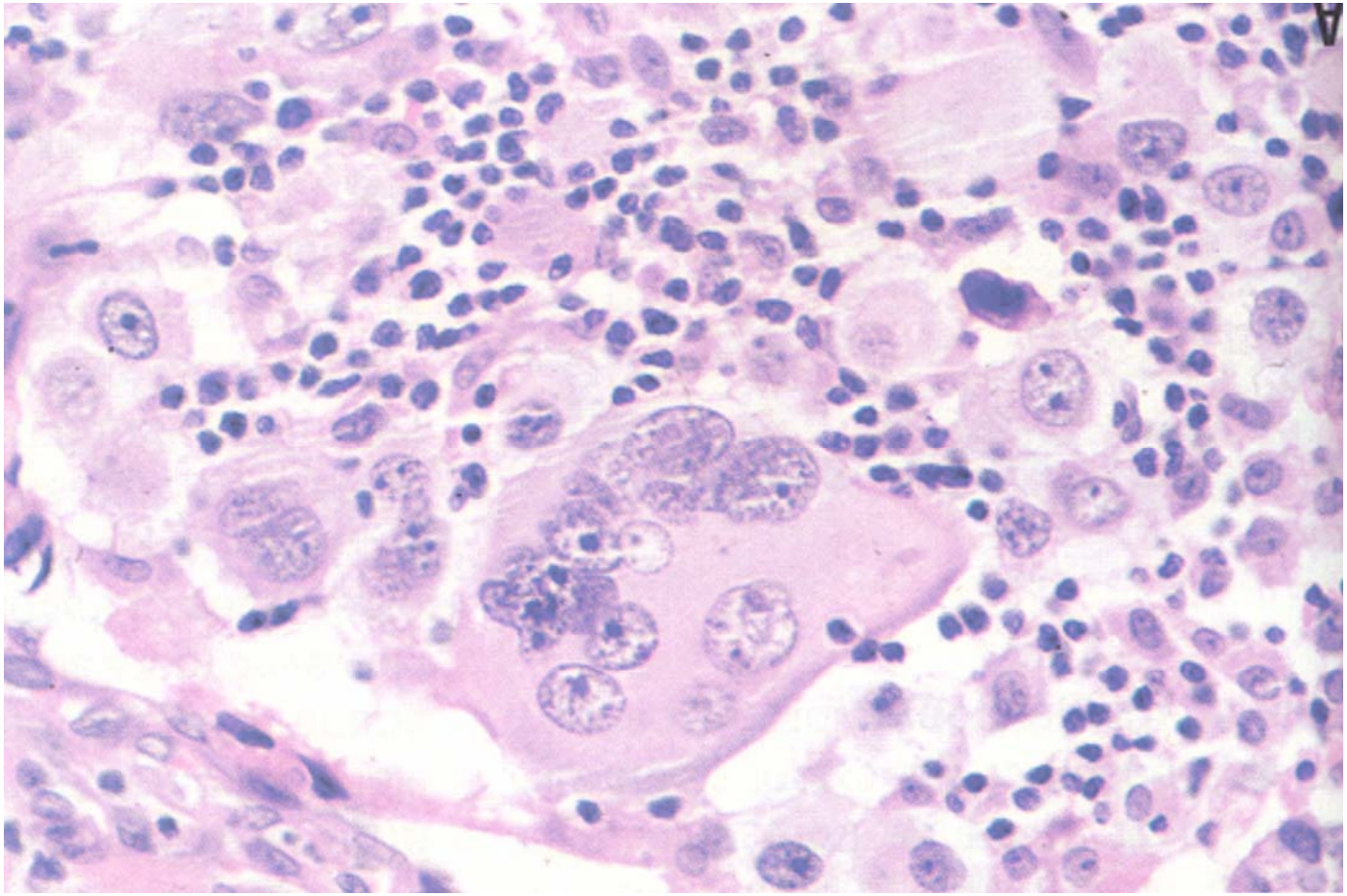
  P53 positive

UDC Spindle cell



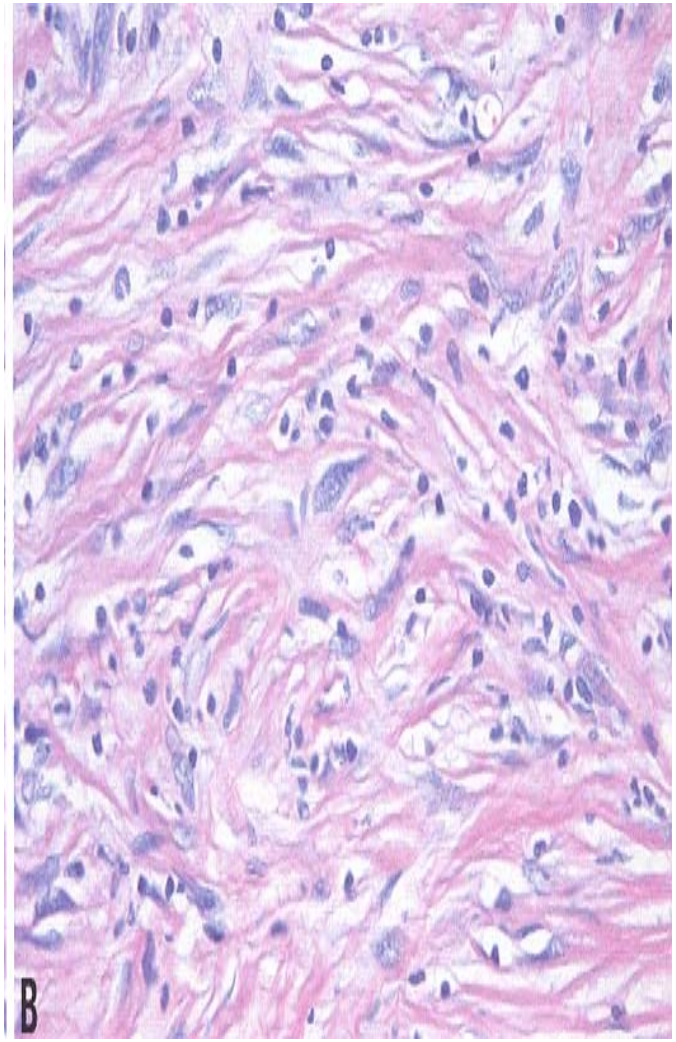
Ref. WHO

UDC Giant cell

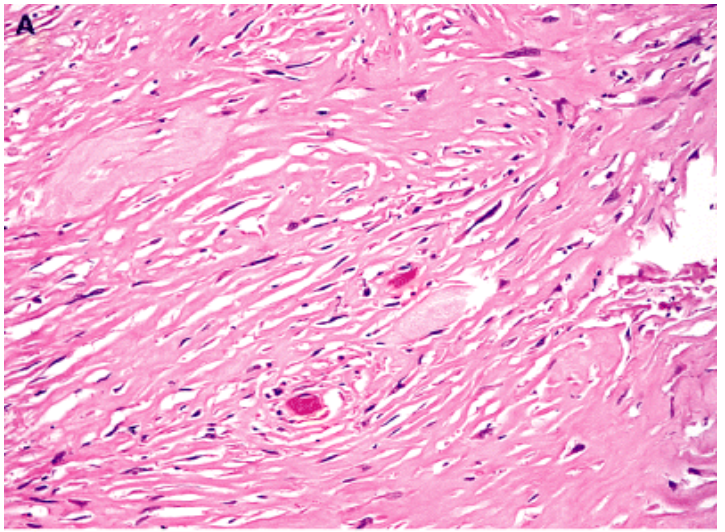


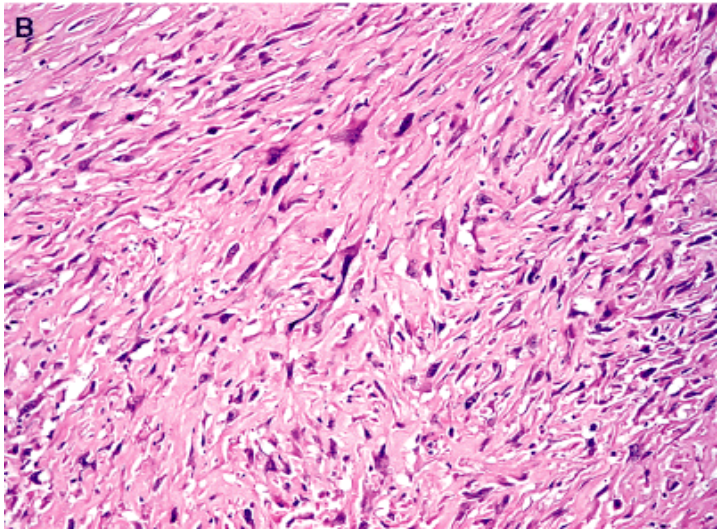
Ref. WHO

Paucicellular UDC



Ref. WHO





Fibrosis

- Riedel's
- Paucicellular anaplastic TC
- Micro PTC
- After ischemic necrosis, regeneration with atypia
- Diffuse sclerosing variant of PTC (TG negative)

3.11Other Malignant tumours

- Squamous cell carcinoma
- Mucoepidermoid carcinoma
- Sclerosing mucoepidermoid carcinoma with eosinophilia
- Mucinous carcinoma
- Carcinoma with thymus-like differentiation (CASTLE) (AJSP 30, 8, aug. 2006)
- Soft tissue: Often SFT
- Angiosarcoma which is also high grade

Other bis

- Teratoma
- Lymphoma and plasmocytoma low grade is MALT and high grade is Diffuse B lymphoma
- Ectopic thymoma
- Smooth muscle tumours
- Angiosarcoma
- PNST
- Paraganglioma
- FDC
- Langerhans cell histiocytosis

3.12 IHC- WHO Book

	Ki67	Bcl2	Bcl1
Normal	<5%	Pos	Negative
Well Diff.	<10%	Pos	Low
Poorly Differentiated	10-30%	Usually pos	Intermediate
Undifferentiated Anaplastic	30%	Negative	High

Chromogranin

- Med Ca
- Solid cell nest
- Parathyroid adenoma
- Meta from Carcinoid lung

TG

- Note: macrophages may contain thyroglobulin in lymph nodes draining thyroid tumors (J Clin Pathol 2001;54:314)
- TG is well known to diffuse through local tissues resulting in artefactual staining that can hamper the diagnosis.

IHC

- CK 7 Neg and CK 20 Neg.
- CK 7 may be positive
- DD HCC, Lung (small cell), Prostate, RCC, Squamous cell CA, …

3.13 TNM and Clinical Stage

- I Intrathyroidal
- II Cervical adenopathy
- III Locally invasive disease
- IV Distant metastases

TNM

- T1 2 cm or less limited to the thyroid
- T2 more 2cm; less than 4 cm limited to the thyroid
- T3 more than 4 cm or extra thyroid extension
- T4a subcutaneous, larynx, trachea, esophagus or nervus recurrens
- T4b invades prevertrebral fascia, carotid artery or mediastinal vessels

TNM stadia

- Thyroid TNM is the only that brings AGE into account

  -Papillary or Follicular Ca, Not Med. Ca
- Under 45 years: Stage 1, Any T, Any N, M0
- Under 45 years: Stage 2, Any T, Any N, M1 Papillary or Follicular Ca

TNM

- If older than 45 years: All anaplastic carcinoma's (undifferentiated) are considered T4
- T4a intrathyroid
- T4b extrathyroid

TNM

- N1a to level 4 pre or para tracheal
- N1b cervical or superior mediastinal

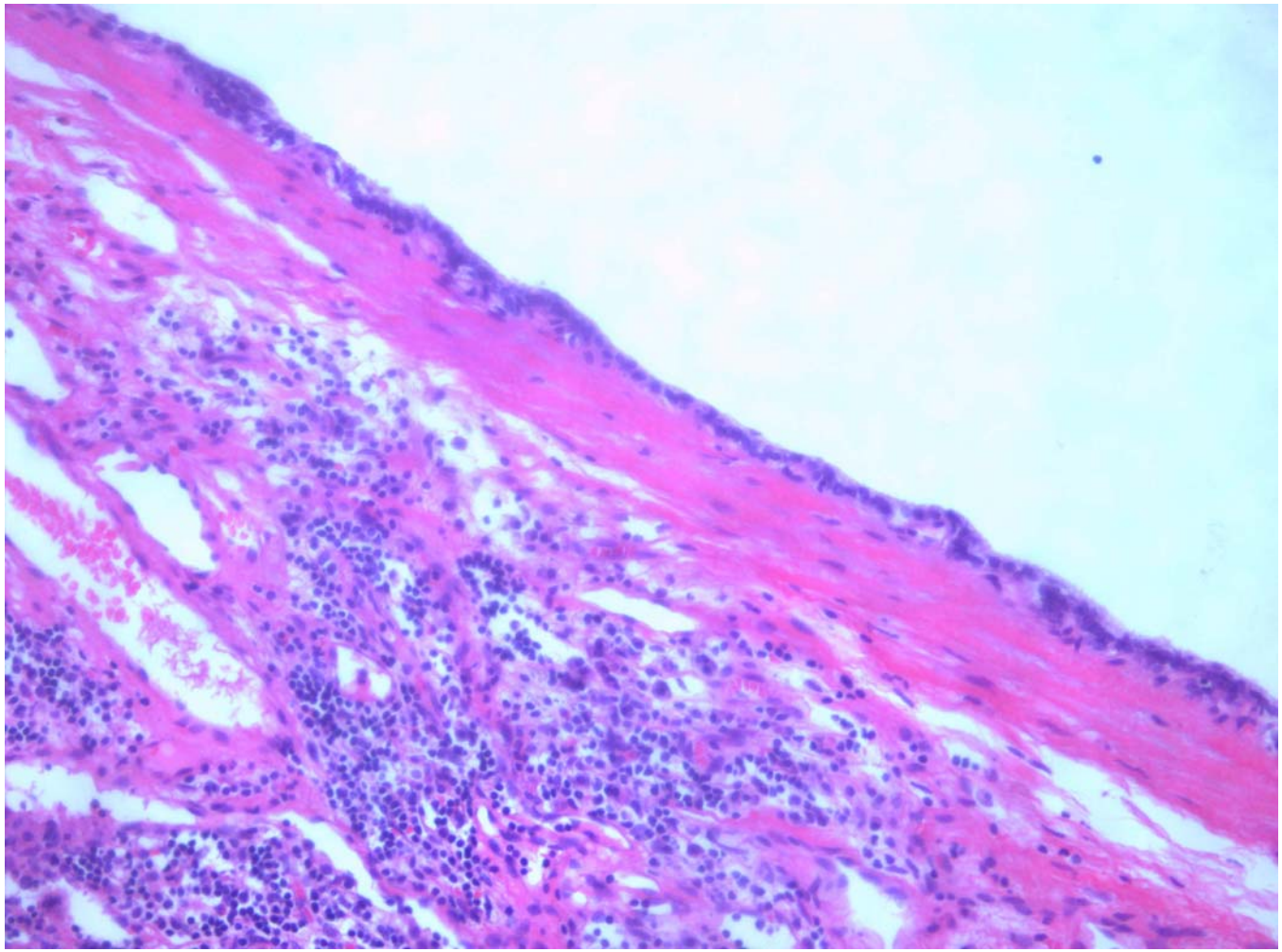
3.14 Metastases

- Fol. Ca

  Lungs and Bones
- PTC

  Lymph nodes. Thyroid tissue in a lymph node is near always a metastasis and it is a metastasis of PTC! (cfr. supra: normal thyroid in lymph nodes)
- A cystic lesion with only slight atypia of the comumnar cells in it, in the neck is often a metastatic PTC !

Cystic Meta of PTC



Meta's to the Thyroid

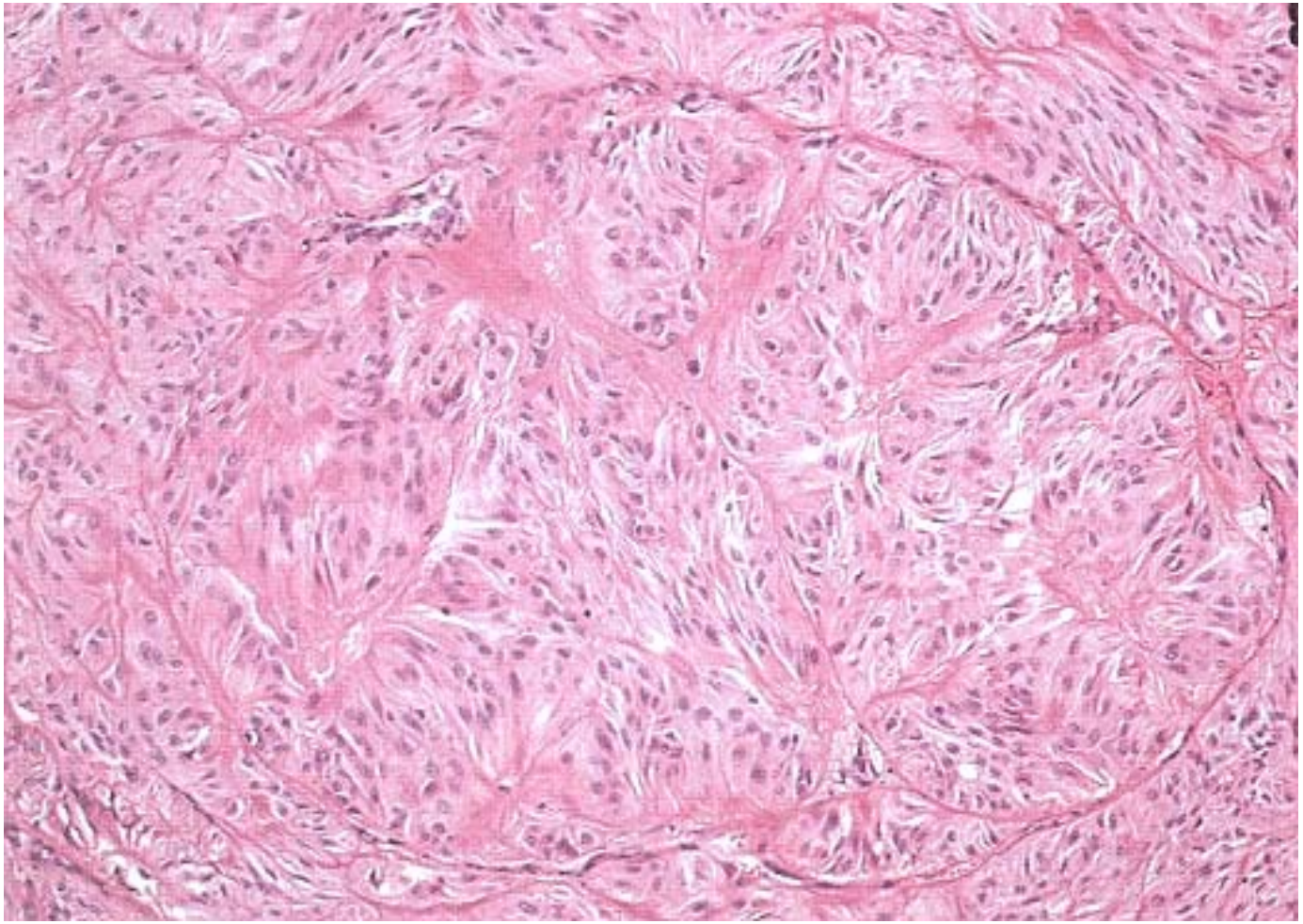
- RCC
- Lobular breast
- Mucinous ca of digestive tract
- Squamous cell ca of digestive tract
- All sorts

3.15 HTA AJSP 24,12, 2000, p.1625 AJSP 30,10, 2006, p.1269

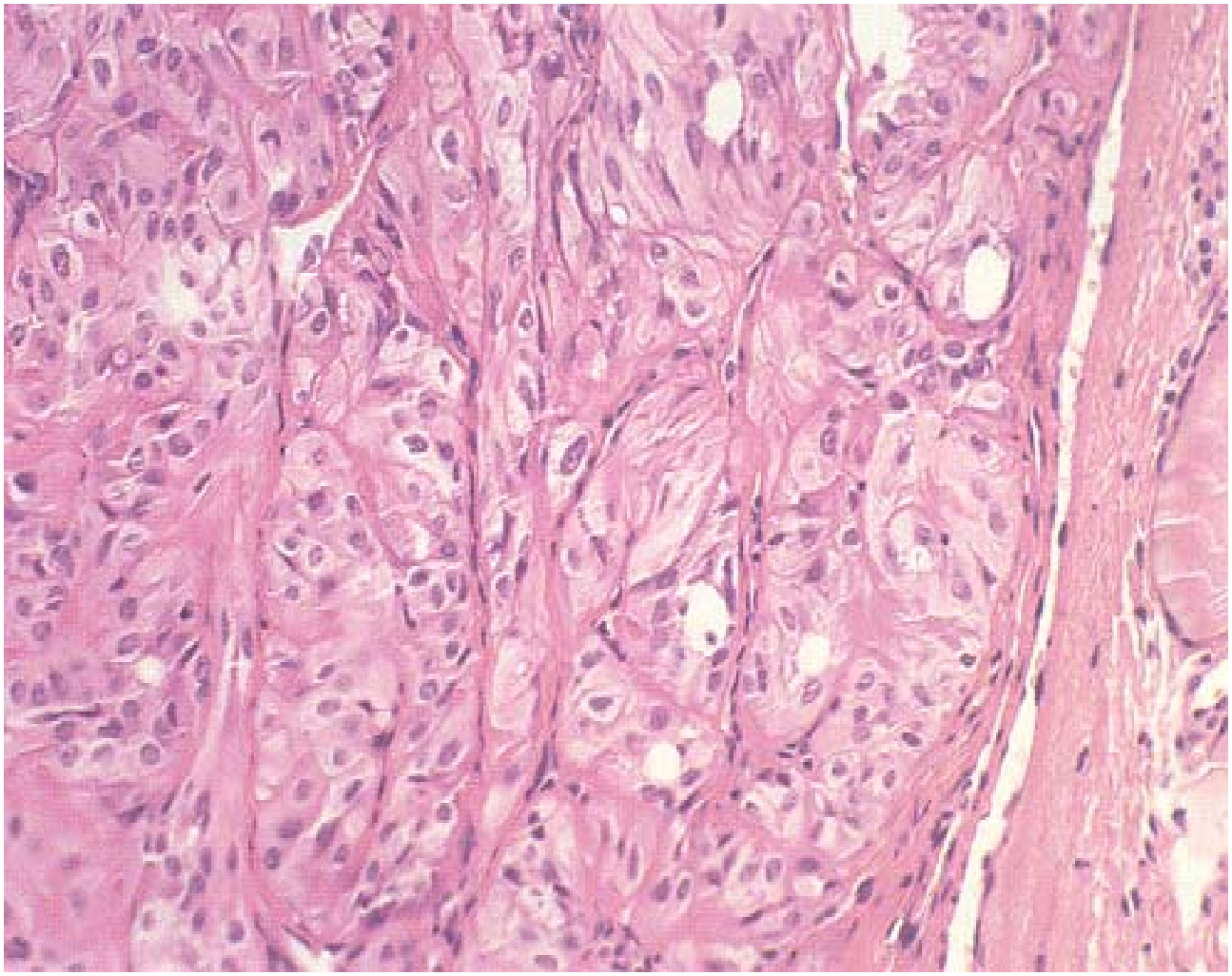
Hyalinizing trabecular adenoma

- Fibrous capsule
- Trabecular arrangement of columns of cells in parallel arrays.
- Sparse mitotic figures.
- Occasional grooving, clearing and inclusions
- Minimal capsular and vascular invasion possible
- No medullary carcinoma.
- DD encapsulated PTCA Excellent prognosis of both.

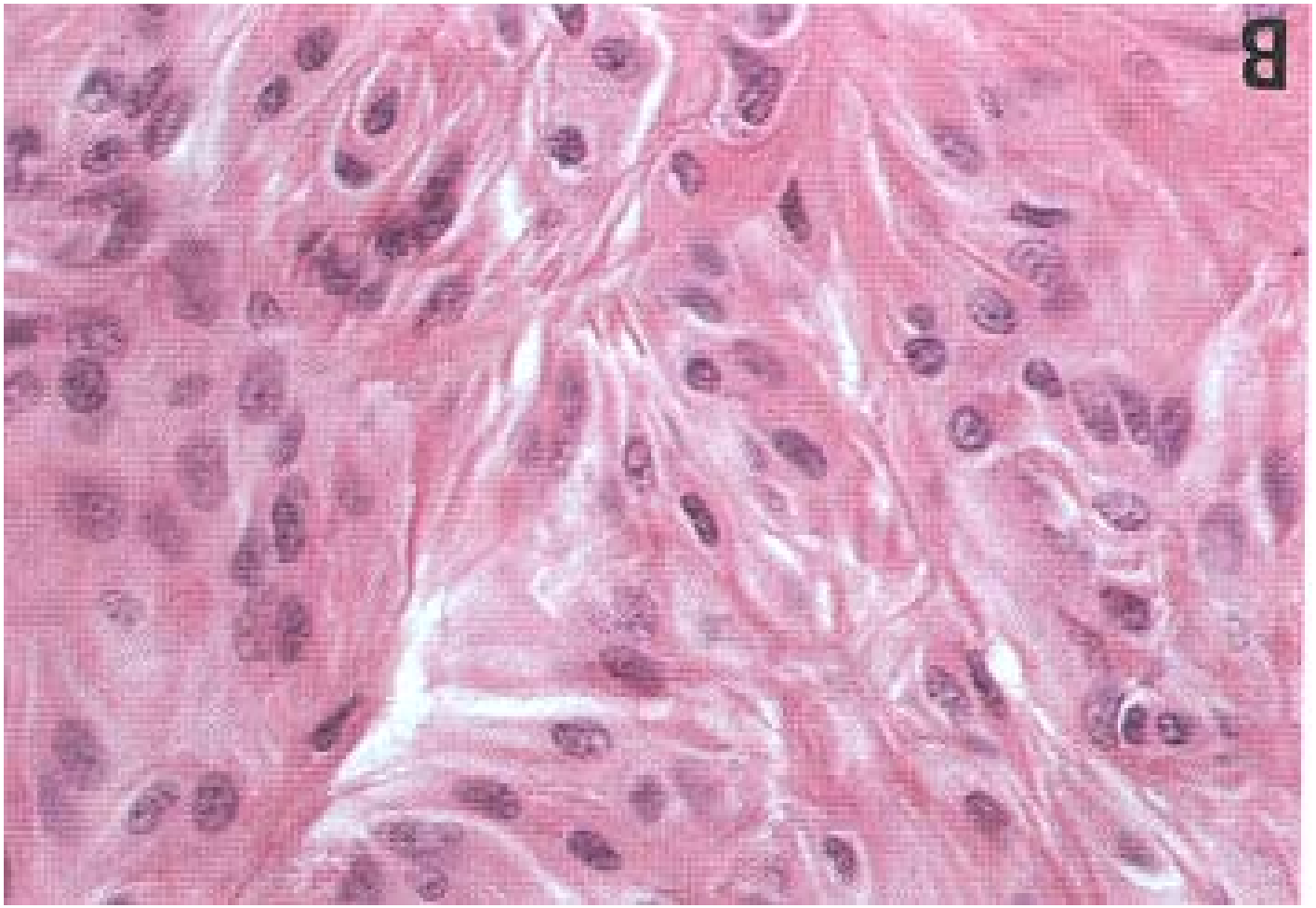
HTT



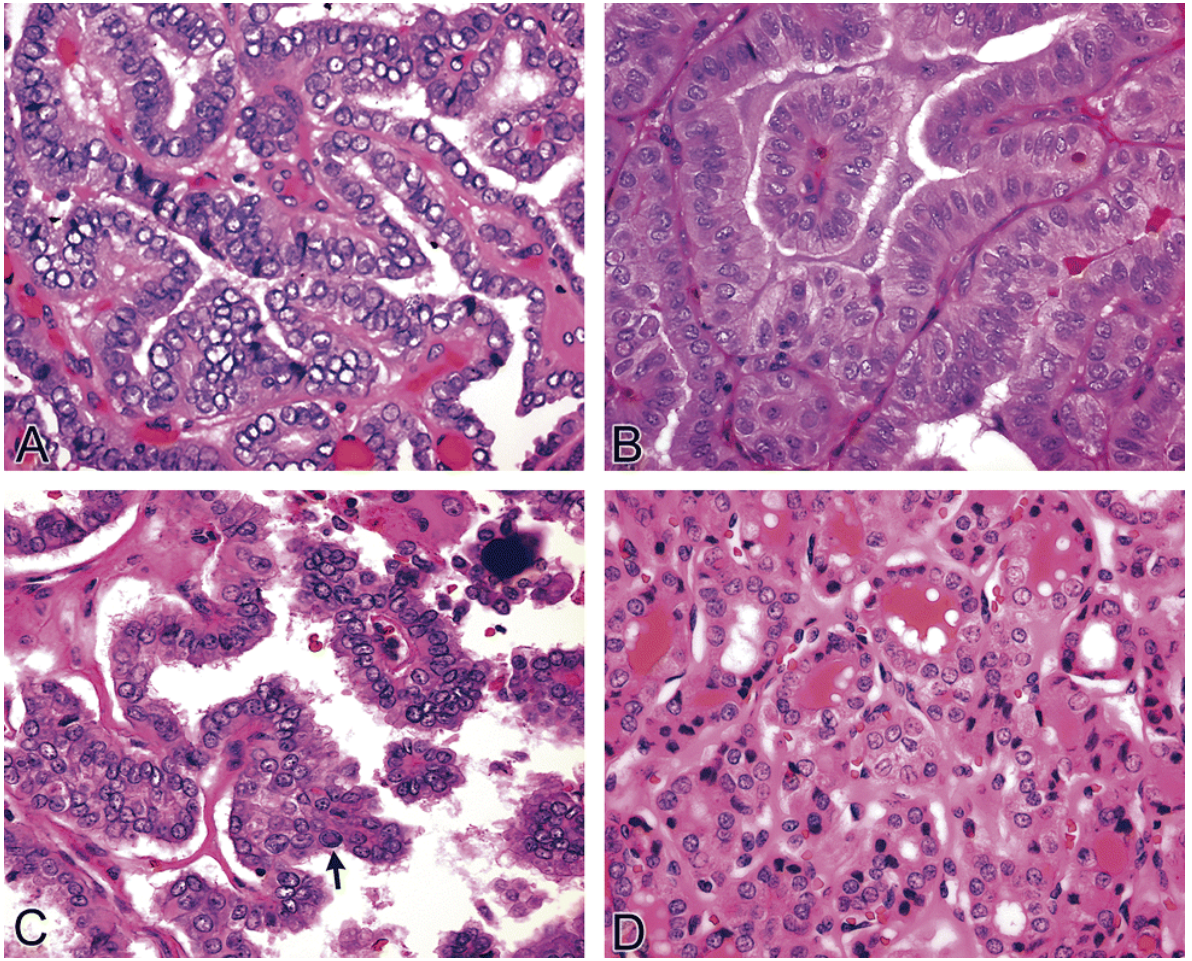
HTT



HTT



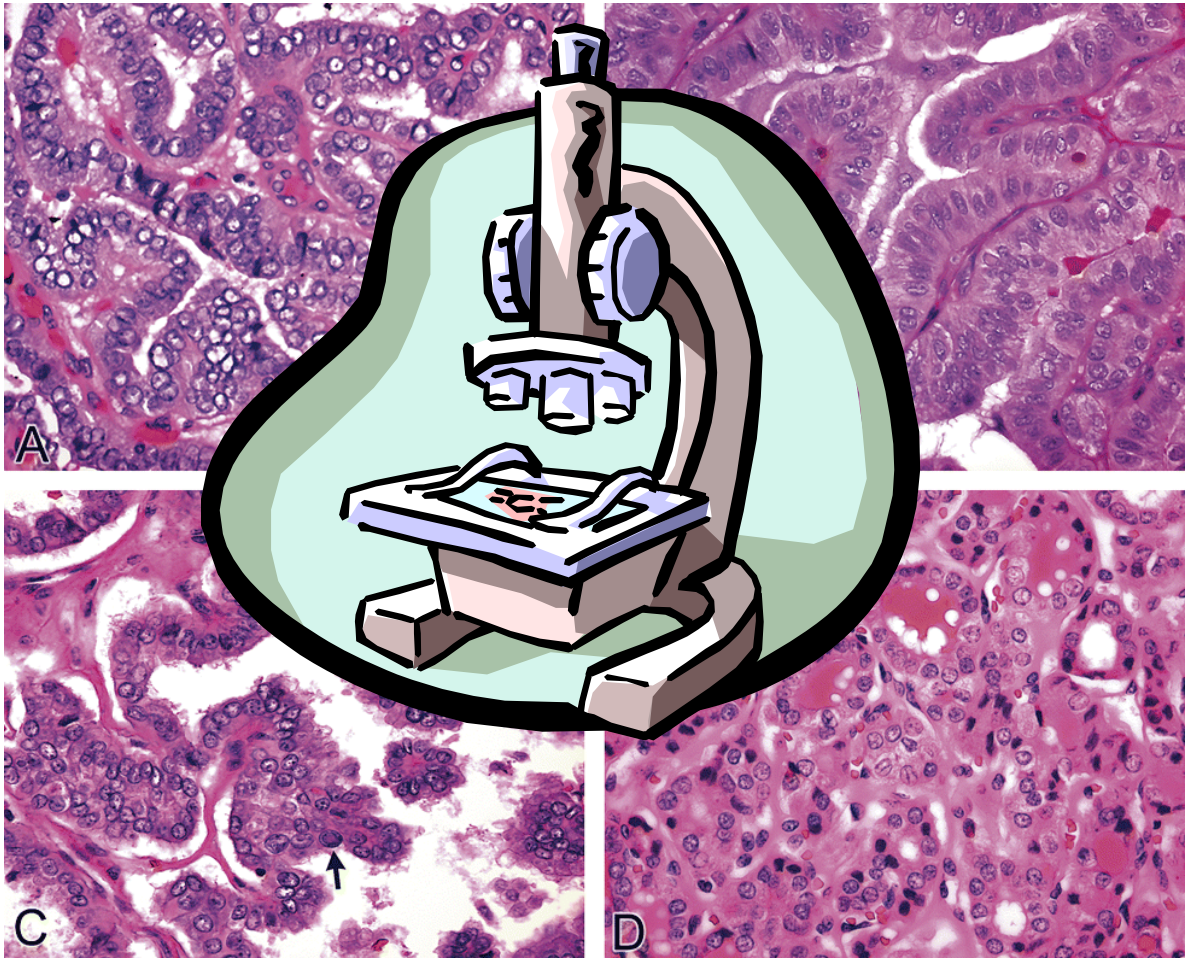
Before coffee: test



AJSP, 30, 2, feb. 2006

Classic PTC

Tall cell variant



PTC with Psammoma bodies

Follicular variant of PTC

Thank You!!!!

- *Colleagues Support*: Dr. G. Jacomen, dr. V. Schelfhout, dr. K. Deraedt, dr. S. Delvaux, dr. S Van Damme!
- *Lab Support*: Marie-José, Nicole, Hilde, Ilse, Annie, Sarah, Gerda
- *Secretarial Support*: Liesbeth, Liesbeth, Véronique, Tamara
- *Hospital Support*: AZ St. Maarten, Duffel-Mechelen; AZ St. Jozef, Malle, AZ H. Familie, Rumst.

Coffee or questions?