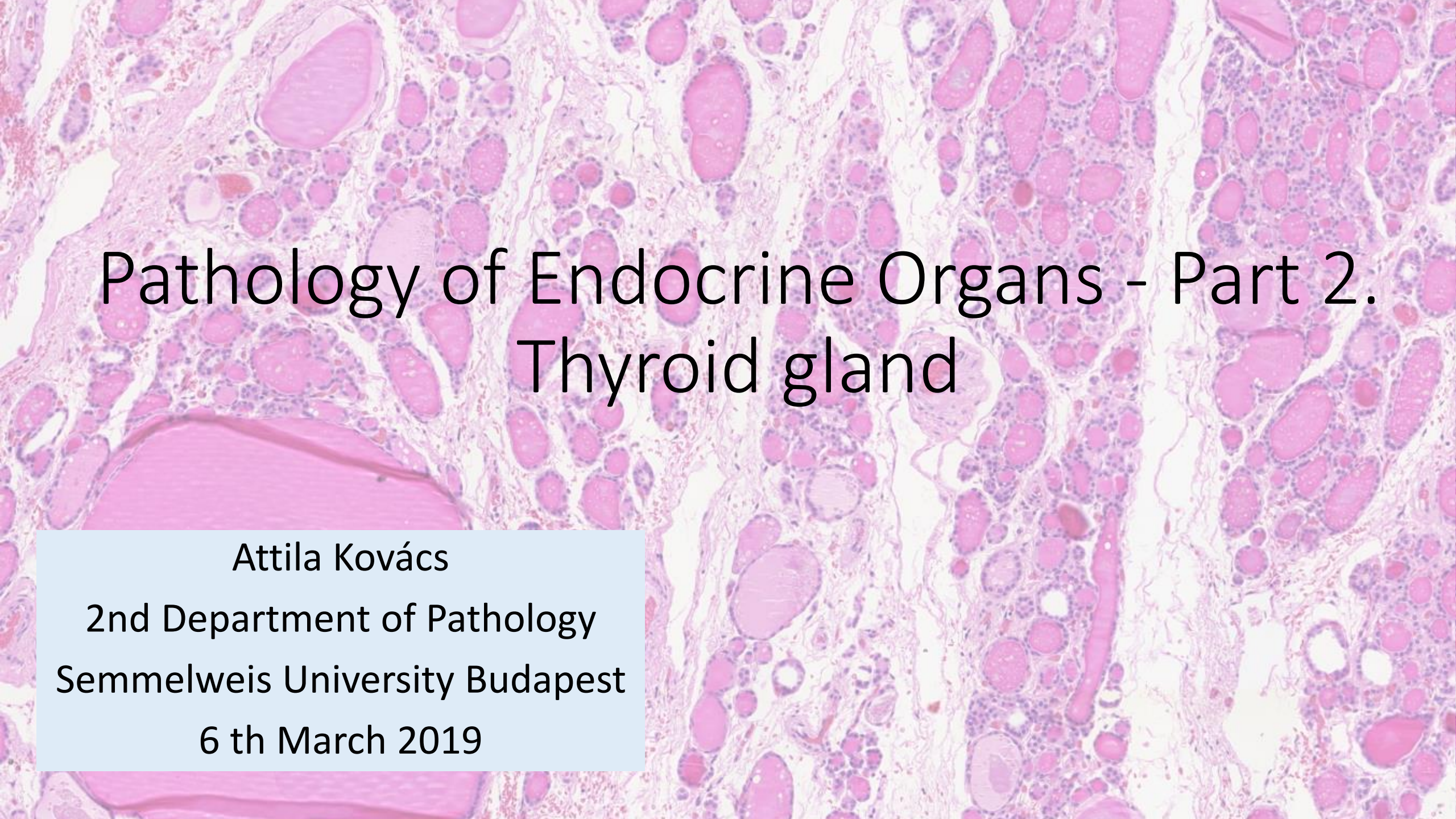

Pathology of Endocrine Organs - Part 2. Thyroid gland

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Outline of the endocrine pathology 1-2.

1. Pathology of endocrine organs
   - Pituitary gland
   - Pineal gland
   - *Thyroid gland*
   - Parathyroid glands
   - Adrenal glands
   - Endocrine pancreas
   - Sex-cord stroma
2. General aspects of neuroendocrine tumors of non-endocrine organs (DNES)
3. Syndromes associated with endocrine tumors

Outline of the lecture

1. Hormonal dysfunctions
    1. Hyperthyroidism
    2. Hypothyroidism
2. Congenital disorders
3. Inflammatory disorders = thyroiditis
4. Graves disease
5. Diffuse and multinodular goiter
6. Neoplasms
    1. Follicular neoplasms (FN)
    2. Papillary thyroid carcinoma (PTC)
    3. Medullary thyroid carcinoma (MTC)
    4. Rare tumors
7. Cytology of the tyroid gland

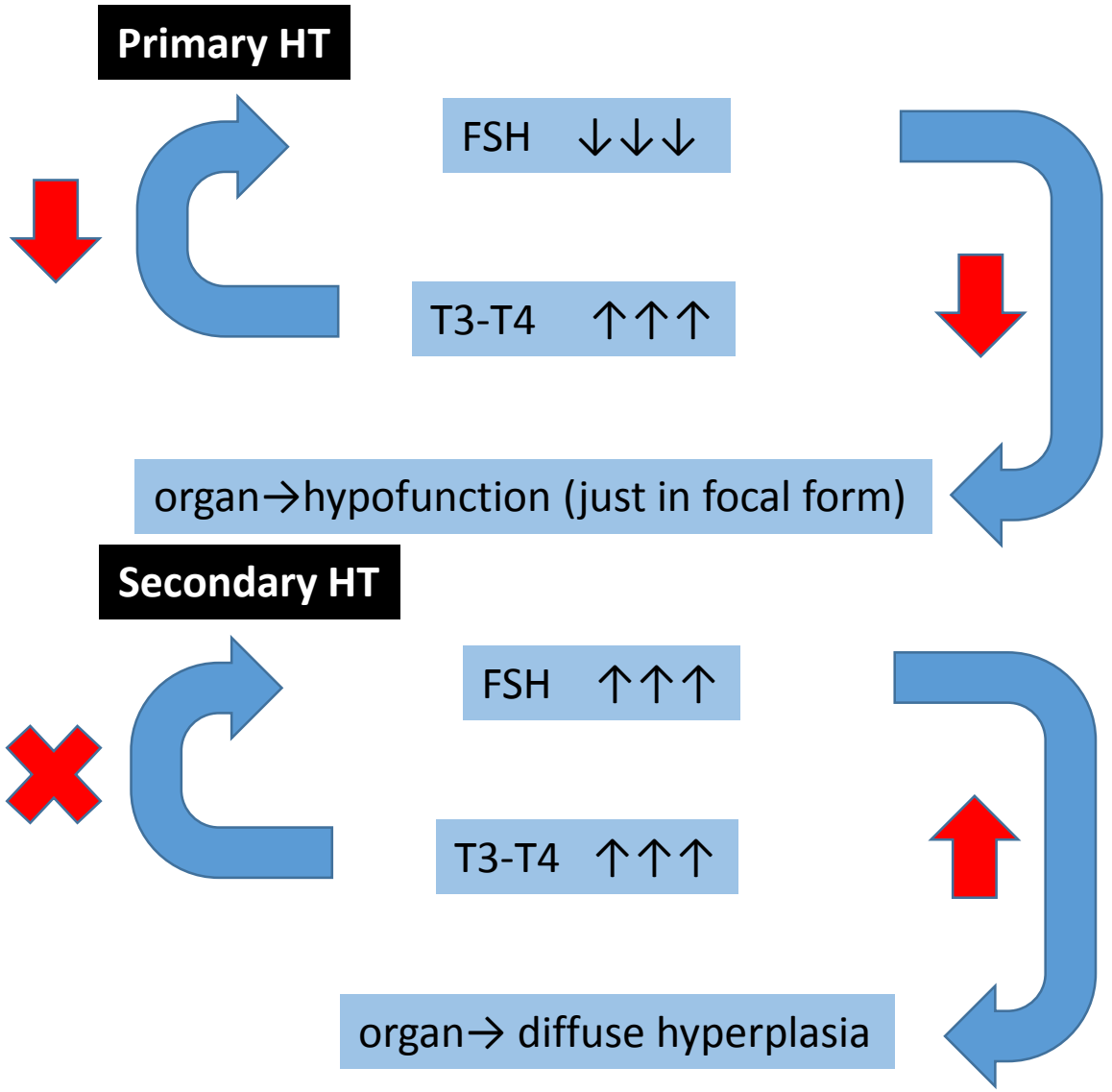
1.1. Hyperthyroidism

- Definition: hyperfunction of the thyroid gland (morphology+increased hormon release)
- Hyperthyroidism ≠ thyrotoxicosis (elevated T3-T4)
- Hyperthyroidism ≠ goiter (enlargement of thyroid gland)
- Thyrotoxicosis without hyperthyroidism:
  - Thyroiditis
  - Struma ovarii
  - Exogenous hormon intake
- Goiter without hyperthyroidism
  - Euthyroid multinodular/colloid goiter

Mechanisms of hyperthyroidism (HT)

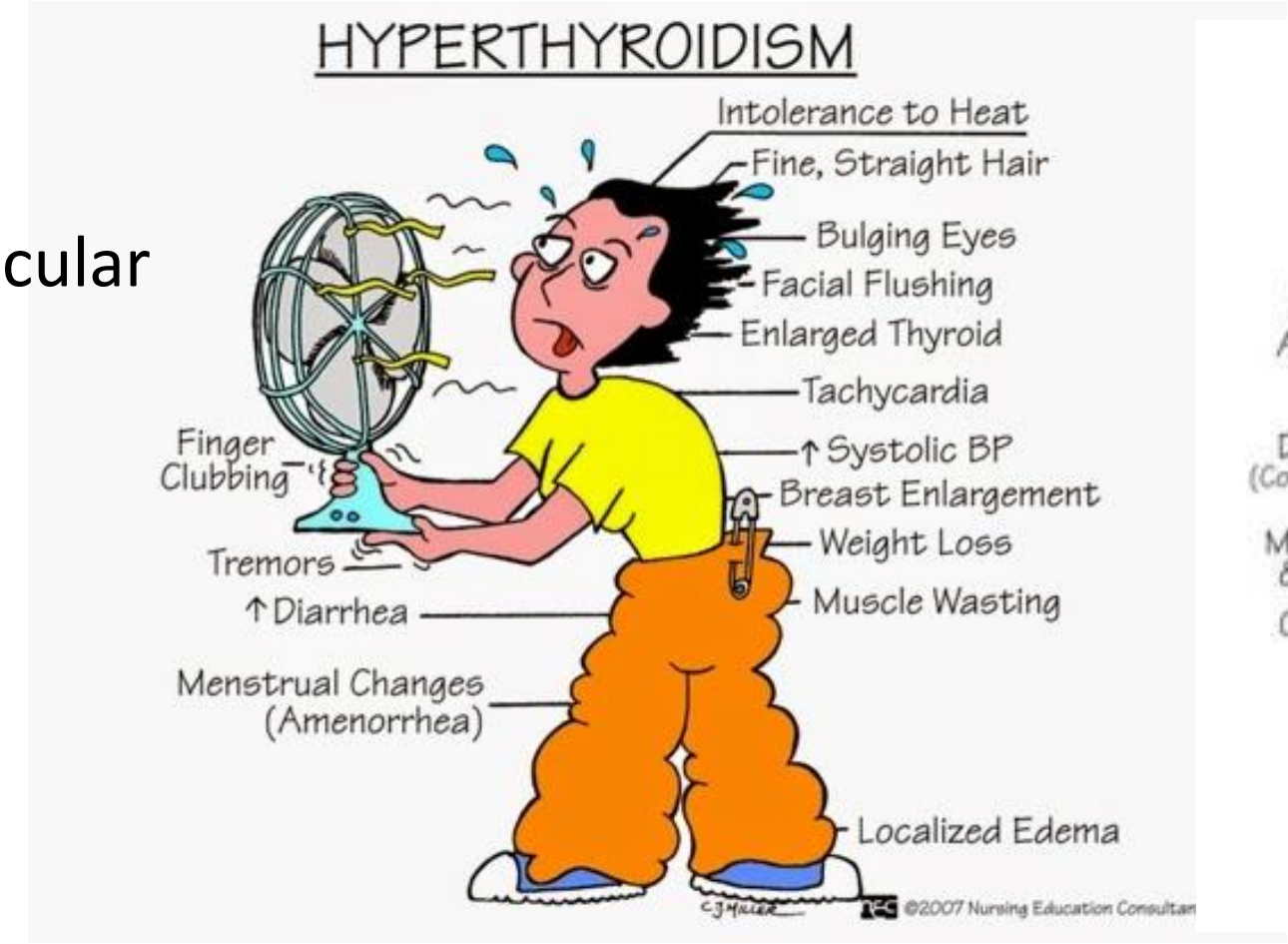
- Primary HT
  - Focal: autonomous nodule/adenoma (never malignant)
  - Diffuse: abnormal activation os follicular epithelium (Graves)

- Secondary HT
  - Very rare
  - FSH sectreting pituitary adenoma
  - Similar changes in thyroid than in Graves disease

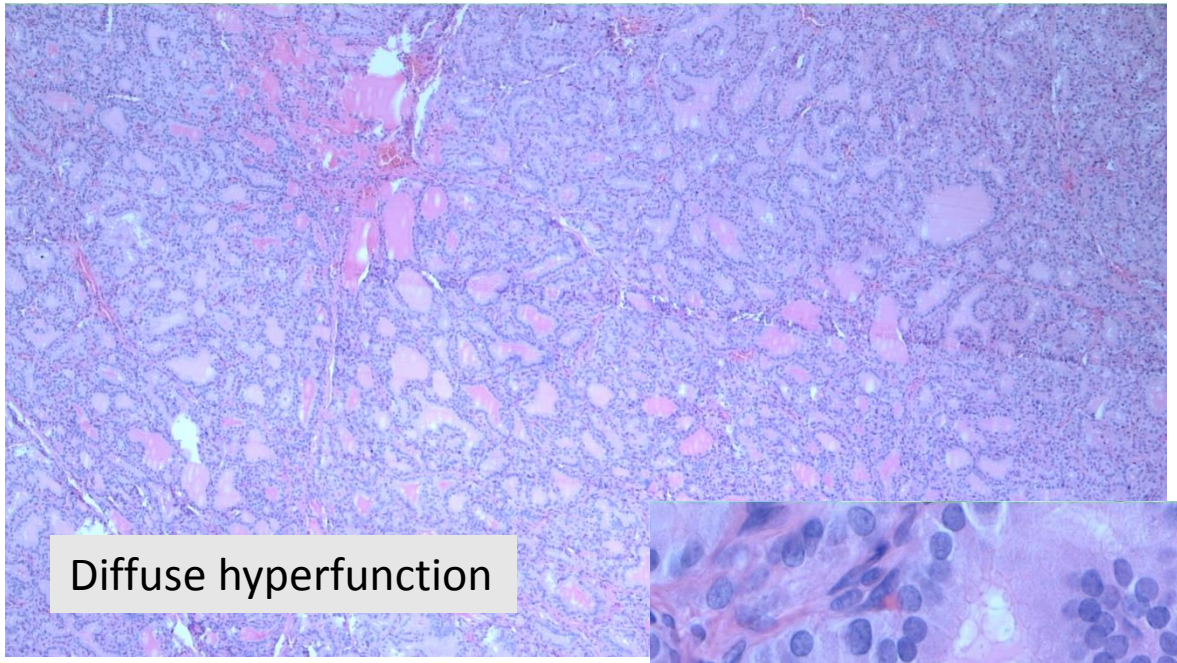


Clinical symptoms of abnormal T3/T4 levels

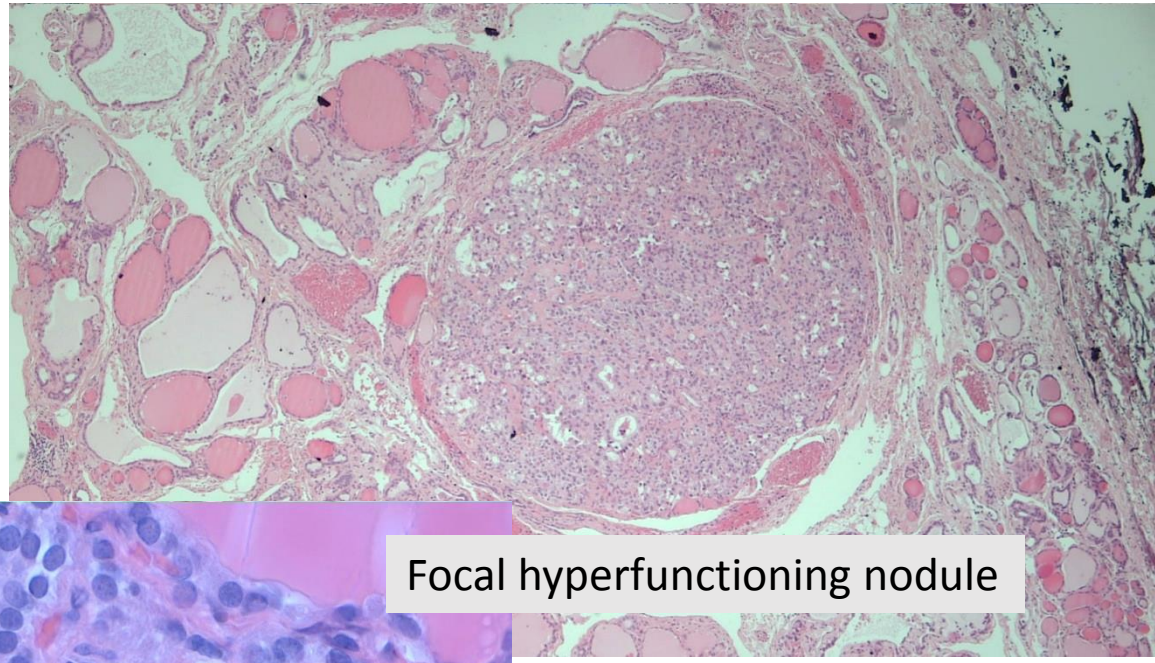
- Ocular
- GI tract
- Neuromuscular
- Cardiac
- Metabolic
- Physic



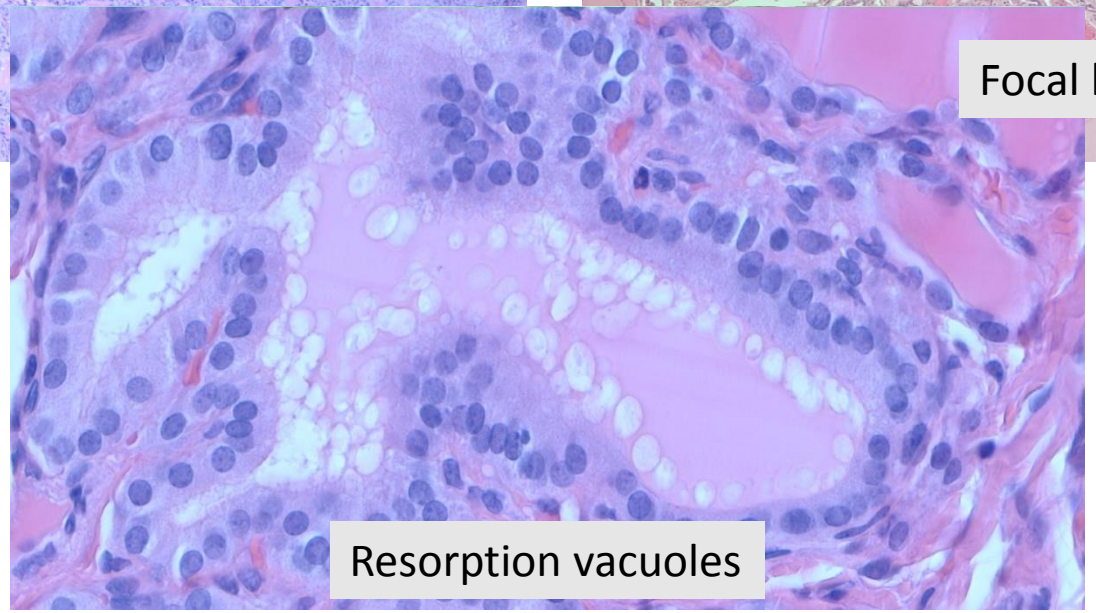
Microscopic morphology of hyperthyroidism



Diffuse hyperfunction



Focal hyperfunctioning nodule

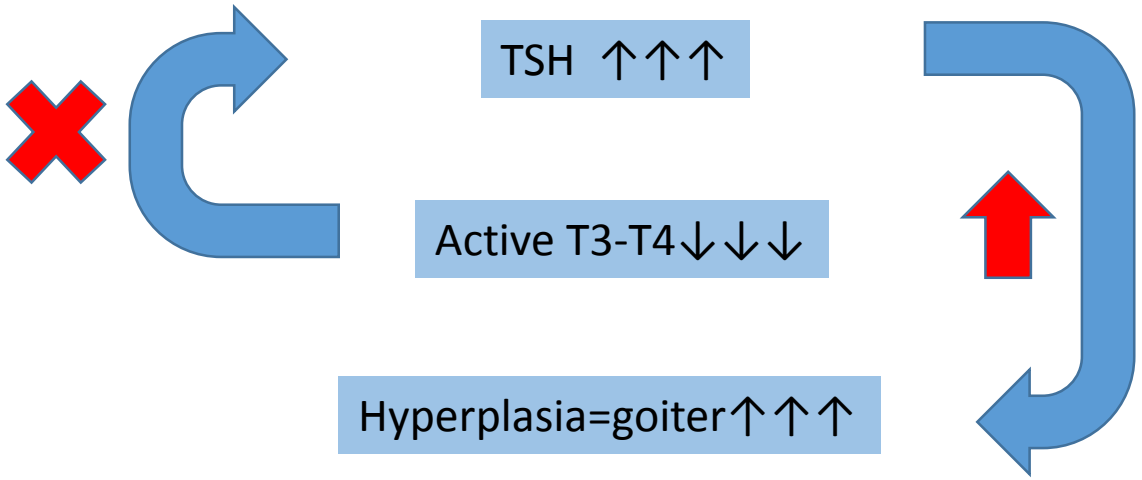


Resorption vacuoles

1.2. Hypothyroidism

- Due to lack of thyroid tissue
  - Thyroid atrophy (end stage Hashimoto)
  - Total thyreoidectomy

- Due to lack of hormon
  - Iodine deficiency
  - Enzimopathy (dyshormonogenetic goiter)



Mechanism of dyshormonogenetic goiter

2. Congenital disorders

- Ectopic thyroid tissue
  - Thyroglossal cyst (base of the tongue=lingual goiter/possible location of thyroid cancer!)
  - Mediastinal
  - Thyroid inclusions in neck lymph nodes (mimics PTC metastases!)

  - Struma ovarii≠ ectopic tissue, but a thyroid differentiation in an ovarian matured teratoma

- Enzimopathy (dyshormonogenetic goiter)
  - Thyroid peroxidase (PTO)
  - „Goitrous cretenism”

3. Thyroiditis

Forms

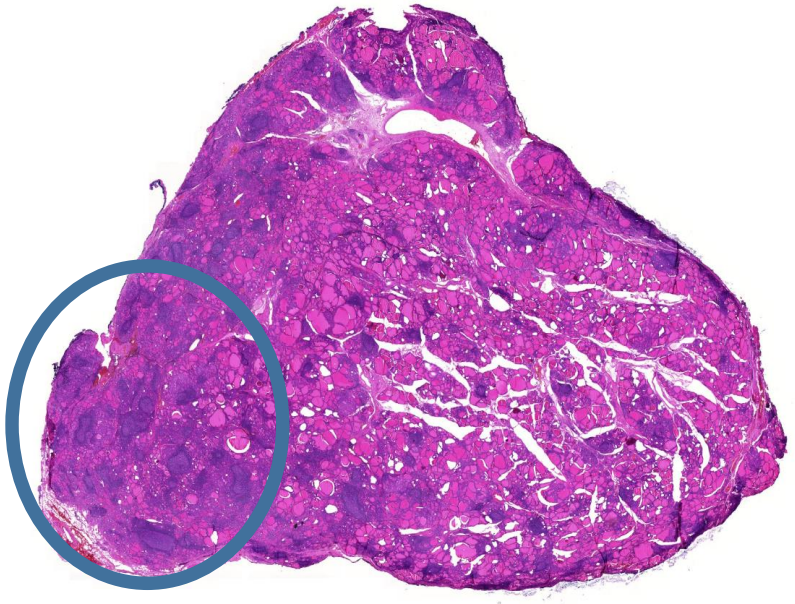
- Hashimoto
- Subacute granulomatous (de Quervain)
- Subacute lymphocytic
- Palpation
- Rare: Riedel

3.1. Hashimoto thyroiditis

- Most common cause of hypothyroidism (late phase)
- Indolent disease
- Etiology: autoimmune
  - Cytotoxic (hypersensitivity type IV)
  - Autoantibody dependent (hypersensitivity type II)
- Frequent association with other autoimmune disorders (SLE, Sjögren etc)
- Risk of malignant transformation from clonal lymphoid proliferation → MALT lymphoma

Macroscopic morphology

- Early stage: none
- Later: mild nodular appearance
  - Clinical presentation: nodule
- End phase: total atrophy
  - Clinical presentation: hypothyroidism, no iodine uptake)



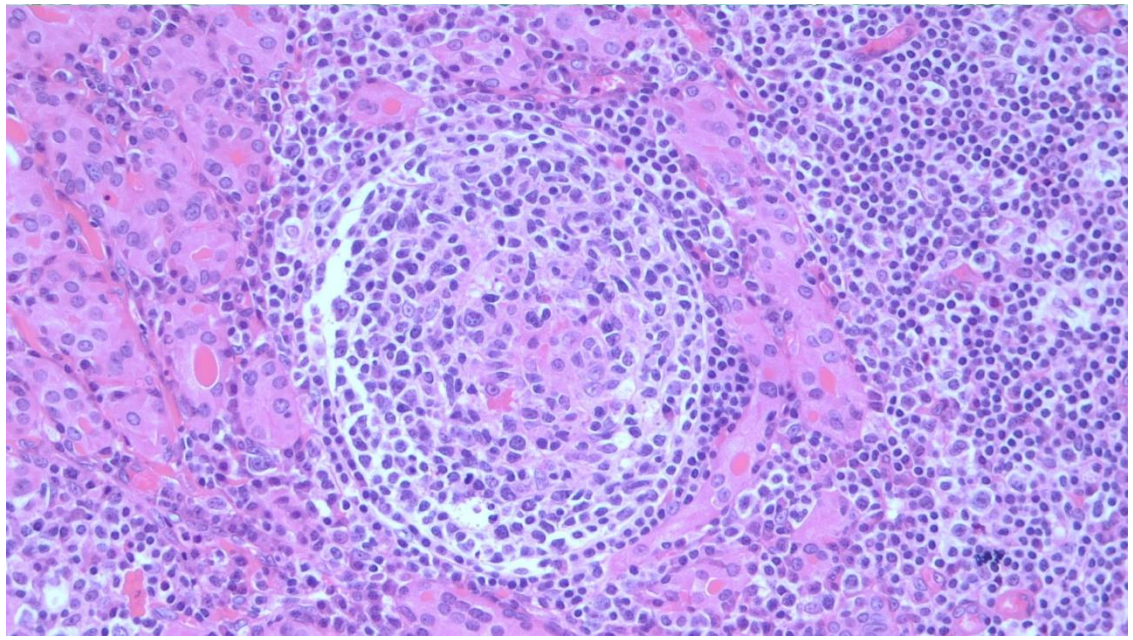
Whiter area:
lymphoid tissue

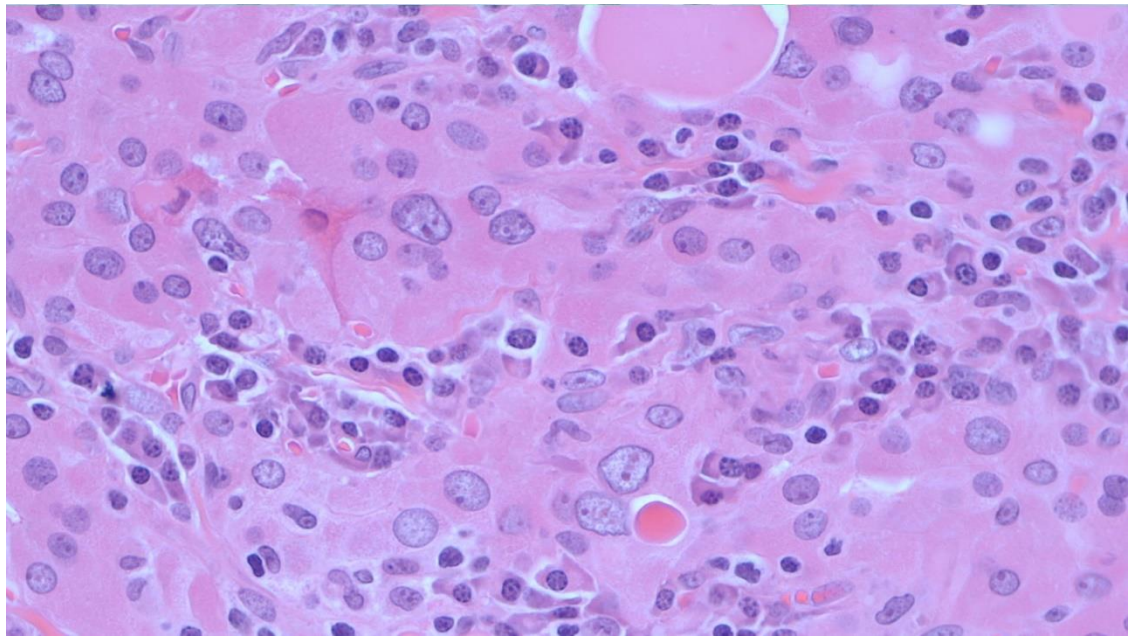
Microscopic morphology

Thyroid follicles:

- Early/mid phase: variable
- End phase: total atrophy

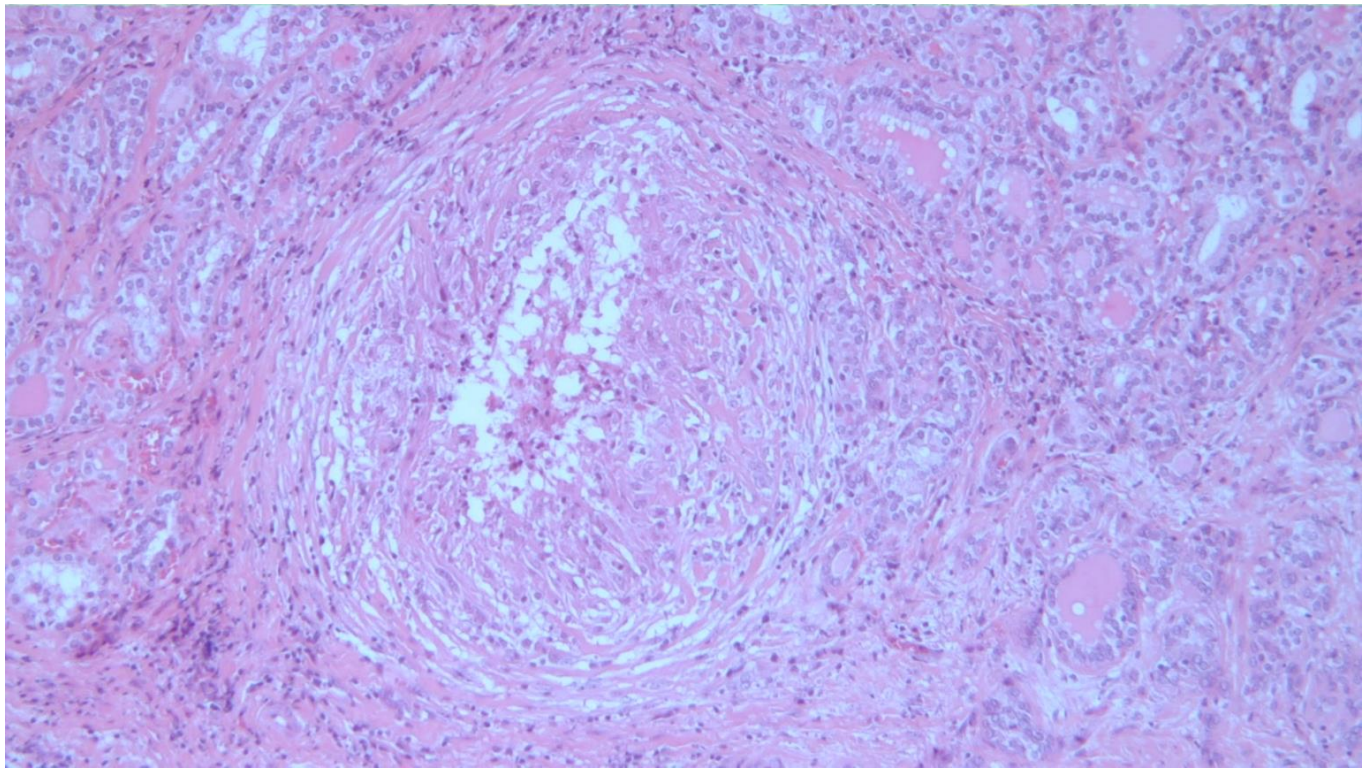
- Lymphatic follicles
- Hürtle (oxiphyl) cell change
  - Mitochondrium-rich cytoplasm
  - Large nuclei





3.2. Subacute granulomatous thyroiditis

- Young-middle aged females
- Painful enlargement of the thyroid gland
- Spontaneus healing



3.3. Subacute lymphocytic thyroiditis

- Similar to Hashimoto
- Postpartum presentation
- Painless
- Rarely progress to hypothyreoidism since inflammatory process is less destructive

3.4. Palpation thyroiditis

- „Traumatic” disruption of follicles → colloid material acts as a „foreign body” → granulomatous reaction
- Asymptomatic, no clinical significance
- Usually incidental microscopic finding

3.5. Riedel thyroiditis

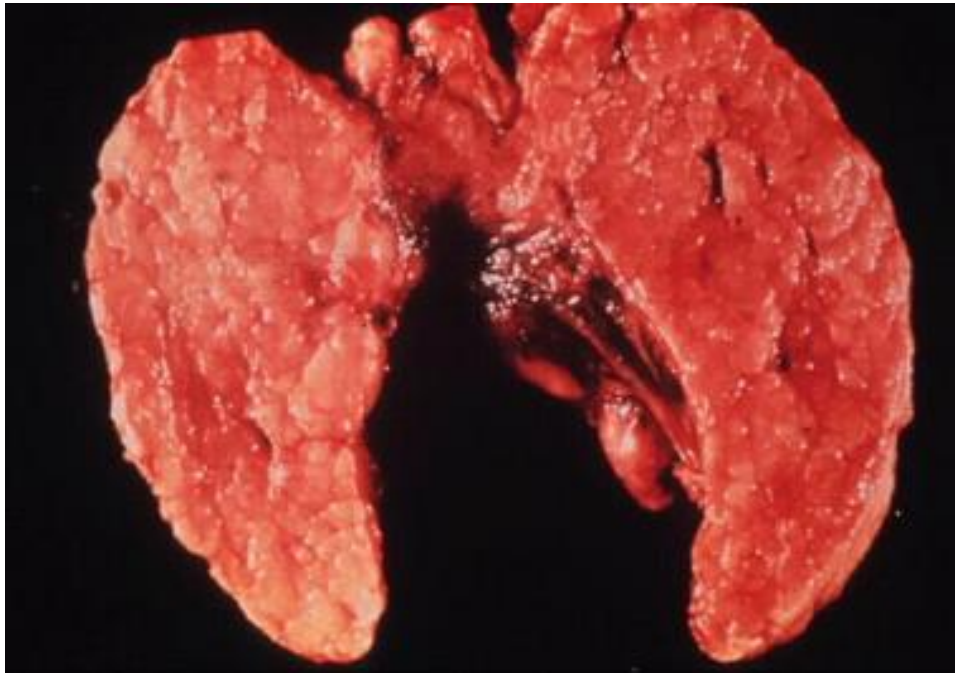
- Exceptionally rare
- Diffuse, „infiltrative” type fibrosis of the thyroid gland
- Extrathyroid involvement
- Clinically: hard fixed mass forming lesion (mimics cancer)
- Etiology: type of the IgG4 related disorder group

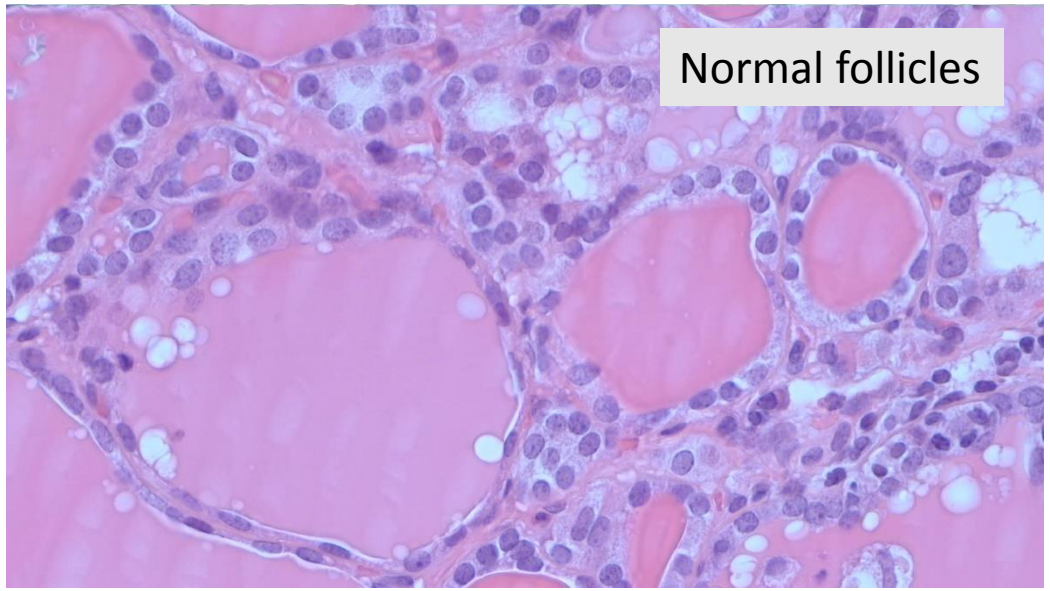
4. Graves disease

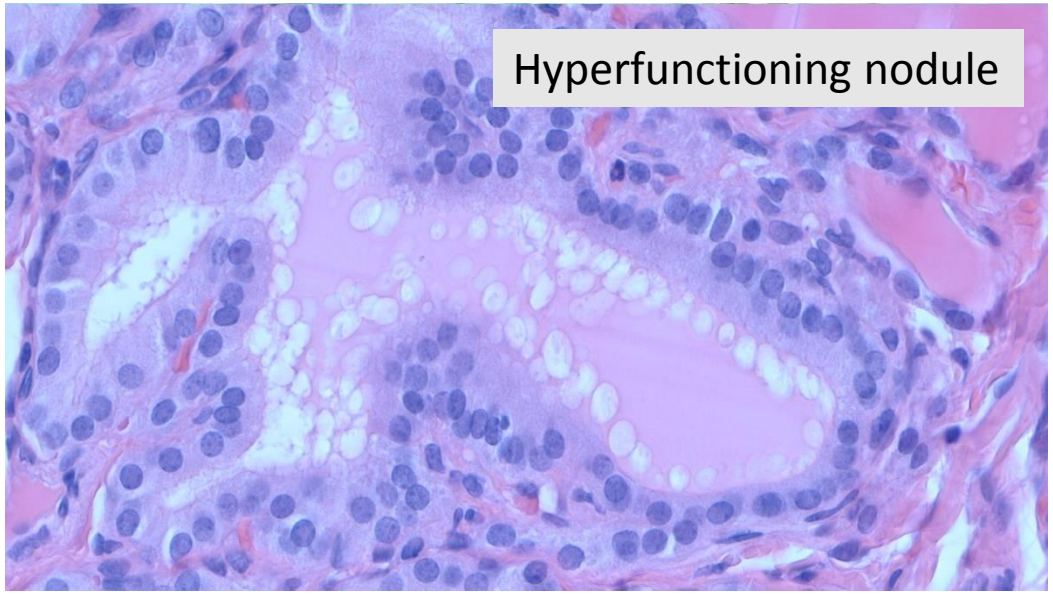
- Autoimmune type disorder lack of inflammatory cells
- Autoantibody related mechanism (hypersensitivity type II)
- Major role: TSH binding IgG → permanent follicular hyperfunction
- No destructive inflammation → if therapy resistant surgery needed

Morphology

- Macro: diffuse type goiter
- Micro: follicular hyperfunction
  - If previously treated variable microscopic changes





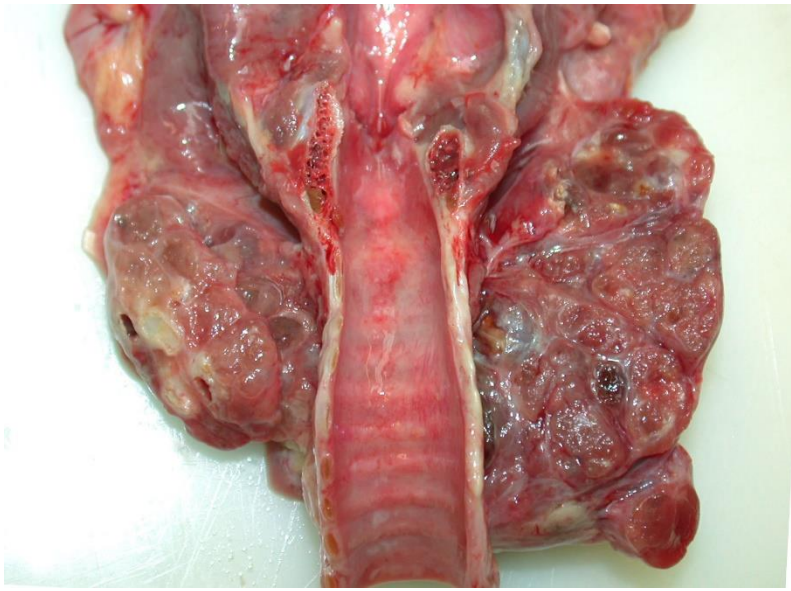


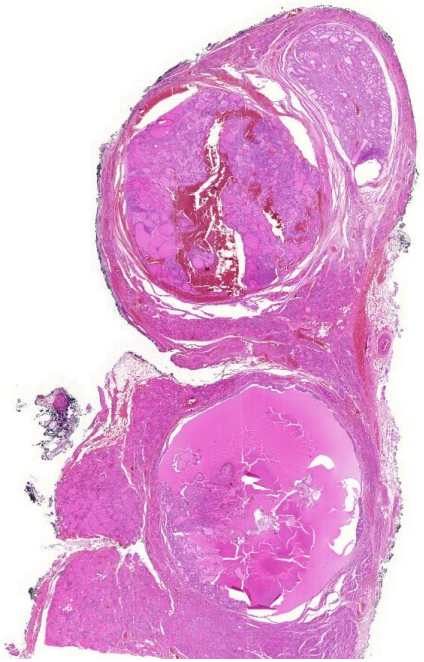
5. Diffuse and multinodular goiter

- Classic diffuse form is rare caused by iodine deficiency
  - Endemic: more than 10% of the population is affected in a given region
- Nodular goiter: multifactorial disease
  - Sporadic, females are more commonly affected
  - Hyperthyroidism: autonomous nodule (Plummer syndrome)
  - No hyperthyreoidism: euthyroid goiter (more common)
    - Mass effect: trachea obstruction, dysphagia
- Cancer risk is slightly elevated (follicular tumors)

Morphology - macroscopy

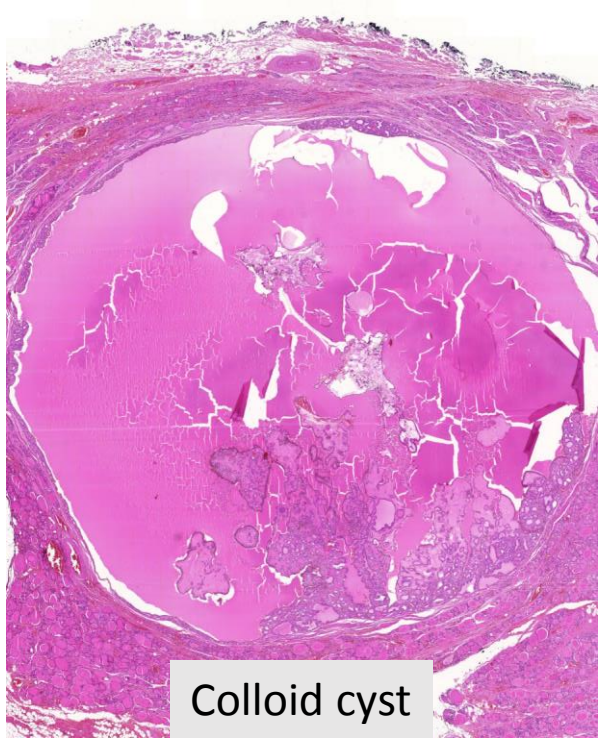
- Asymetric nodular enlargement of the thyroid
- Fused follicles can form colloid cyst
- Frequent degeneration: hemorrhage, calcification, fibrosis

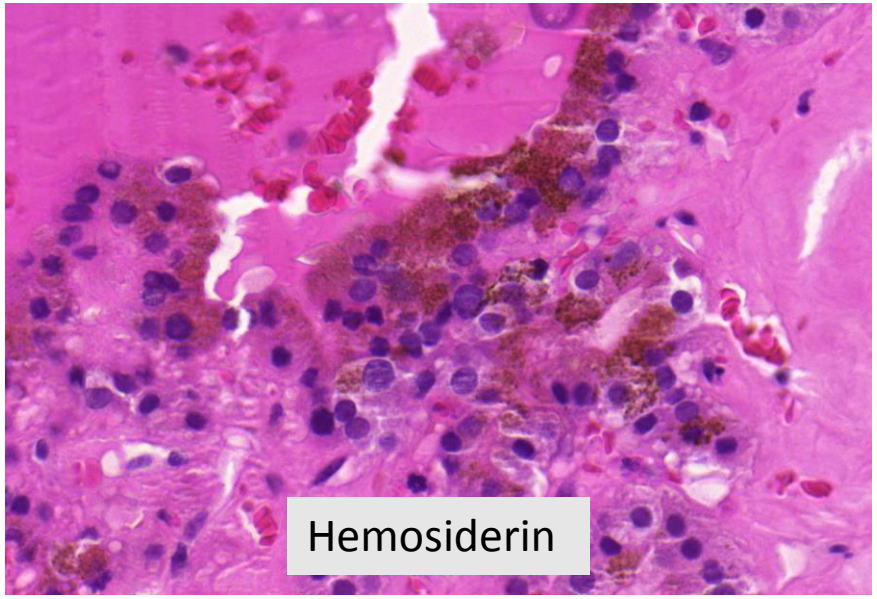


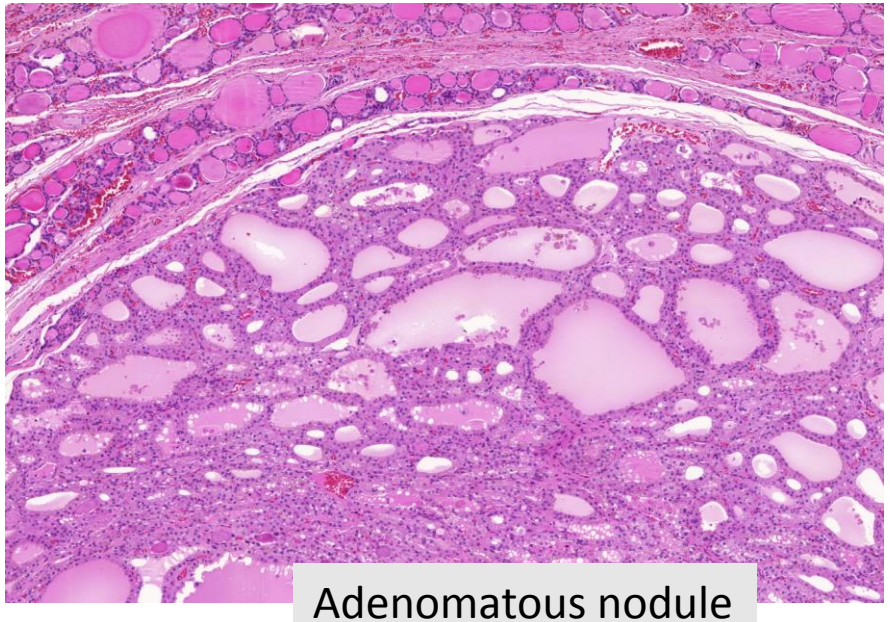


Morphology - microscopy

- Colloid rich follicles – flat epithelium
- Adenomatous nodule – cuboidal/columnar epithelium
- Hemosiderin/ cholesterol depositions


Colloid cyst


Hemosiderin


Adenomatous nodule

Neoplasias

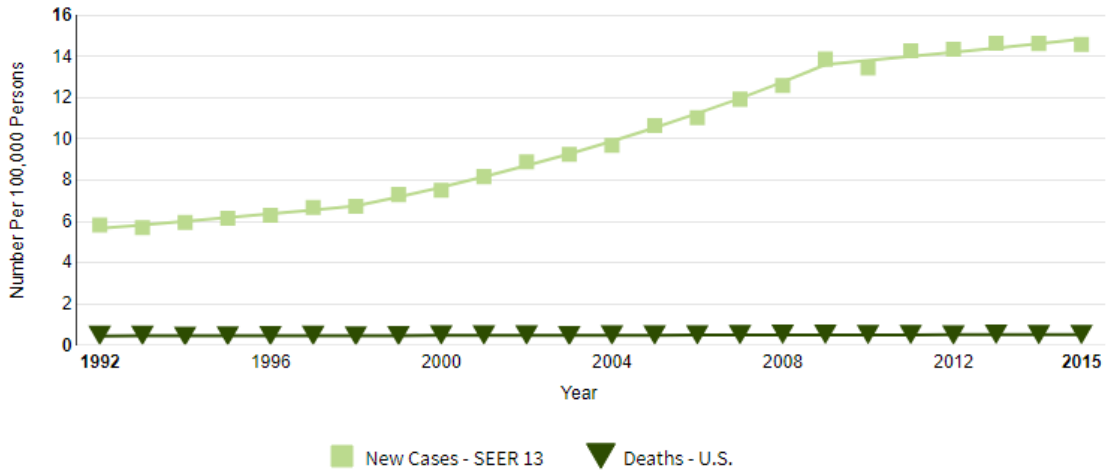
Thyroid cancer – some statistics

- One of the most frequent human cancer, especially <50 years
- One of the less lethal human cancer
- Increased incidence due to improving accuracy of imaging (US, MRI etc.)

Estimated New Cases in 2018	53,990
% of All New Cancer Cases	3.1%

Estimated Deaths in 2018	2,060
% of All Cancer Deaths	0.3%

Percent Surviving 5 Years
98.1%
2008-2014

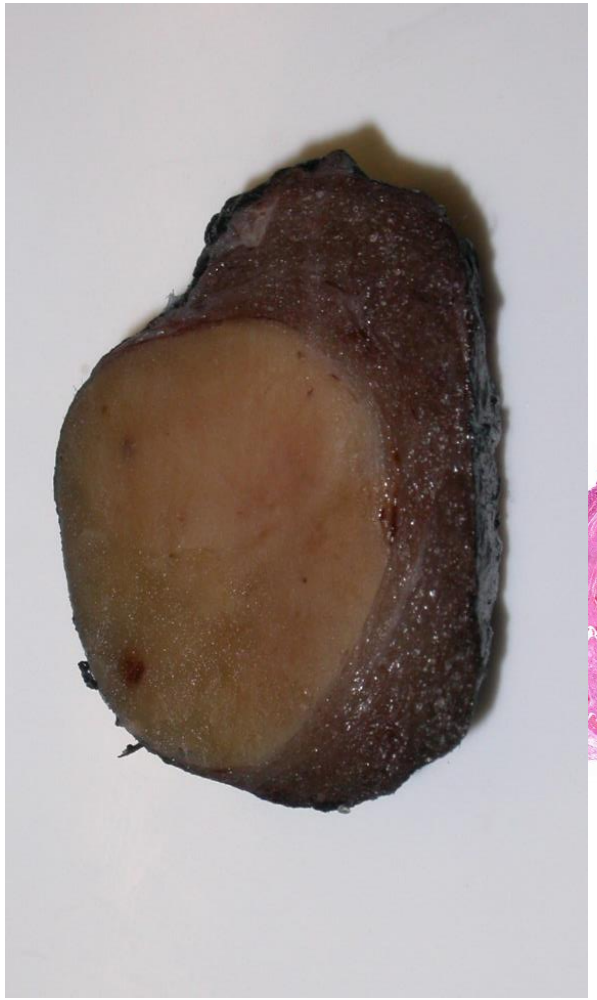


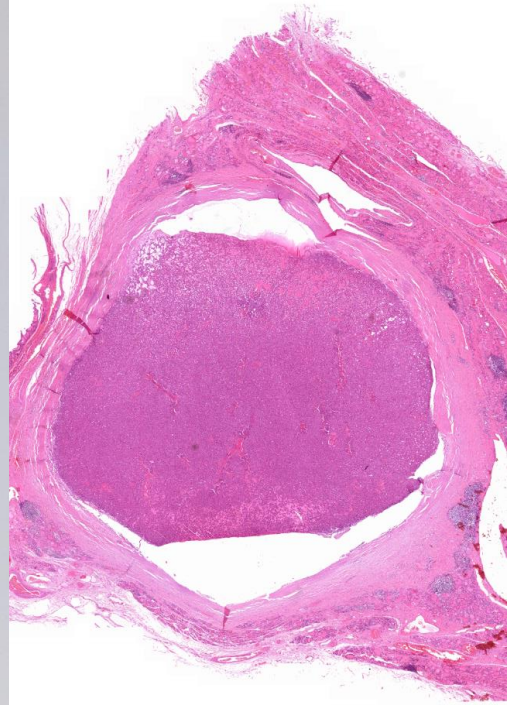
6.1. Follicular neoplasias

- Definition: encapsulated follicular tumor resemble normal thyroid follicles
- Clinically: solitary nodule
- Usually hormonally inactive (rarely „toxic adenoma”)
- Frequent RAS mutation
- Benign: follicular adenoma
- Malignant: follicular carcinoma
  - No significant difference in cytomorhology
  - Diagnostic criteria: capsular and/or vascular invasion
  - Hematogenous spread: brain, lung, bone metastases

Morphology - macroscopy

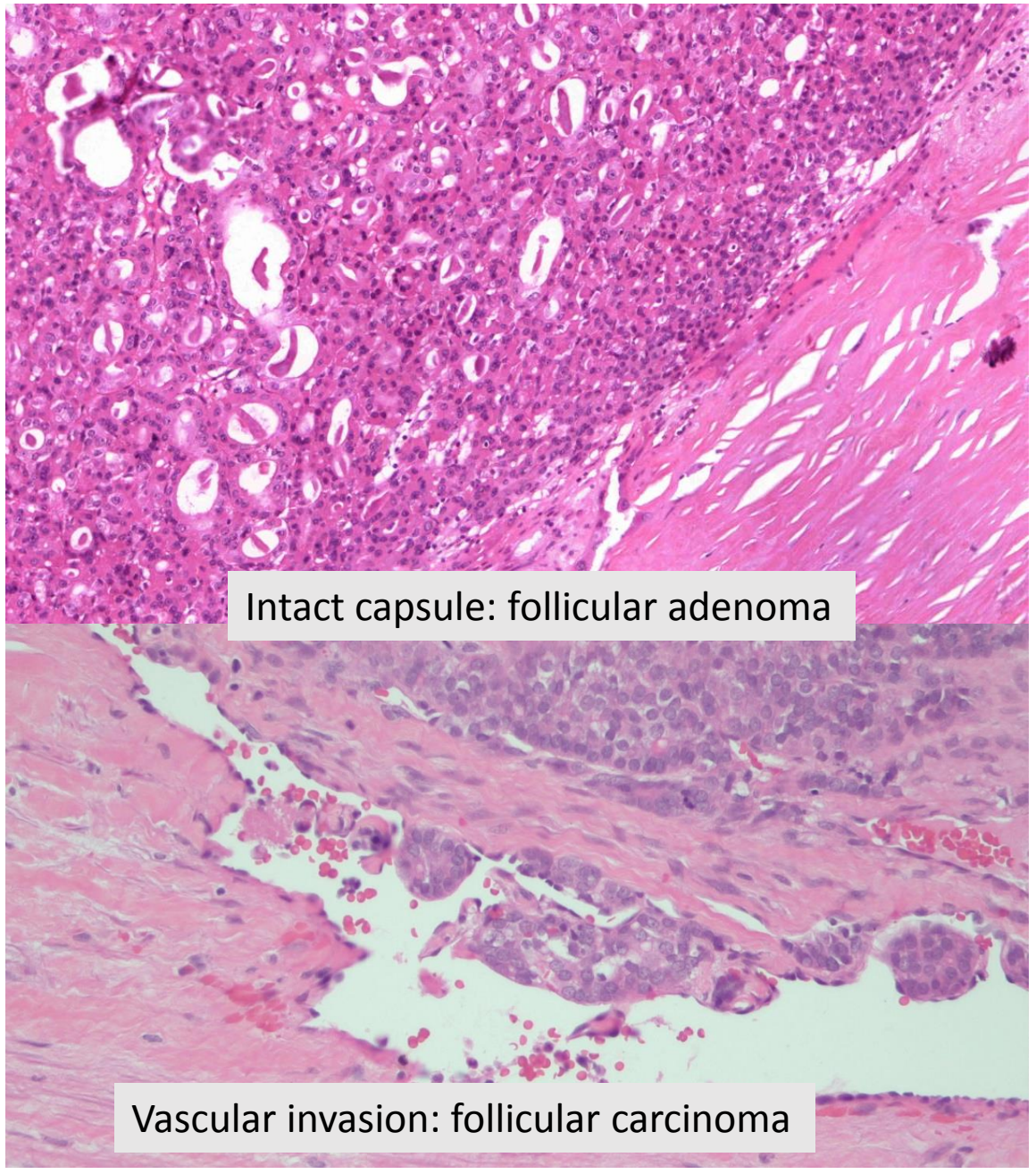
- Well circumscribed nodule with thin capsule
- Relatively small
- Normal surrounding thyroid
- Much more homogenous than nodular goiter





Morphology - microscopy

- Generally microfollicular pattern
- Well differentiated follicular epithelium
- Very strict assessment of capsular/vascular invasion→ the whole lesion must be examined=>20 slides per case!

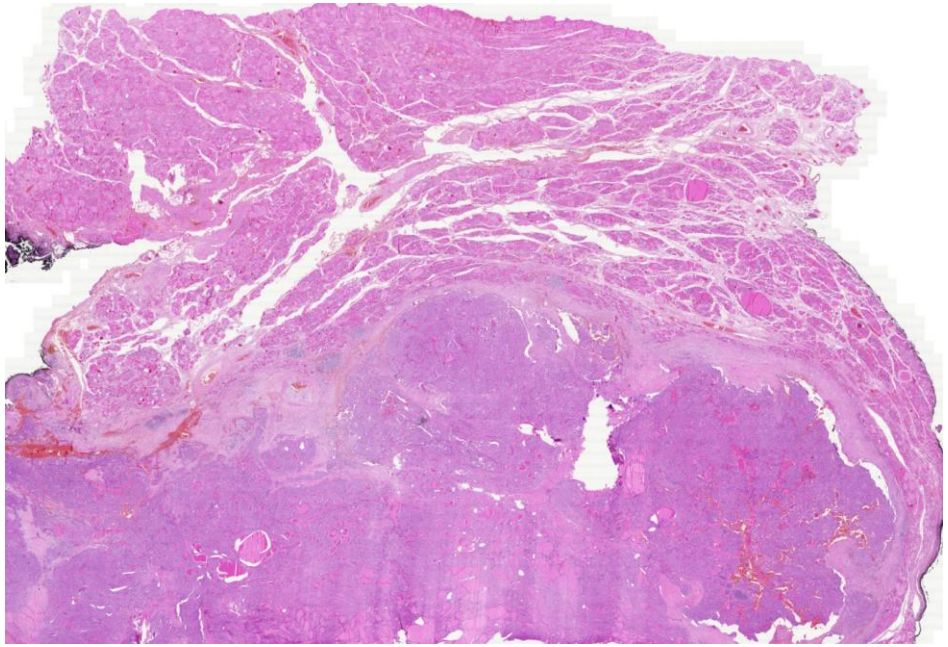


6.2. Papillary thyroid carcinoma

- Most common form of thyroid cancer
- Ionizing radiation is an important risk factor
- „Officially” all PTC are malignant, no precancerosis (microcarcinomas), but >95% OS
- Frequent in young patients
  - Worse prognosis in old age
- Never associated with hyperthyroidism
- Painless thyroid nodule
- Frequent neck lymph node metastasis (lymphatic spread)
- Distant metastases are rare
- Ret/PTC rearrangement is the most common genetic abnormality

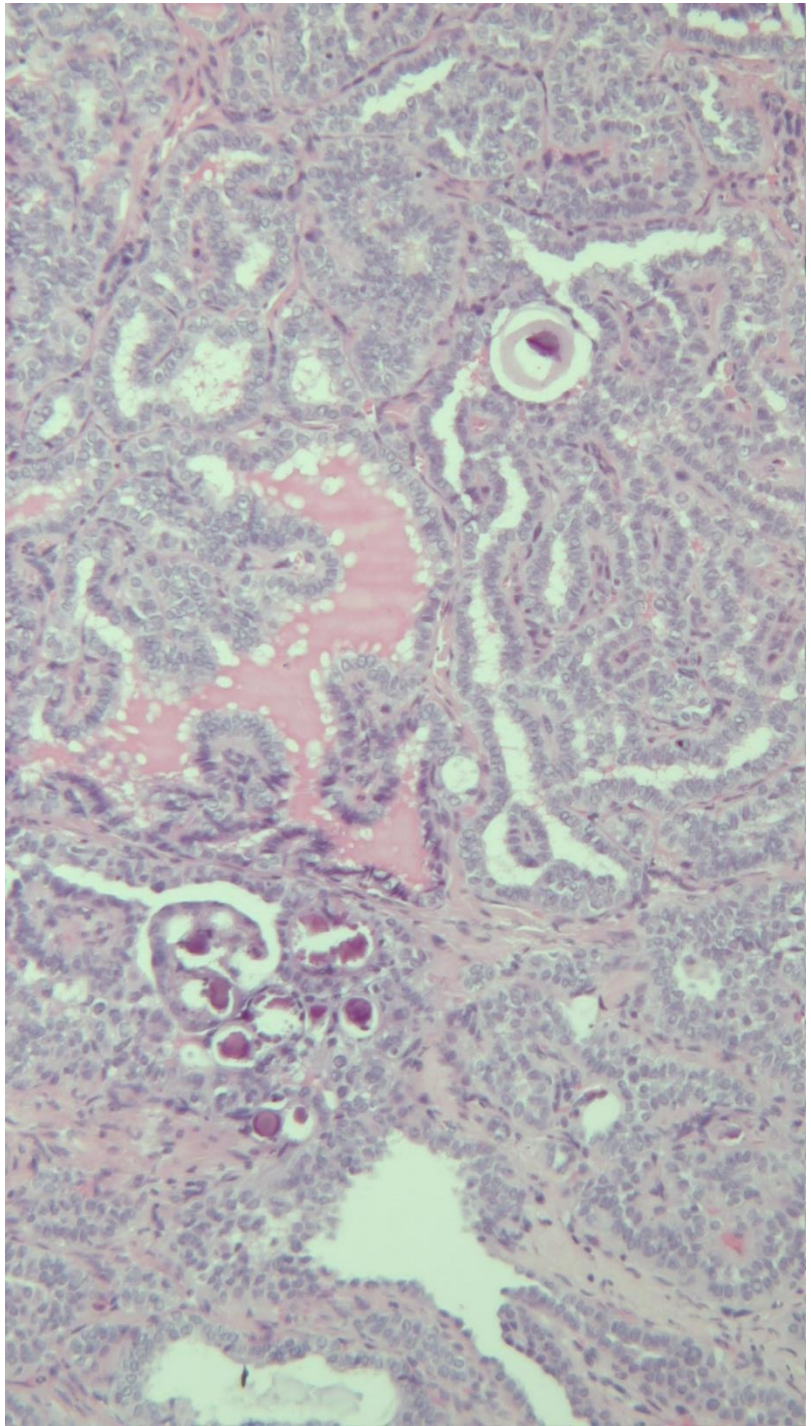
Morphology - macroscopy

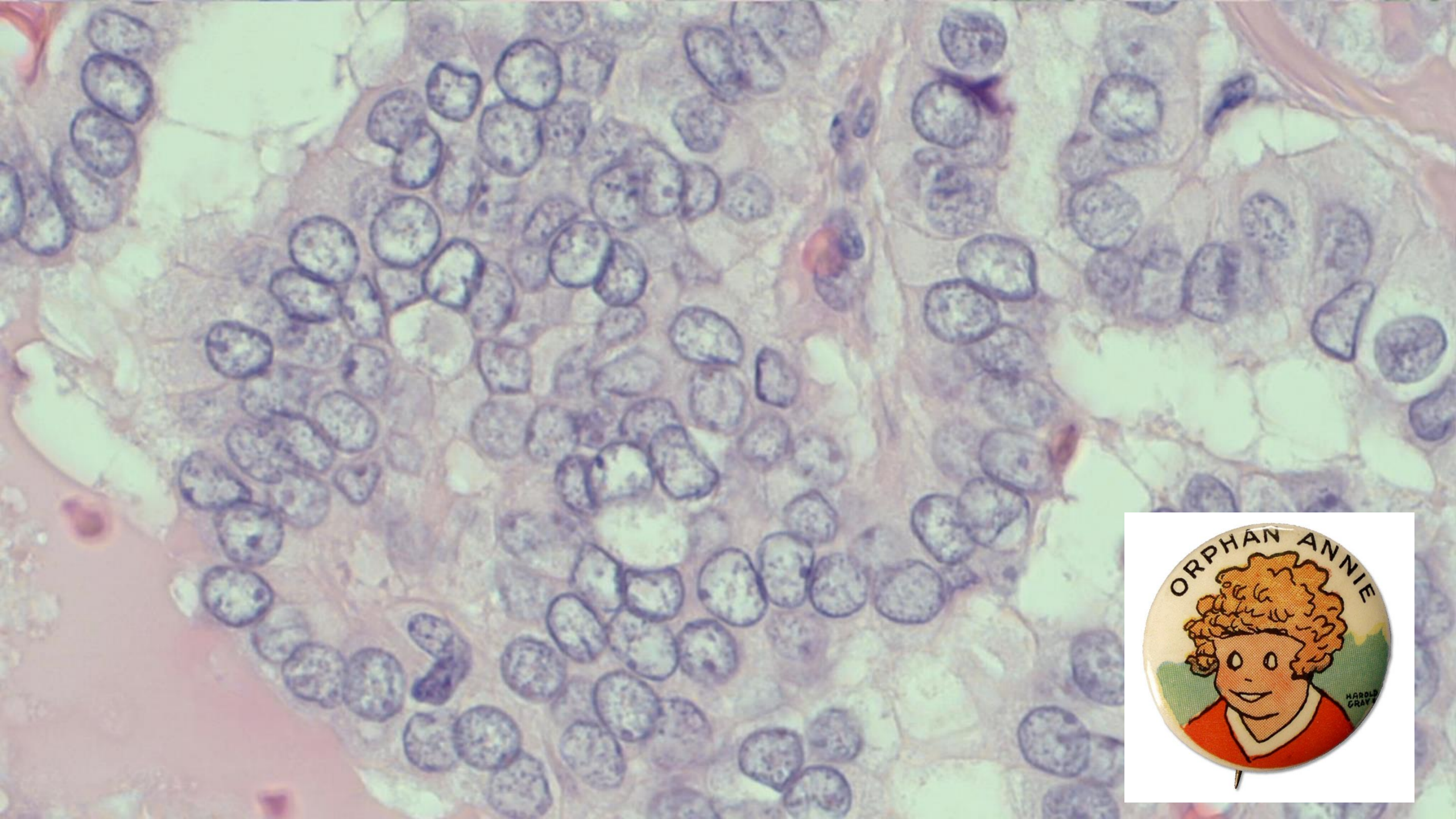
- Well circumscribed or infiltrative tumor, usually not encapsulated (except a rare form)
- Gray and tough tumor
- Frequent microcalcification (US detectable)

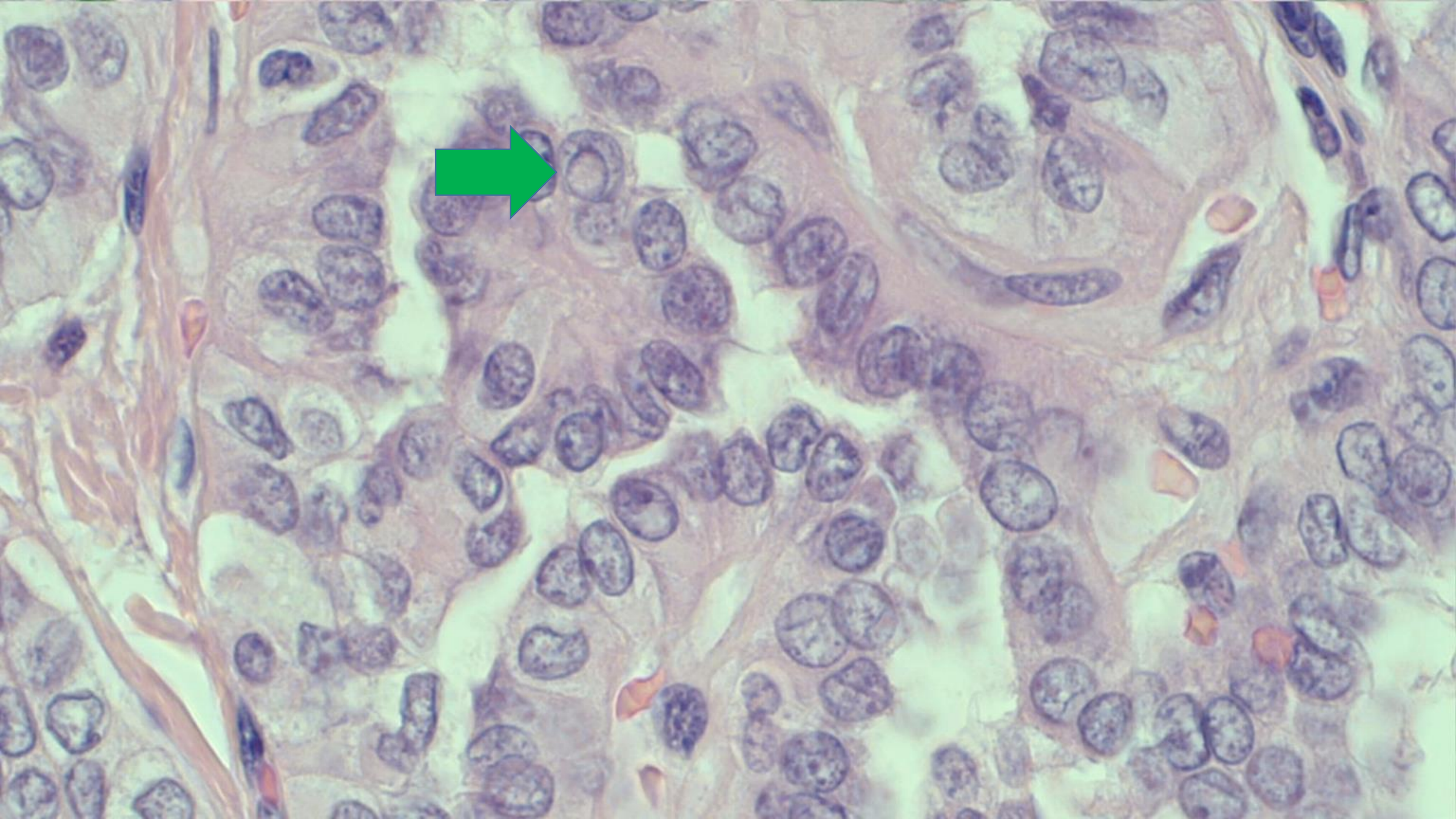


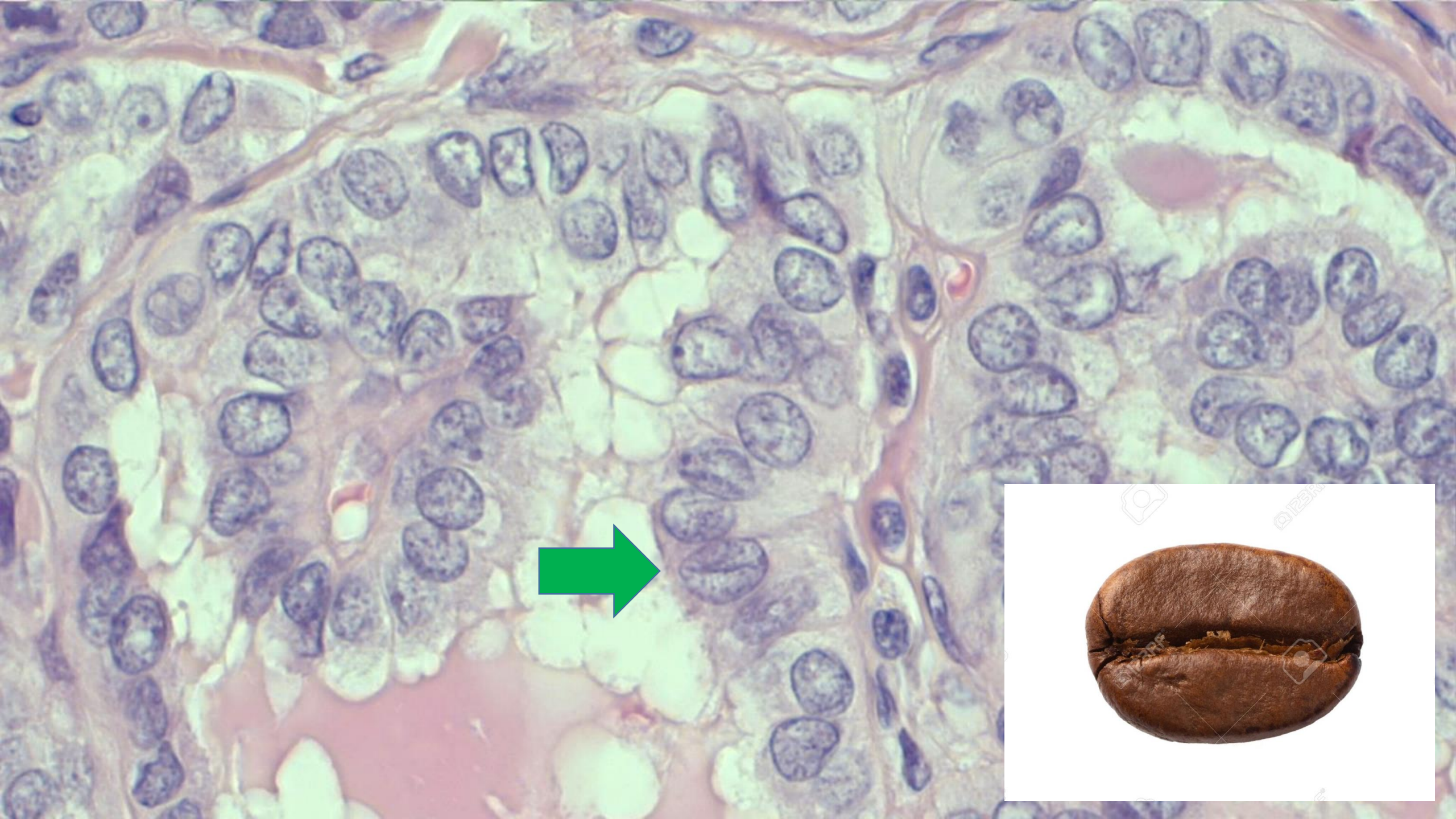
Morphology - microscopy

- Generally papillated but pure papillary architecture is very rare (papillary+follicular)
- Pure follicular form exists
- Nuclear crowding
- Psammoma bodies
- Diagnosis of PTC is based on nuclear features hence cytologically detectable
  a) „Clear nuclei” (Orphan Annie)
  b) Nuclear grooves (coffee bean)
  c) Pseudoinclusions



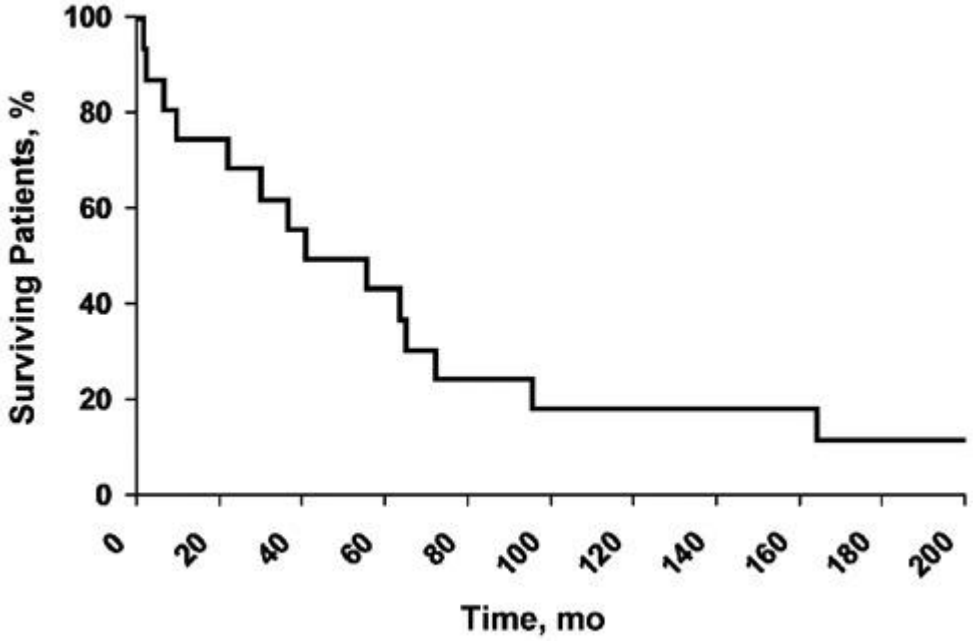

ORPHAN ANNIE
HAROLD GRAY





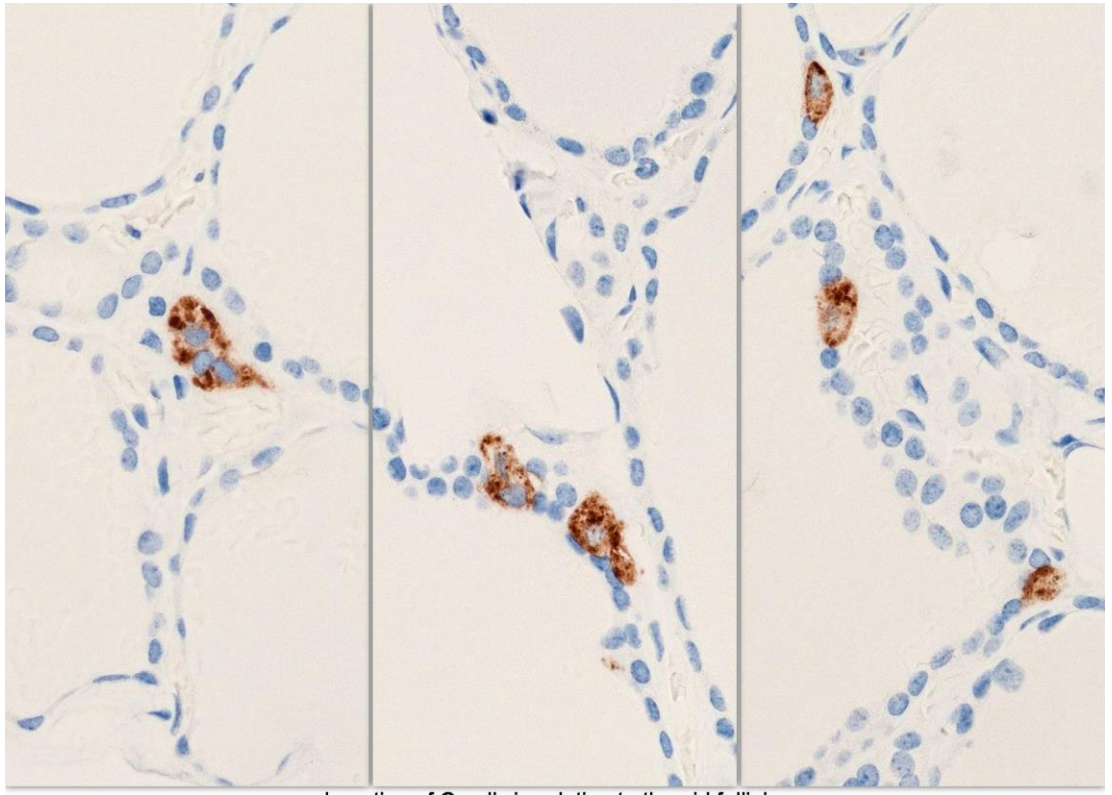
6.3. Medullary thyroid carcinoma

- Malignant neuroendocrine tumor of the thyroid gland
- Deriving from C-cells
- Acivating RET mutation
- 20% familial: MEN 2 syndrome
  - C-cell hyperplasia/early onset MTC → preventive thyreoidectomy
- 80% sporadic
  - Older age
- Frequently metastatic but slow progression



C-cells

- Part of DNES
- Calcitonin secretion
  - Its function is not significant
  - No symptom of overproduction
  - Tumor marker of MTC
- C-cells are not detectable by H&E



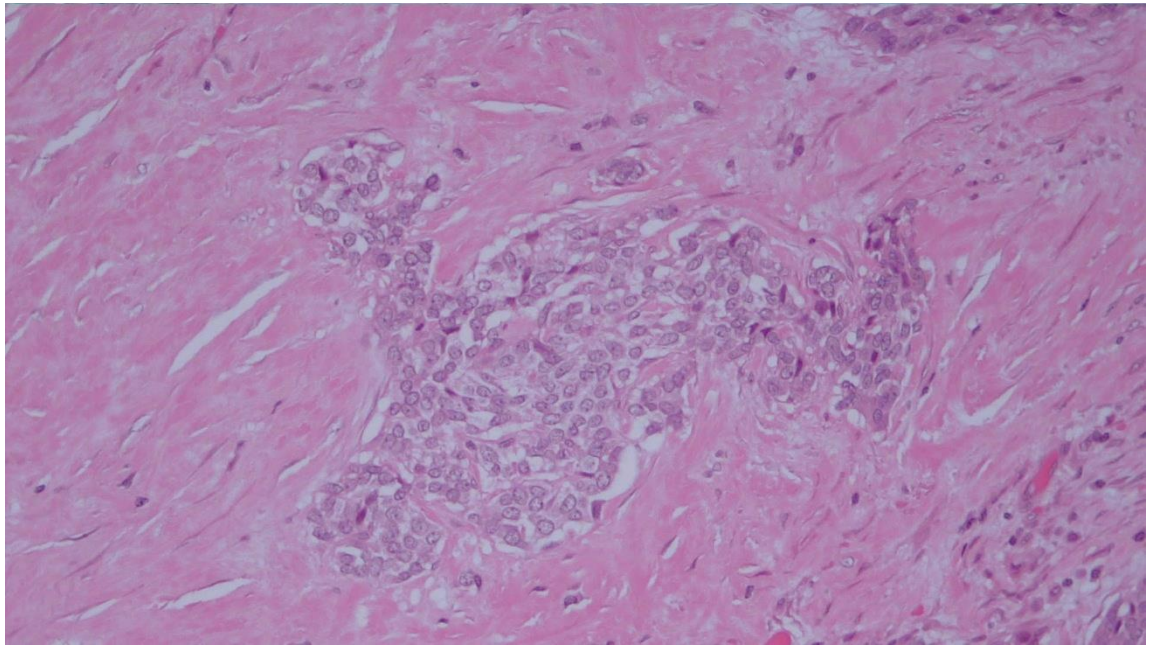
Location of C cells in relation to thyroid follicle:
interstitial, subfollicular, and superficial (mCEA IHC, high power)

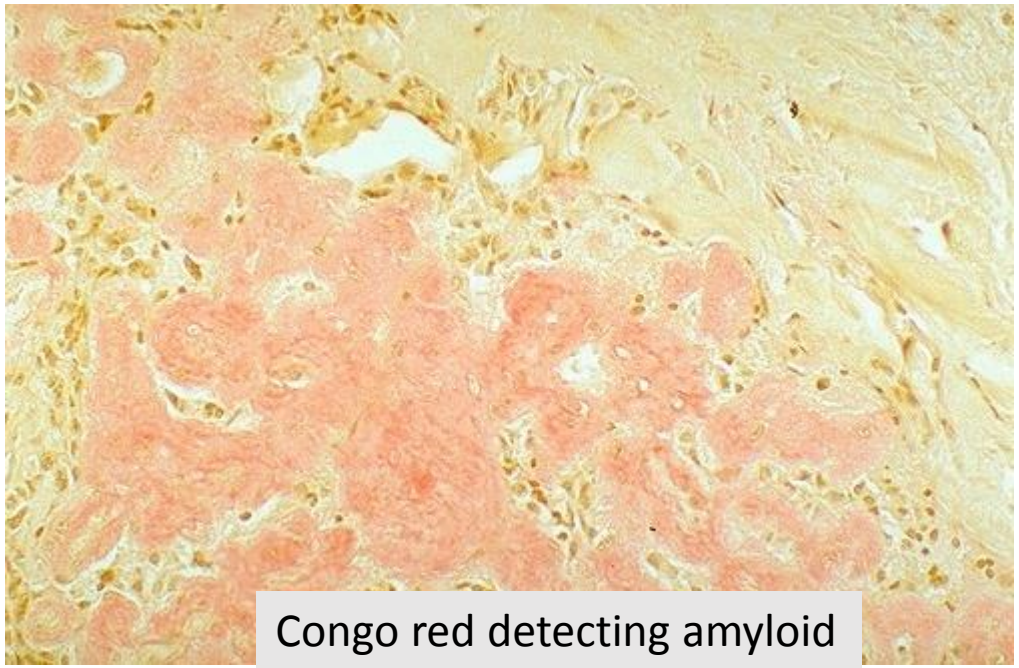
Morphology - macroscopy

- Relatively circumscribed tumor
- Very tough
- Frequent lymph node metastases → radical neck dissection is needed

Morphology - microscopy

- Resemble to other neuroendocrin tumors
- Monotonous cytomorphology/ low mitotic count
- Amyloid stroma
- Neuroendocrine markers and calcitonin positivity

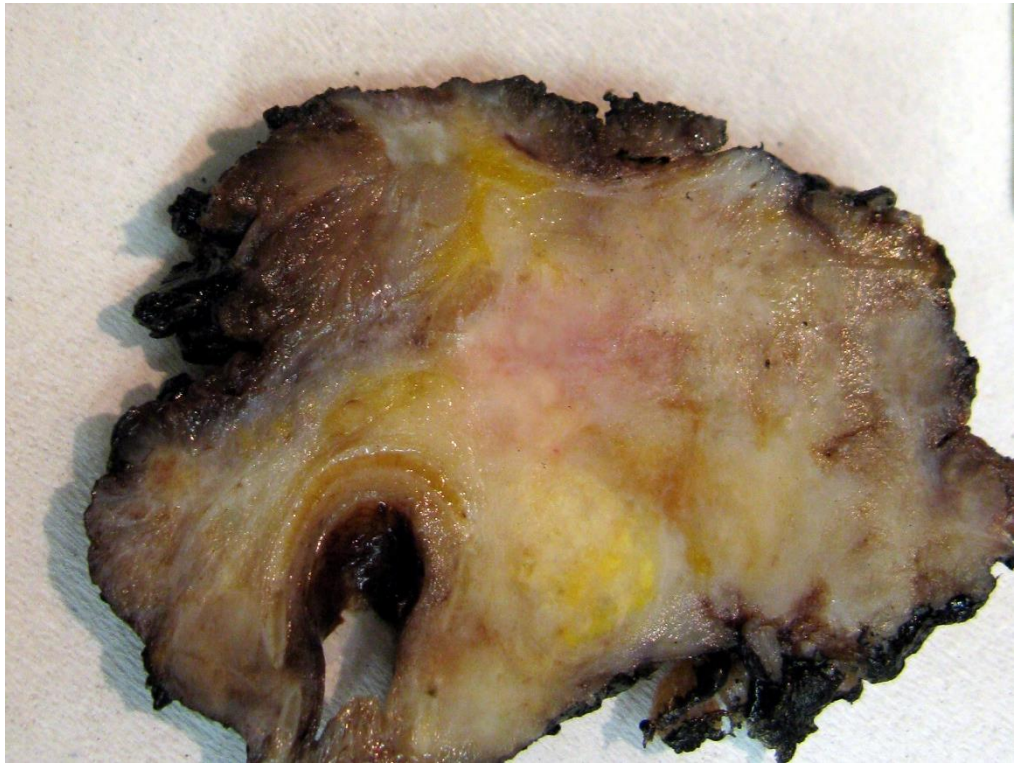




Congo red detecting amyloid

6.4. Rare thyroid neoplasms

- Anaplastic carcinoma
  - Frequently „sarcomatoid” morphology
  - Worse prognosis, survival <1 year
- Lymphoma
  - Associated with Hashimoto thyroiditis
  - MALT type
- Metastases
  - Rare site of metastases
  - Renal cell carcinoma, lung- GI tract cancers



Anaplastic carcinoma infiltrating the larynx

Diagnostic management of a thyroid nodule

- Very common lesion
  - 2-6% with palpation
  - 19-35% with ultrasound
  - 8-65% in autopsy data
- Physical examination
- Ultrasound - *morphology*
- Scintigraphy – *function*
  - Warm nodule
  - Cold nodule

Fine needle aspiration

- Role: select patients for surgical resection = select malignant cases
- Why not CNB?:
  - High morbidity (hemorrhage-hematoma)
  - Unnecessary since the diagnosis of malignancy is based on cytomorphology (except follicular neoplasias – note: CNB is inappropriate to detect capsular/vascular invasion)
- Indications of FNA
  - Solitary nodule
  - Dominant nodule >1 cm
  - Suspicious US findings (eg. microcalcification)
  - Cold nodule of solid architecture
- Reporting: Bethesda classification

The Bethesda System for Reporting Thyroid Cytopathology

57th Annual Scientific Meeting
American Society of Cytopathology

Diagnostic Category	Risk of Malignancy	Usual Management
Nondiagnostic	——	Repeat FNA with u/s
Benign	0-3%	Clinical follow-up
Atypical Follicular Lesion of Undetermined Significance	5-15%	Repeat FNA
Suspicious for Follicular Neoplasm	15-30%	Surgical lobectomy
Suspicious for Malignancy	60-75%	Near-total thyroidectomy or surgical lobectomy
Malignant	97-99%	Near-total thyroidectomy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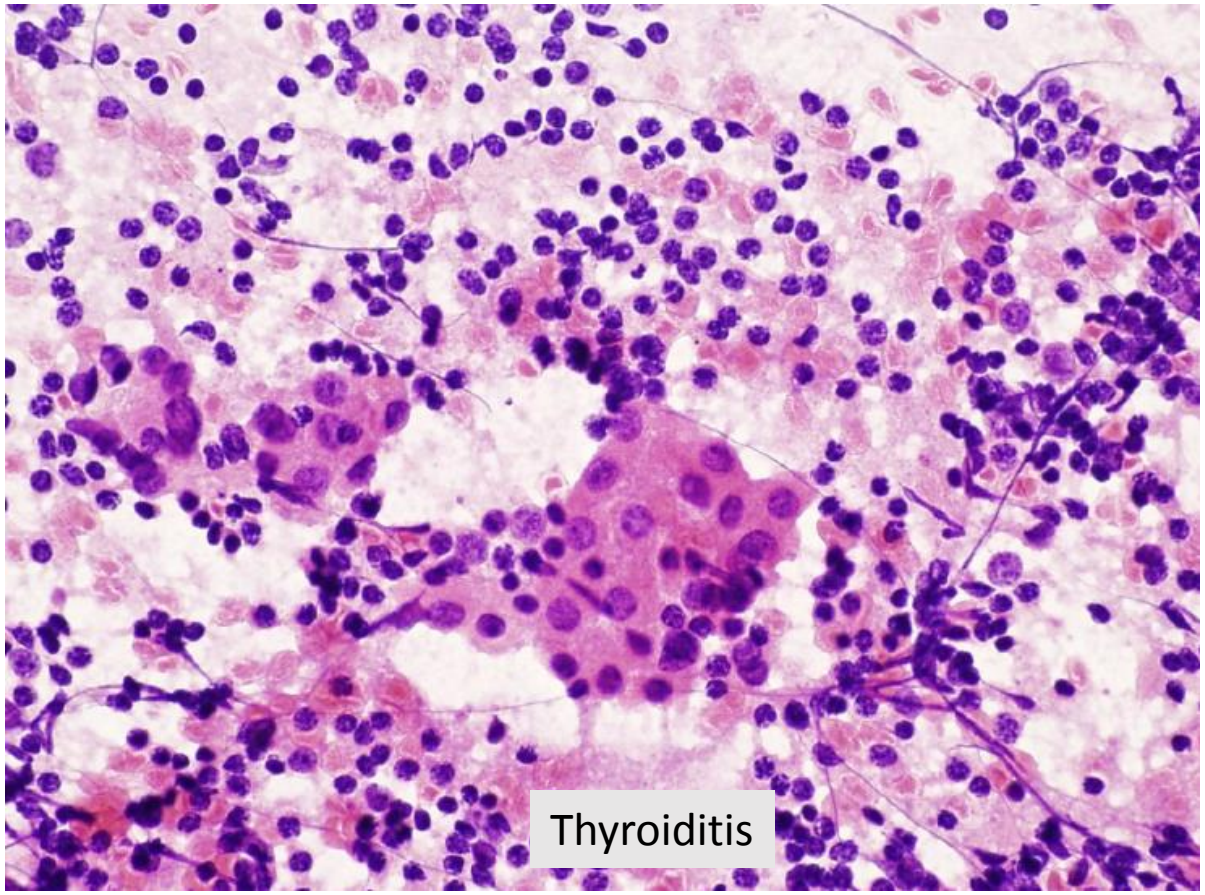
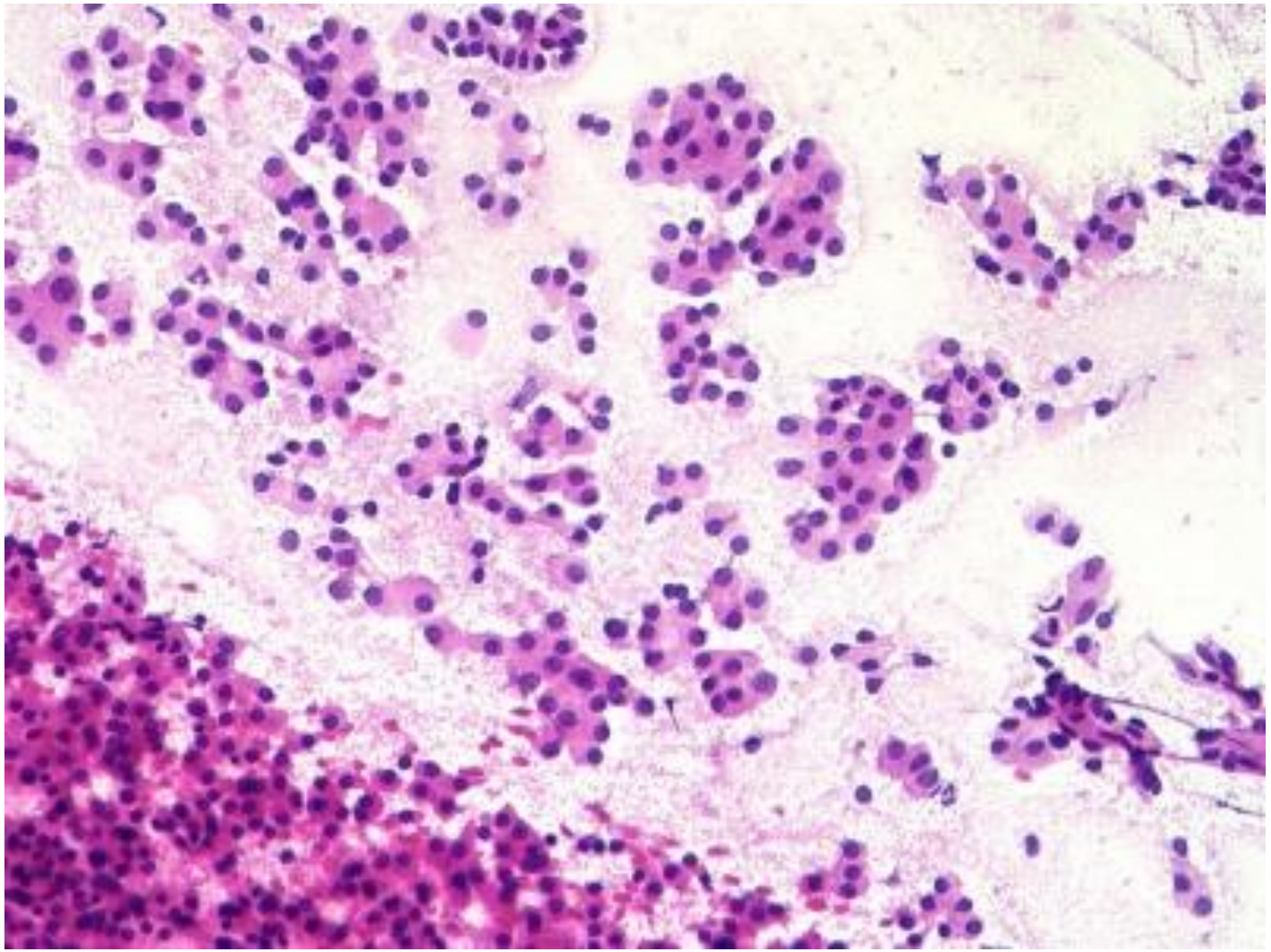
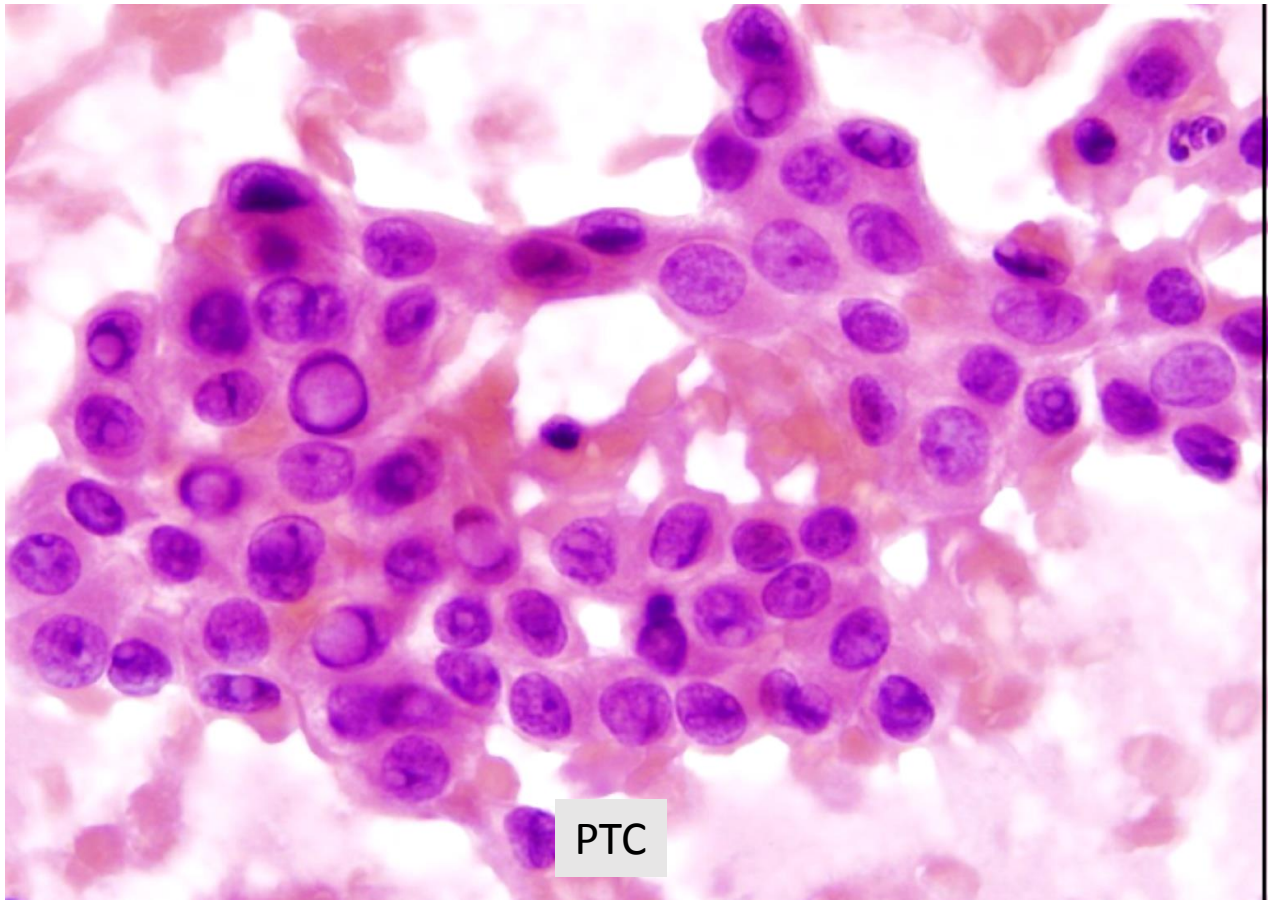
Bethesda II. - Benign



Bethesda IV. – Follicular neoplasia



Bethesda VI. – Malignant



Take home messages

- Both neoplastic and non-neoplastic thyroid diseases are very common
- Thyroiditis is the most common cause of hypothyroidism – frequently delayed diagnosis
- FNA is a gold standard in diagnosing thyroid nodules
- Thyroid cancer has increasing incidence, occuring in young patients but shows very good prognosis