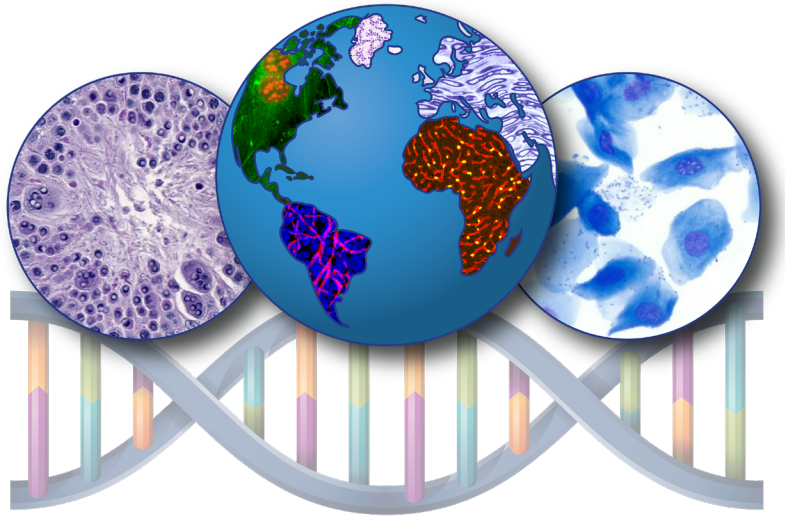
Proliferative Lesions of the Rodent Thyroid Gland



Division of Translational Toxicology Global Toxicologic Pathology Training Program

National Institutes of Health • U.S. Department of Health and Human Services

Proliferative Lesions of the Thyroid Gland

- Follicular Cell
  - Hyperplastic Lesions
    - Hyperplasia, Follicular Cell
  - Benign Tumors
    - Adenoma, Follicular Cell
  - Malignant Tumors
    - Carcinoma, Follicular Cell
- C Cell
  - Hyperplastic Lesions
    - Hyperplasia, C-Cell
  - Benign Tumors
    - Adenoma, C-Cell
  - Malignant Tumors
    - Carcinoma, C-Cell

Thyroid Gland – Hyperplasia, Follicular Cell

Histopathological Features

- Increased numbers of cuboidal to low columnar follicular epithelial cells
  - The cells that line the follicles and produce thyroxine
- Crowding and piling up of cells may occur
- May form papillary projections into the lumen
- May be **focal**, **cystic**, or **diffuse**
- Not encapsulated
- May be accompanied by hypertrophy (increased height and volume)
- Minimal to no compression of adjacent parenchyma
- Occurs in rats and mice

Thyroid Gland – Hyperplasia, Follicular Cell

Hyperplasia, Follicular Cell, Focal

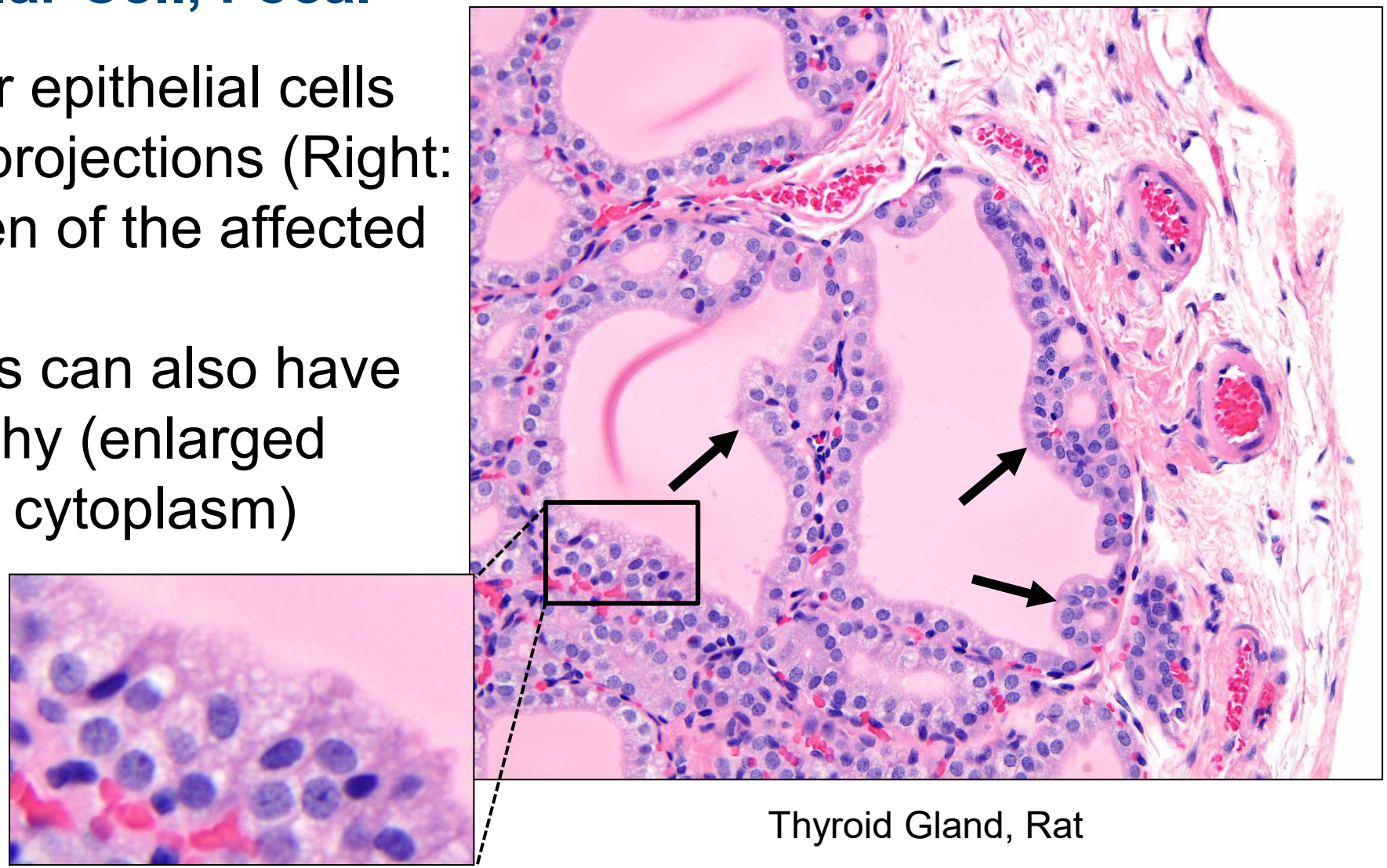
Crowded follicular epithelial cells formed form small papillary projections (arrows) into the lumen of the affected follicle (*)

Thyroid Gland, Mouse

Thyroid Gland – Hyperplasia, Follicular Cell

Hyperplasia, Follicular Cell, Focal

- Hyperplastic follicular epithelial cells form small papillary projections (Right: arrows) into the lumen of the affected follicles
- The hyperplastic cells can also have features of hypertrophy (enlarged cells with vacuolated cytoplasm) (inset)

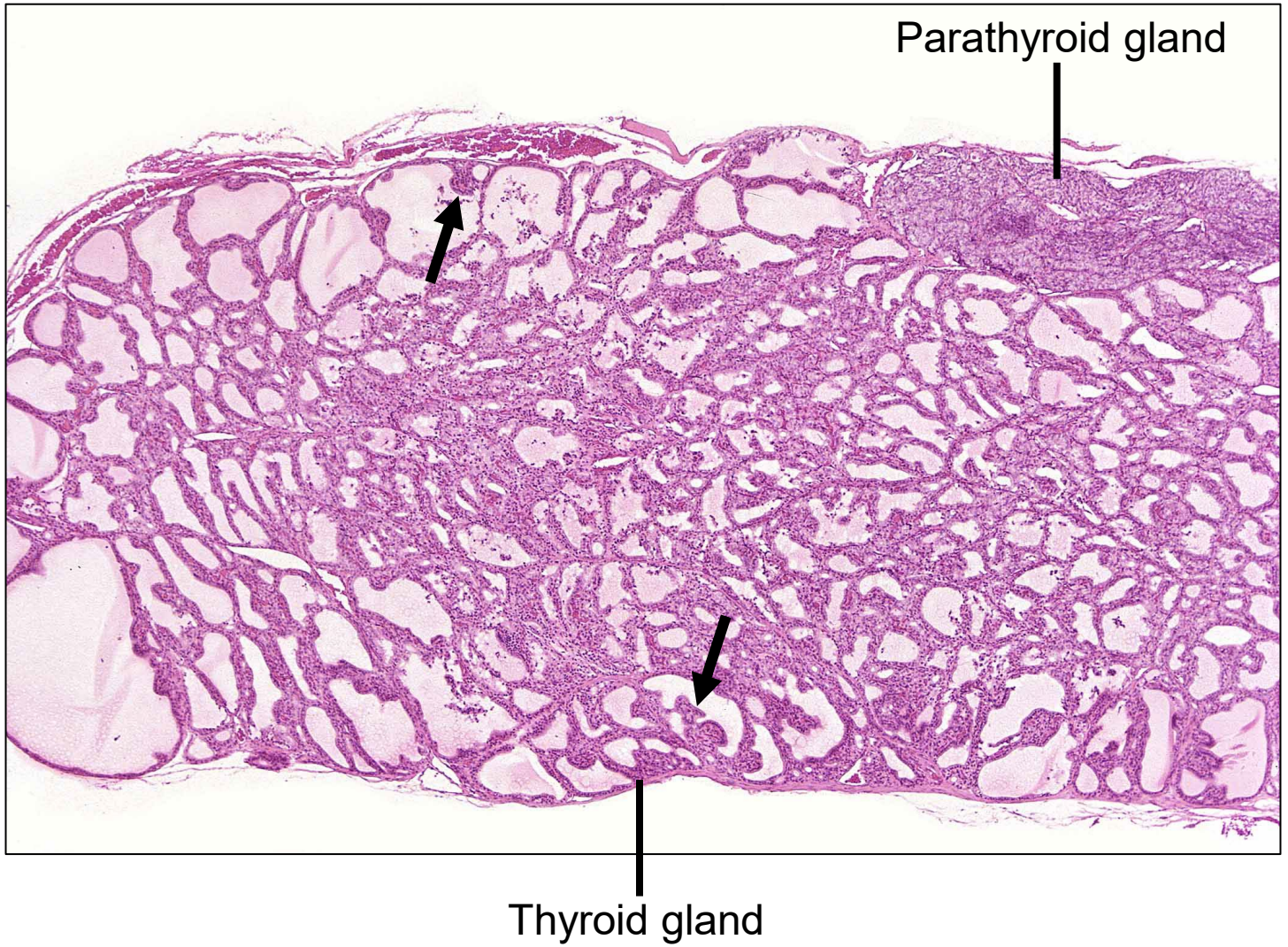


Thyroid Gland, Rat

Thyroid Gland – Hyperplasia, Follicular Cell

Hyperplasia, Follicular Cell, Diffuse

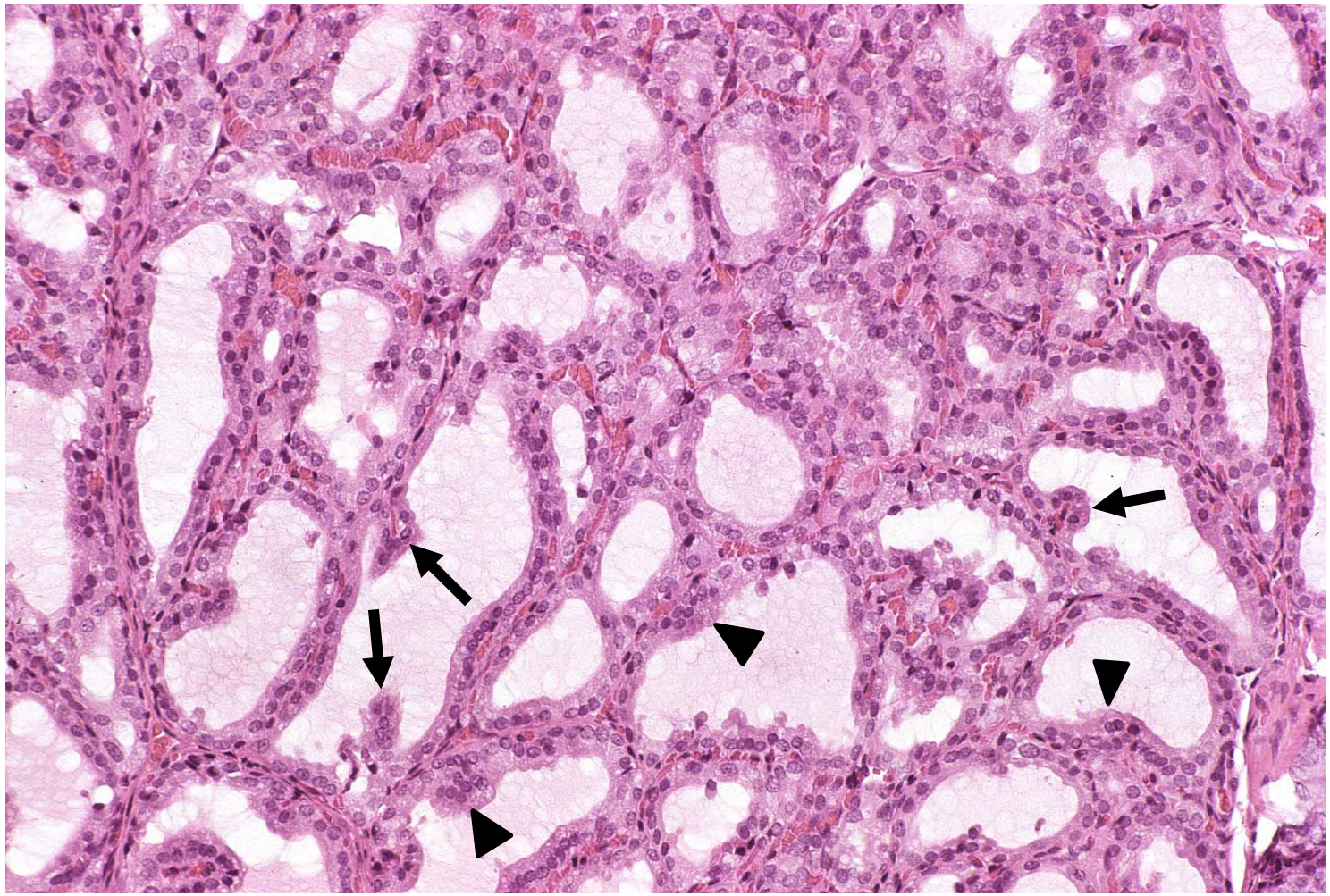
- Hyperplasic epithelial cells line all follicles; may cause overall enlargement of gland
- Hyperplastic follicular epithelial cells may form small papillary projections (arrows) into the follicular lumen
- Follicles often smaller



Thyroid Gland – Hyperplasia, Follicular Cell

Hyperplasia, Follicular Cell, Diffuse

- Higher magnification of diffuse hyperplasia from the previous slide
- The hyperplastic cells line all follicles (arrowheads) and form occasional small papillary projections (arrows) into the follicular lumen



Thyroid Gland – Adenoma, Follicular Cell

Histopathological Features

- Benign nodular proliferation of follicular epithelial cells
- Well demarcated and may be partially or completely encapsulated
- Often compresses adjacent parenchyma
- Single or multiple layers of cuboidal to columnar cells
- Greater degree of cellular atypia than in hyperplasia
- Increased nuclear-to-cytoplasmic ratio, eosinophilic to basophilic cytoplasm that may be vacuolated, and variably distinct nucleoli
- Growth patterns are **follicular**, **cystic**, **papillary**, and **solid**
  - More than one pattern may be present in the same adenoma
  - Growth patterns are modifiers and their inclusion in the diagnosis is optional
- Occurs in rats and mice

Thyroid Gland – Adenoma, Follicular Cell

Histopathological Features of Growth Patterns

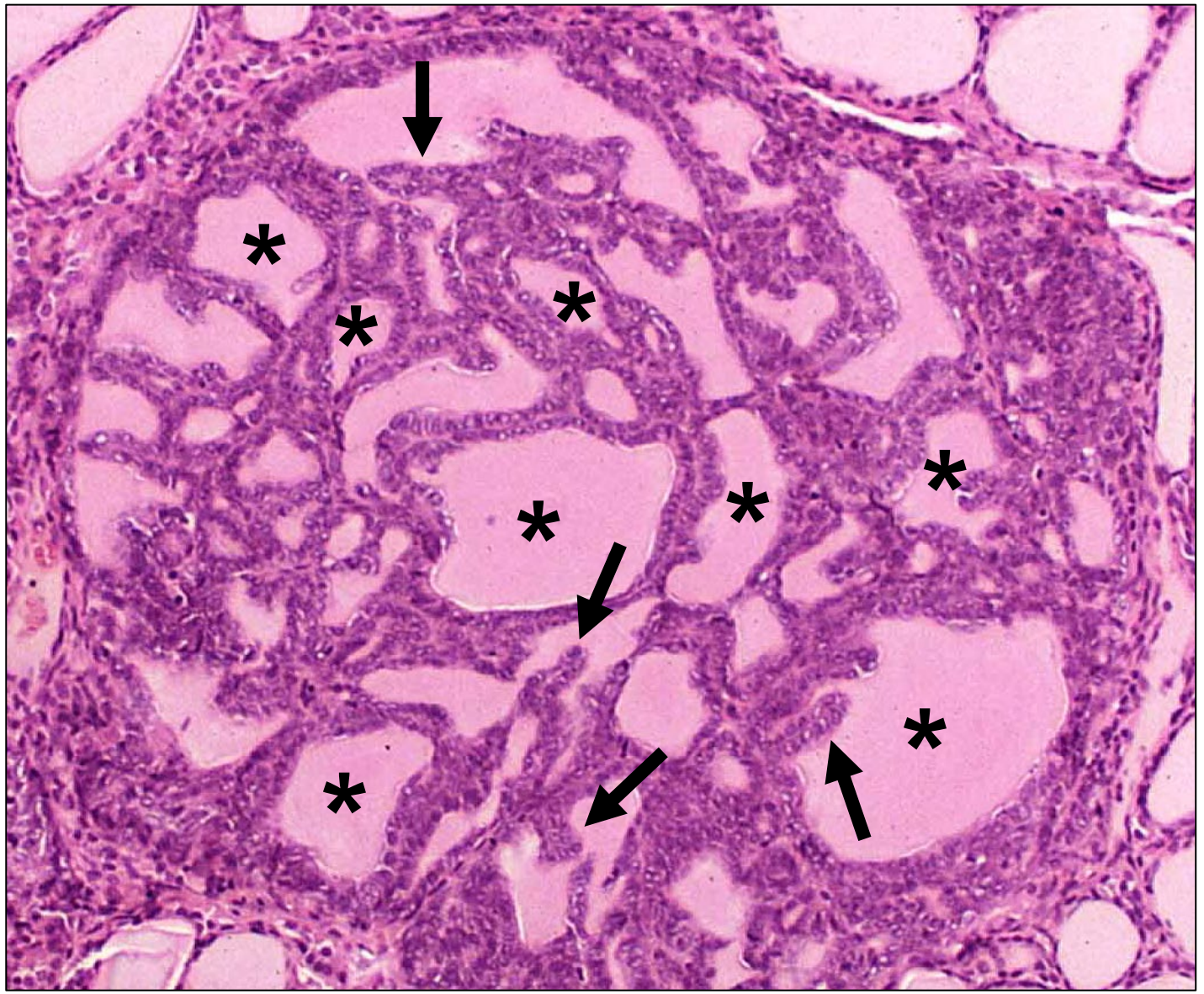
- **Follicular**
  - Variably sized, densely packed follicles
- **Cystic**
  - Large, dilated follicles
- **Papillary**
  - Follicles with complex branching papillary structures protruding into the lumens
- **Solid**
  - Cells are arranged in solid sheets, nests, or lobules
  - May resemble C-cell tumors, but small colloid-containing follicles are often present
  - Immunohistochemistry is positive for thyroglobulin, negative for calcitonin

Thyroid Gland – Adenoma, Follicular Cell

- Well-demarcated follicular cell adenoma (arrows)
- Slight compression of adjacent parenchyma (arrowheads)
- Follicular and papillary growth patterns

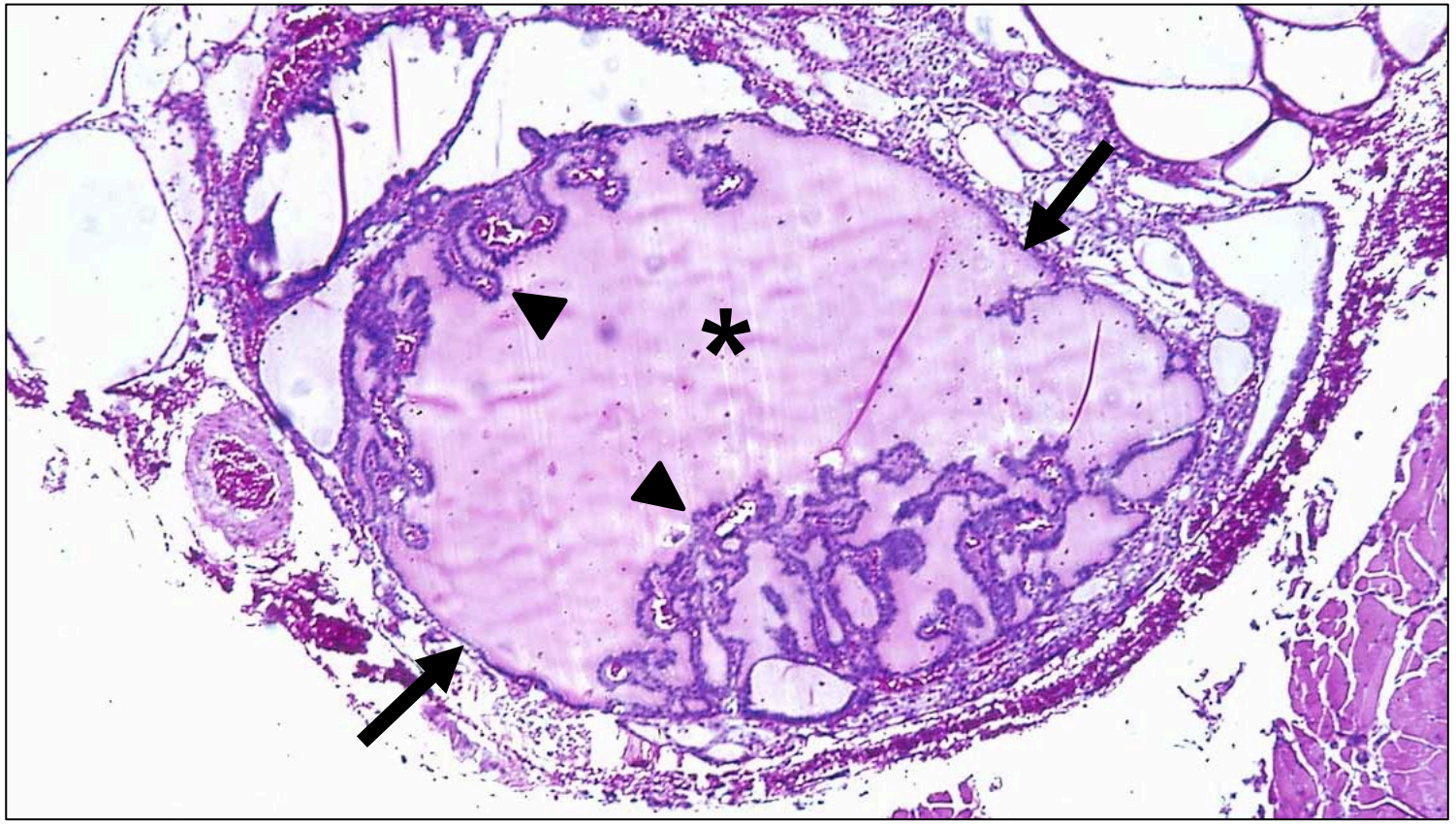
Thyroid Gland – Adenoma, Follicular Cell

- Higher magnification of follicular cell adenoma from the previous slide
- Neoplastic follicular cells are well differentiated and form variably sized follicles (*) and papillary projections (arrows)



Thyroid Gland – Adenoma, Follicular Cell

- Well-demarcated follicular cell adenoma (arrows)
- Compression of adjacent thyroid parenchyma
- Cystic (*) and papillary (arrowheads) growth patterns



Thyroid Gland, Rat

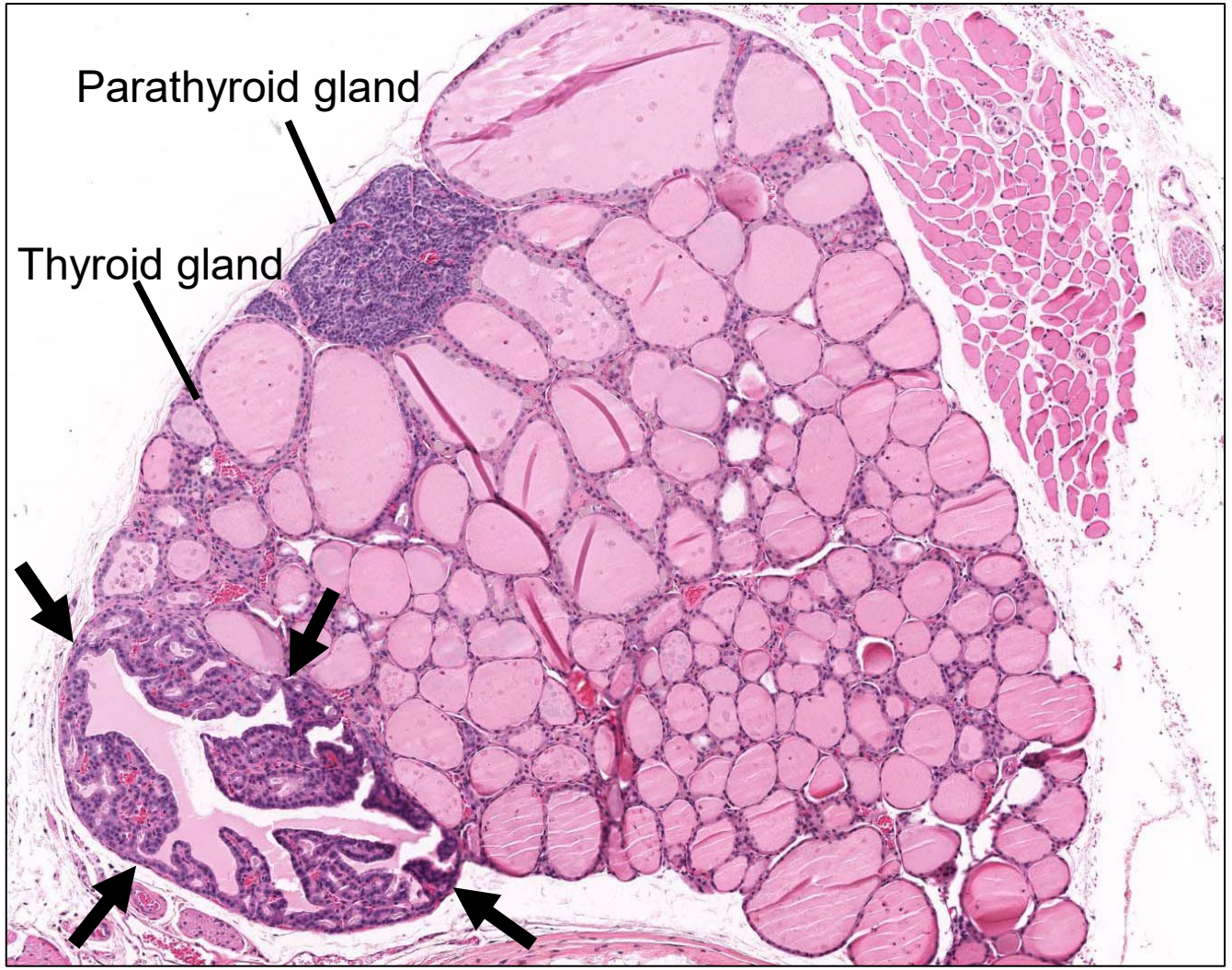
Thyroid Gland – Adenoma, Follicular Cell

- Higher magnification of follicular cell adenoma from previous slide
- Well-differentiated neoplastic follicular cells forming papillary projections (arrows)
- Compression of adjacent thyroid follicles (arrowheads)

Thyroid Gland, Rat

Thyroid Gland – Adenoma, Follicular Cell

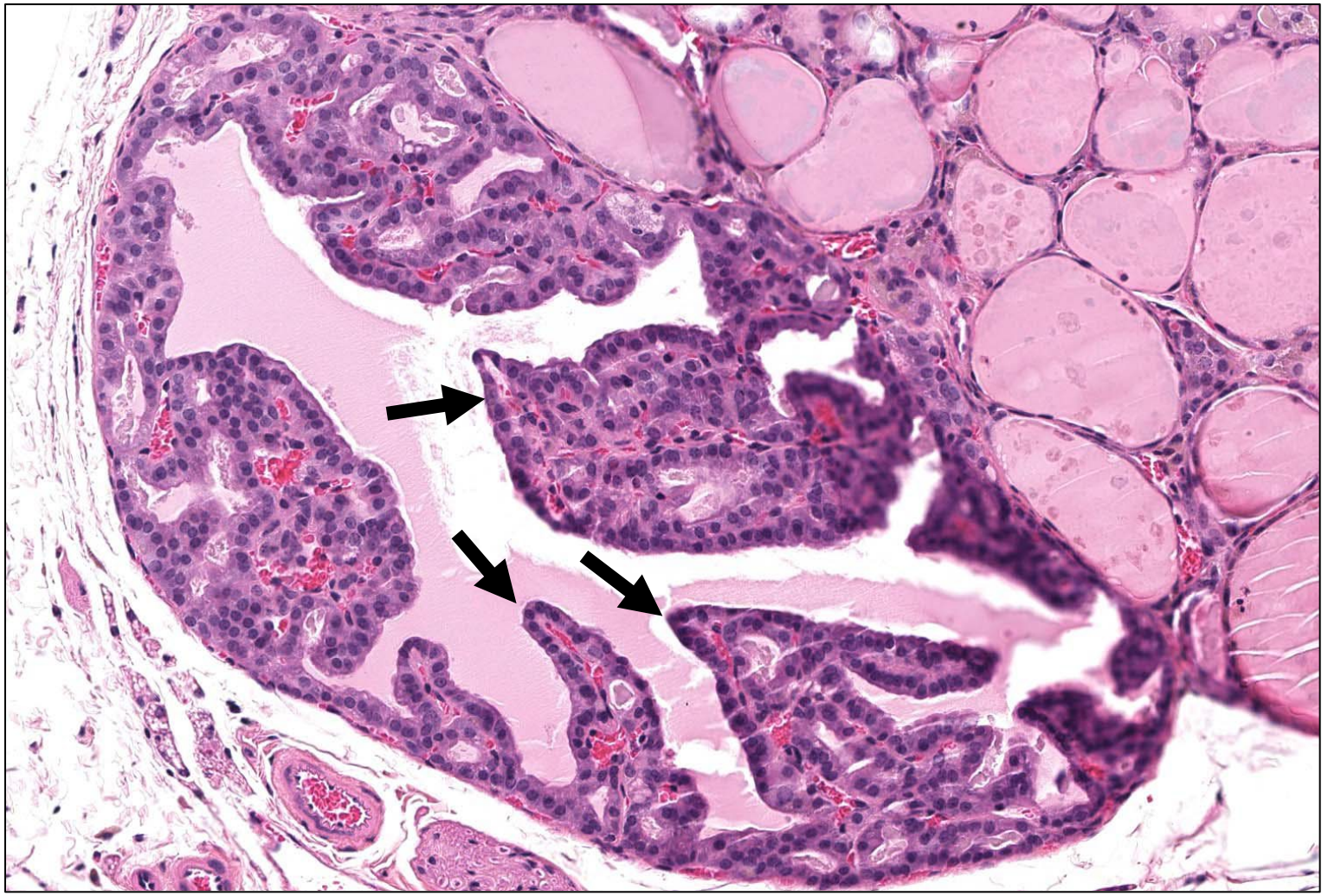
- Well-demarcated follicular cell adenoma (arrows)
- Papillary growth pattern
- Neoplastic cells can have basophilic (image on right), eosinophilic, or vacuolated cytoplasm



Thyroid Gland, Mouse

Thyroid Gland – Adenoma, Follicular Cell

- Higher magnification of well-demarcated follicular cell adenoma from previous slide
- Well-differentiated neoplastic follicular cells are forming papillary projections (arrows)



Thyroid Gland, Mouse

Thyroid Gland – Carcinoma, Follicular Cell

Histopathological Features

- Malignant proliferation of follicular epithelial cells
- Poorly demarcated mass tumor with capsular and/or vascular invasion
- Metastasis may occur
- Scirrhous reaction (fibrosis), necrosis, hemorrhage, and mineralization may be present
- Cellular atypia or pleomorphism (varied in size and shape) may be present
- May have numerous mitotic figures
- Growth patterns include **follicular**, **papillary**, **pleomorphic**, and **solid**
  - Growth patterns are modifiers and their inclusion in the diagnosis is optional
- May progress from adenomas
- Occurs in rats and mice

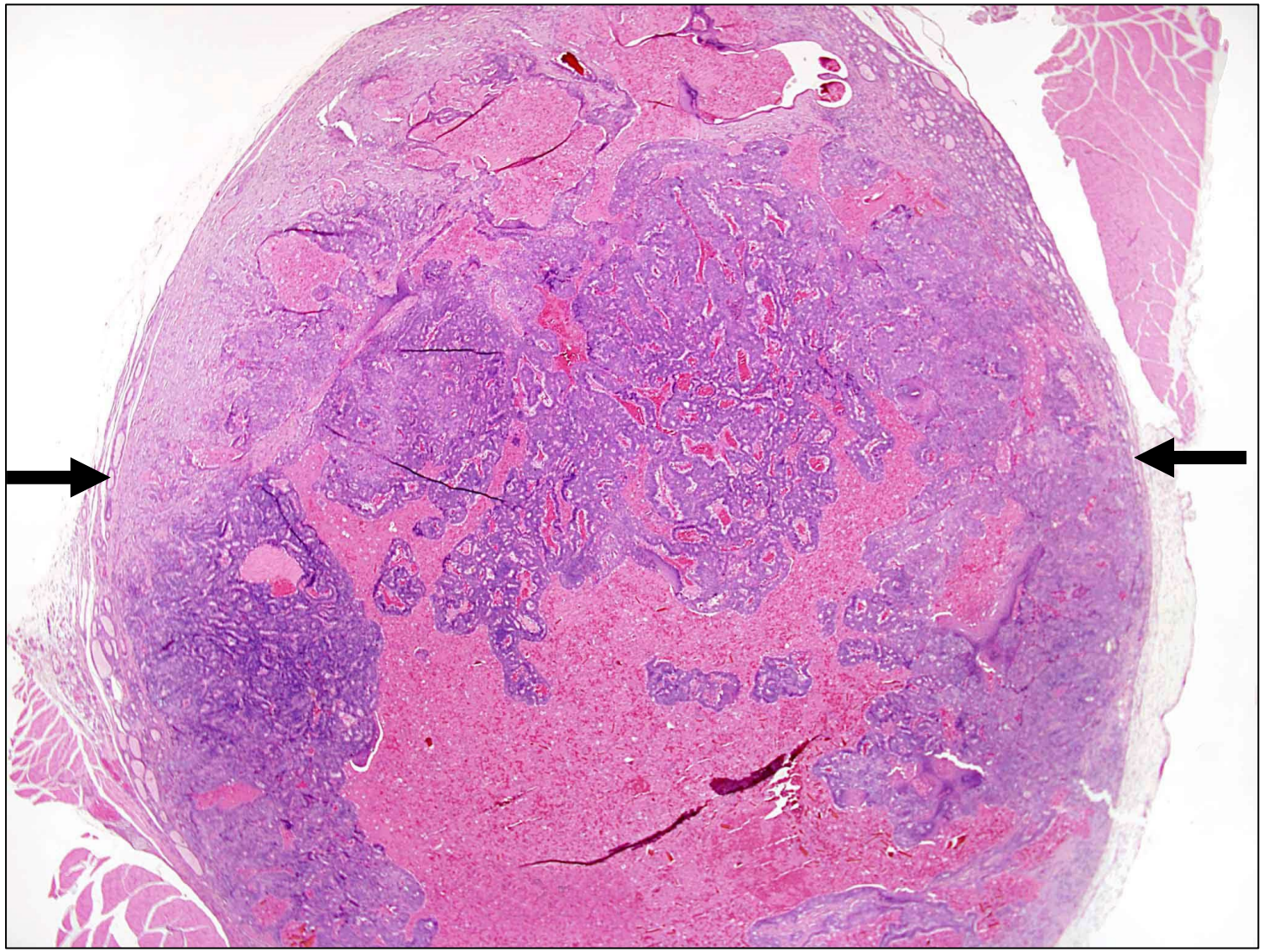
Thyroid Gland – Carcinoma, Follicular Cell

Histopathological Features of Growth Patterns

- **Follicular**
  - Irregular follicles formed by multiple layers of epithelial cells
- **Papillary**
  - Irregular papillary structures formed by single or multiple layers of epithelial cells
- **Pleomorphic**
  - Pleomorphic (varied in size and shape and/or nuclear appearance) or anaplastic (poorly differentiated) cells that may be multinucleated
- **Solid**
  - Atypical polygonal cells arranged in solid sheets
  - May resemble C-cell tumors

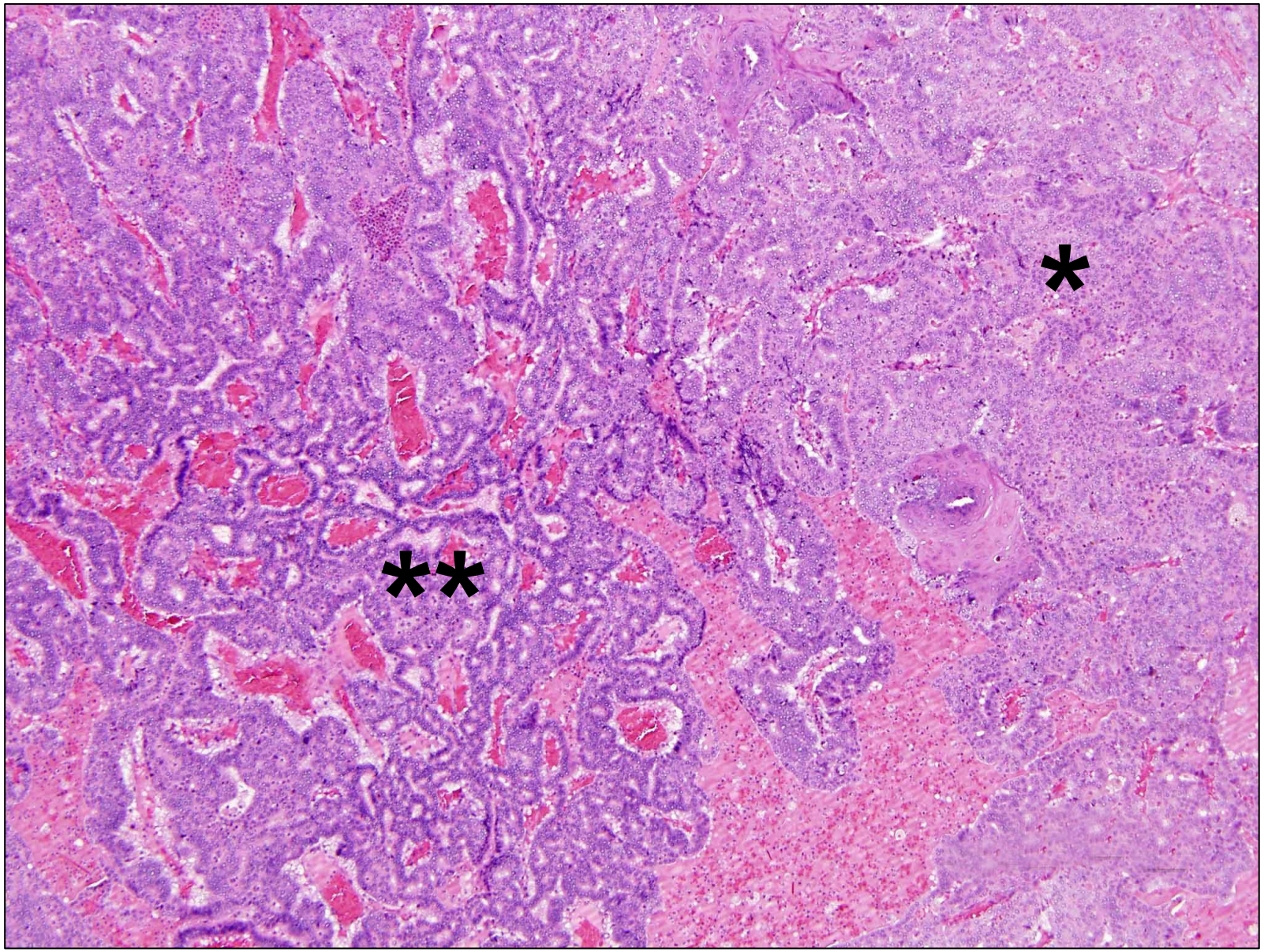
Thyroid Gland – Carcinoma, Follicular Cell

- Follicular cell carcinoma (arrows) in the thyroid gland
- Tumor effaces the thyroid gland



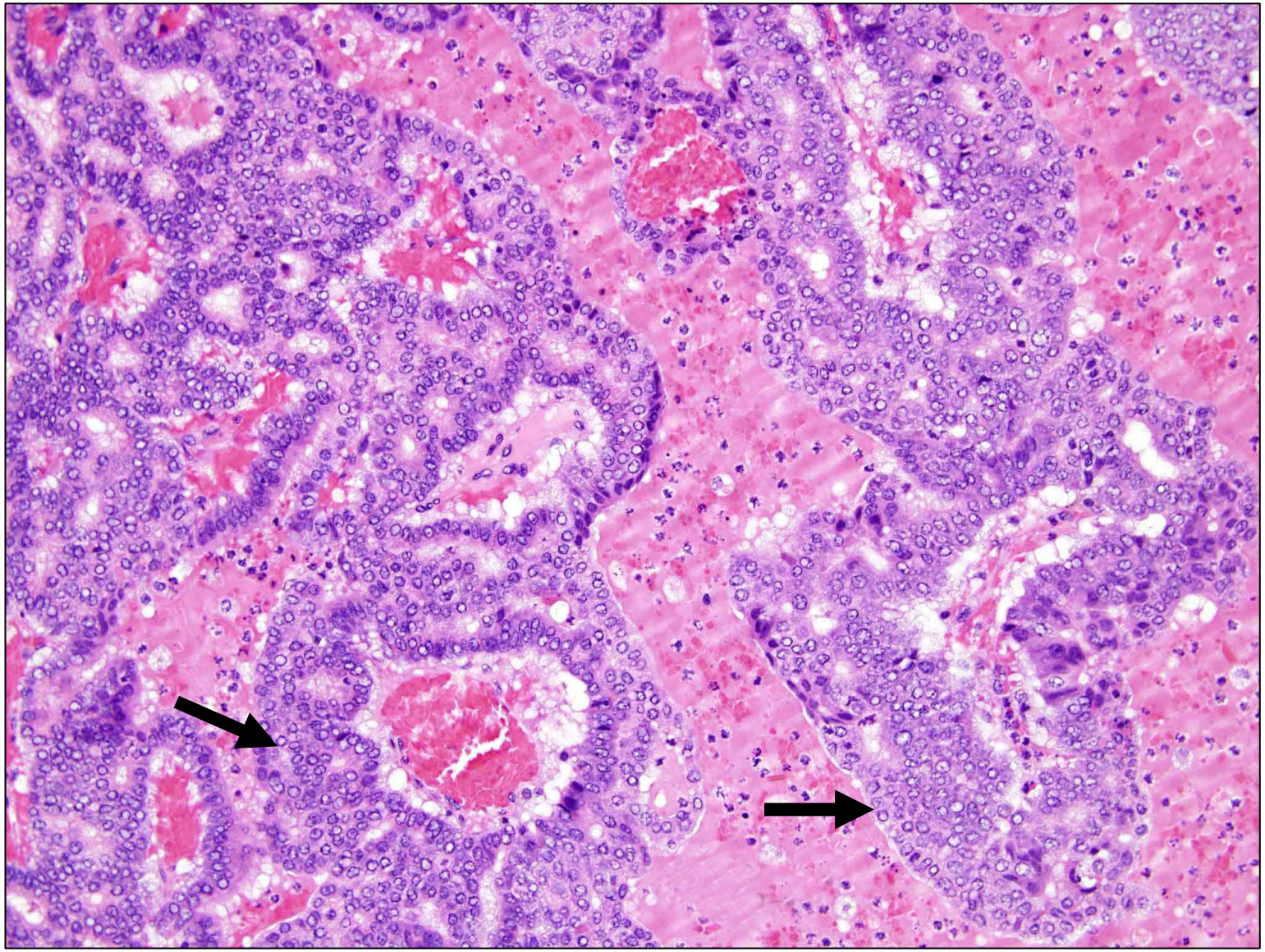
Thyroid Gland – Carcinoma, Follicular Cell

- Higher magnification of follicular cell carcinoma from previous slide
- Mixture of solid (*) and papillary (**) growth patterns



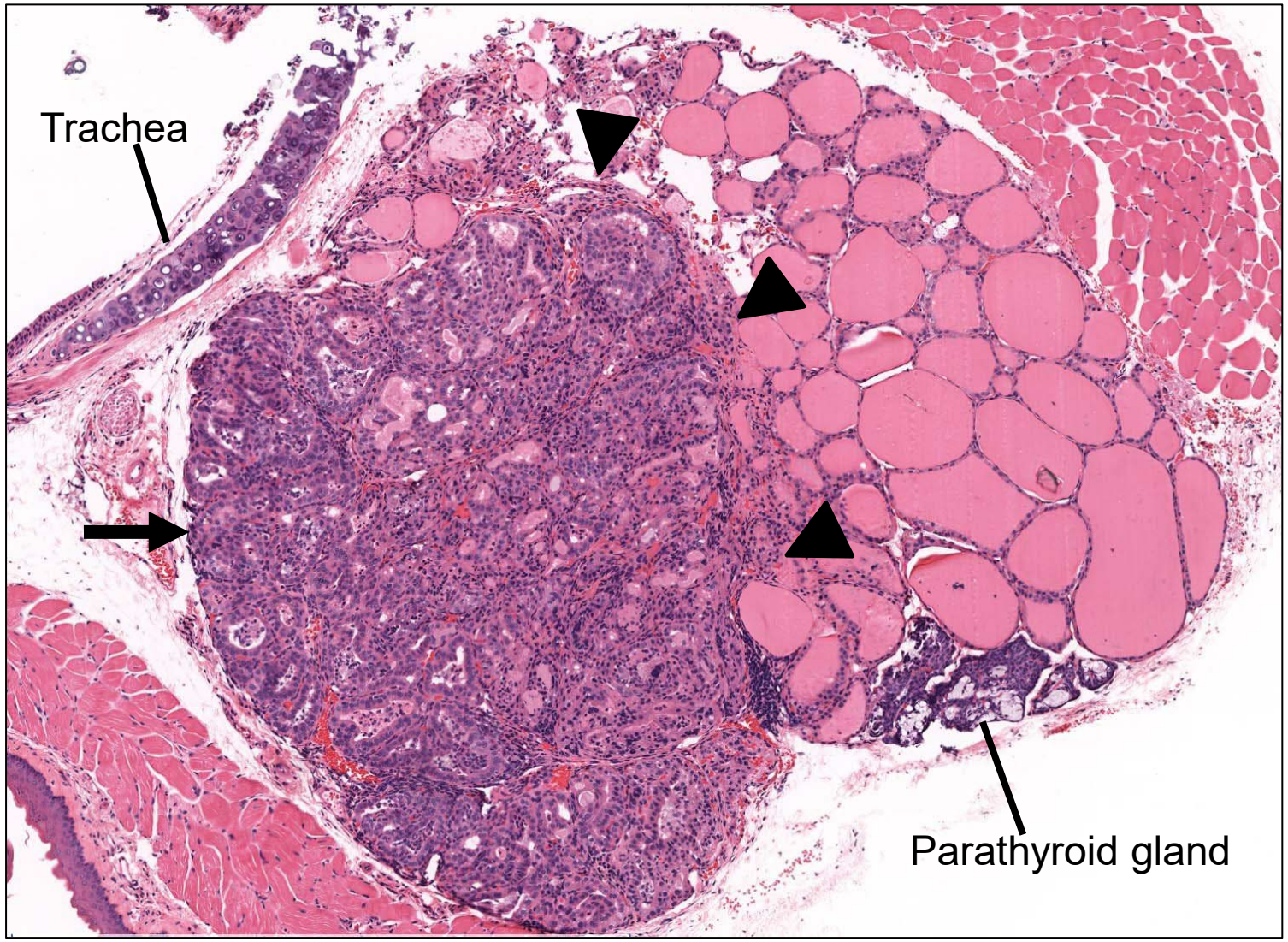
Thyroid Gland – Carcinoma, Follicular Cell

Higher magnification showing irregular papillary structures formed by multiple layers of disorganized epithelial cells (arrows)



Thyroid Gland – Carcinoma, Follicular Cell

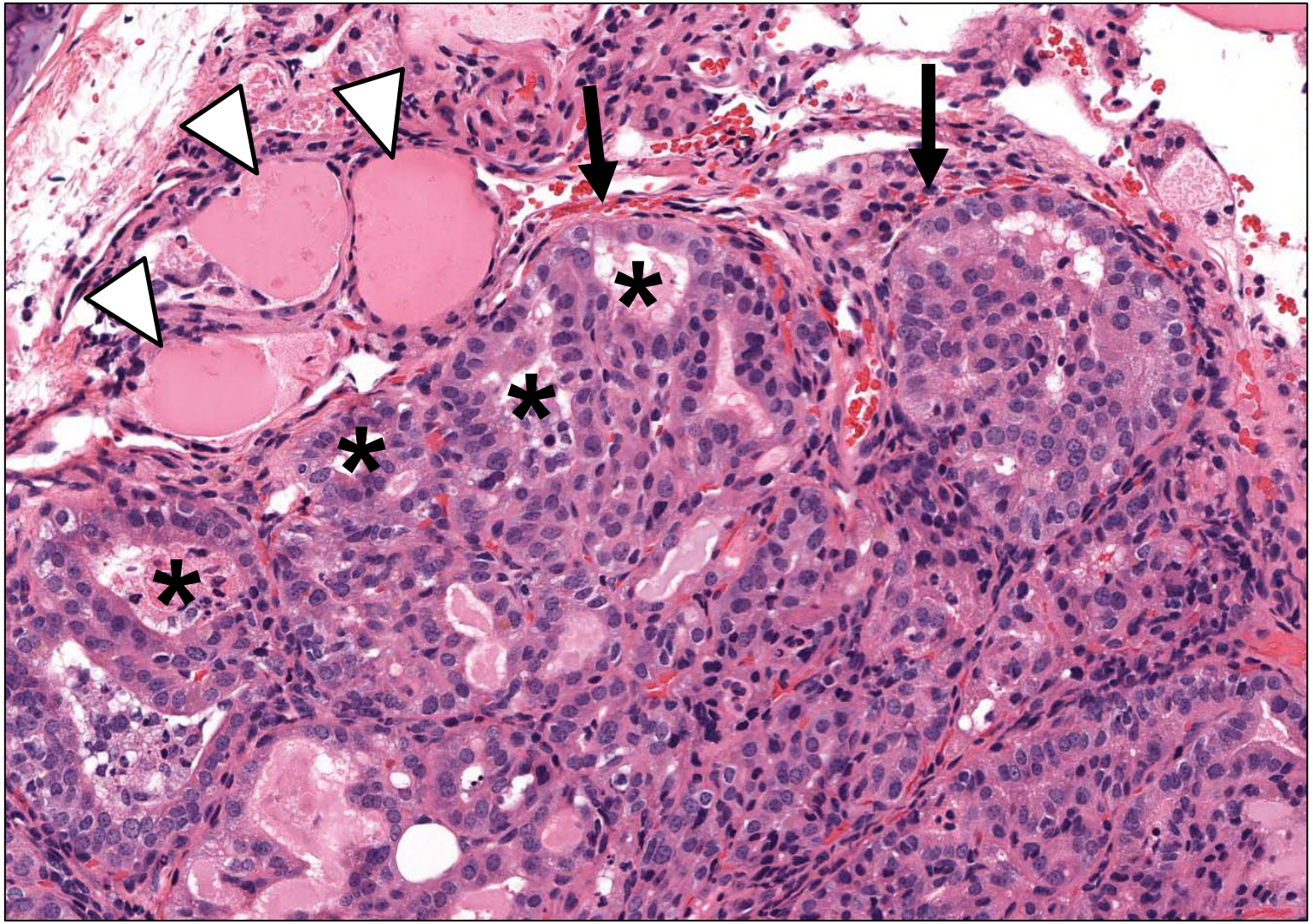
- Follicular cell carcinoma (arrow)
- Invasion of adjacent thyroid parenchyma is present (arrowheads)



Thyroid Gland, Mouse

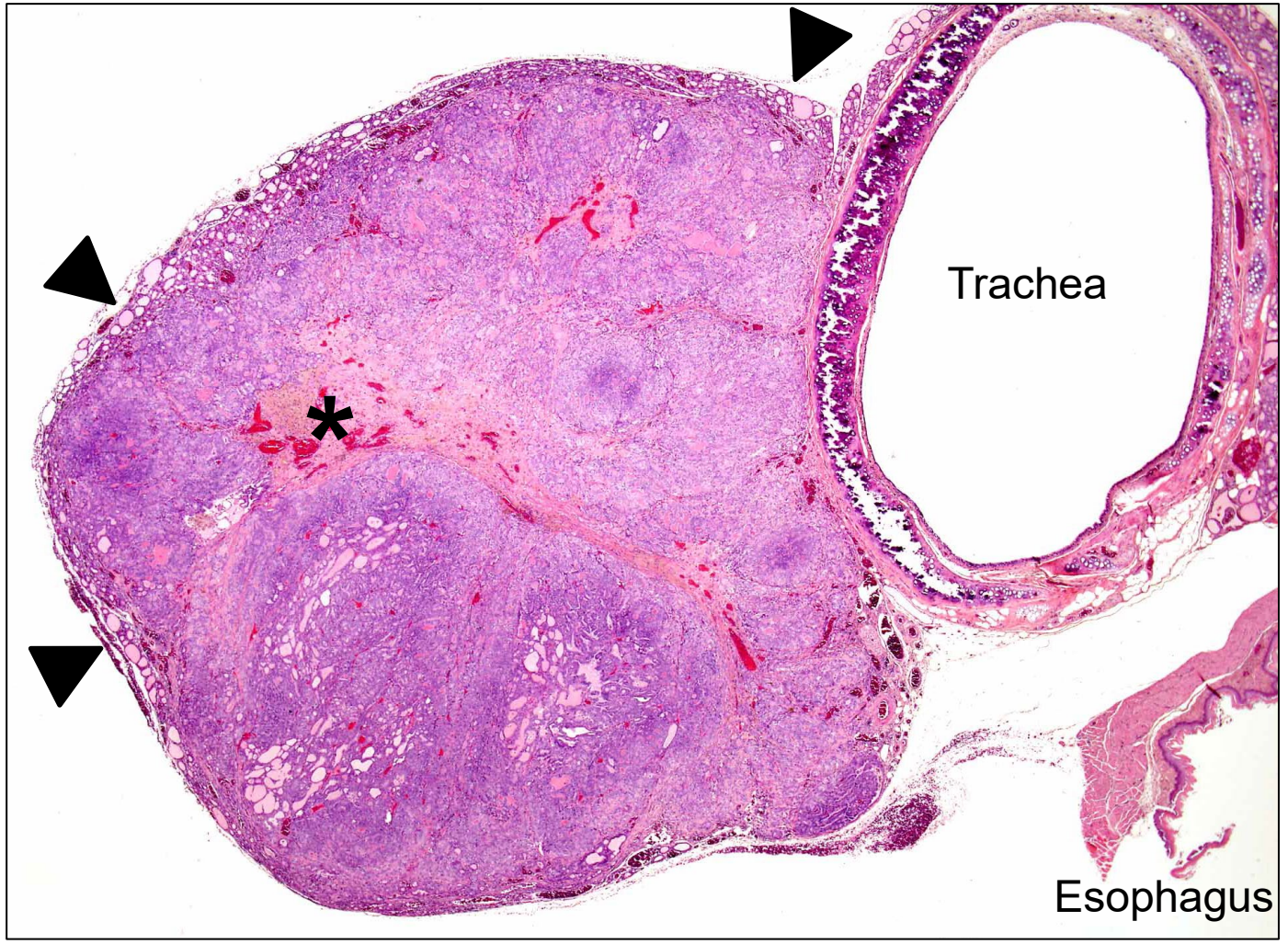
Thyroid Gland – Carcinoma, Follicular Cell

- Higher magnification of tumor on previous slide
- Irregular follicles (*) formed by neoplastic cells
- Invasion of adjacent thyroid parenchyma (arrows)
- Preexisting follicles (arrowheads) are present along the edge of the tumor



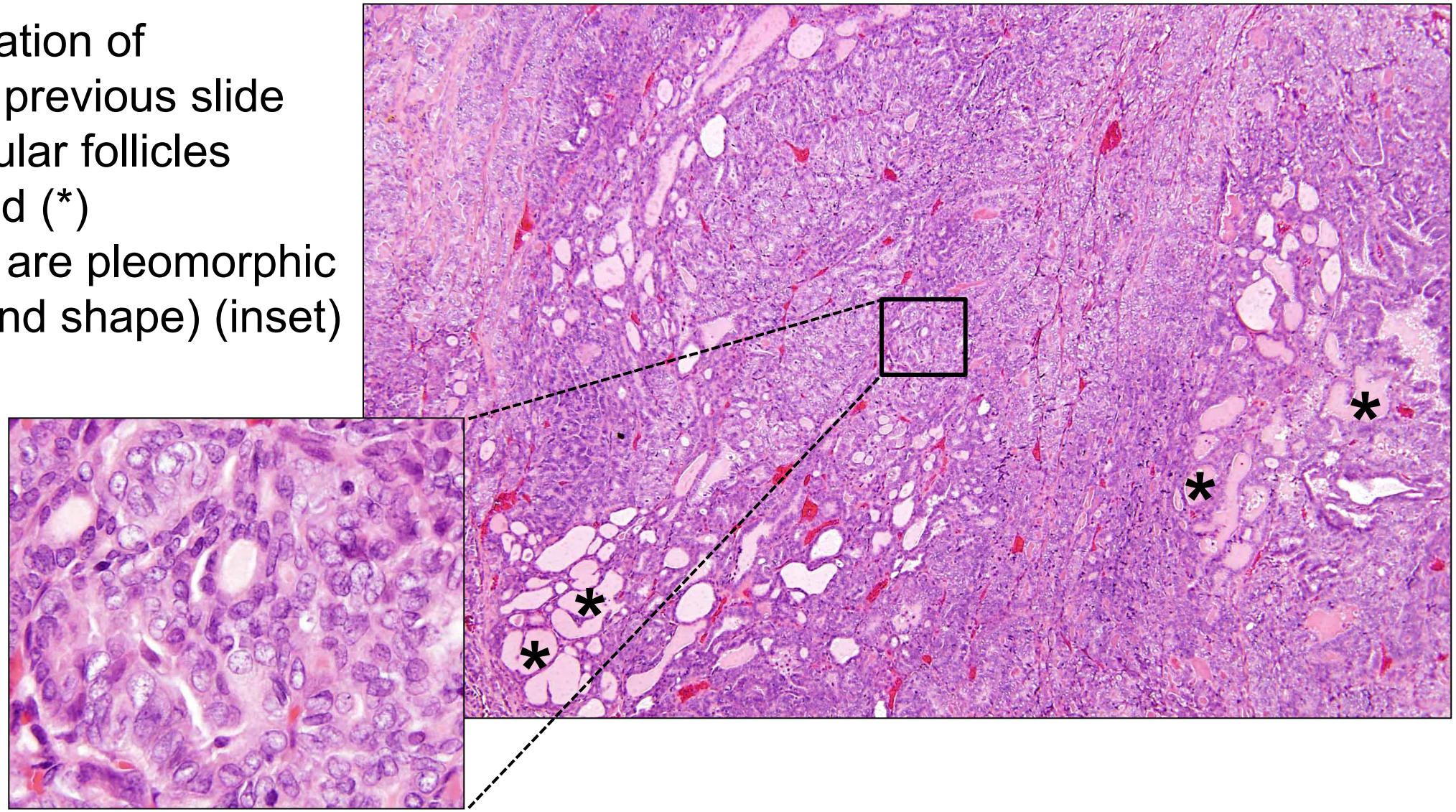
Thyroid Gland – Carcinoma, Follicular Cell

- Follicular cell carcinoma effaces the thyroid gland
- Small residual foci of remnant thyroid follicles are present along the periphery of the tumor (arrowheads)
- Pale eosinophilic area of necrosis (*)



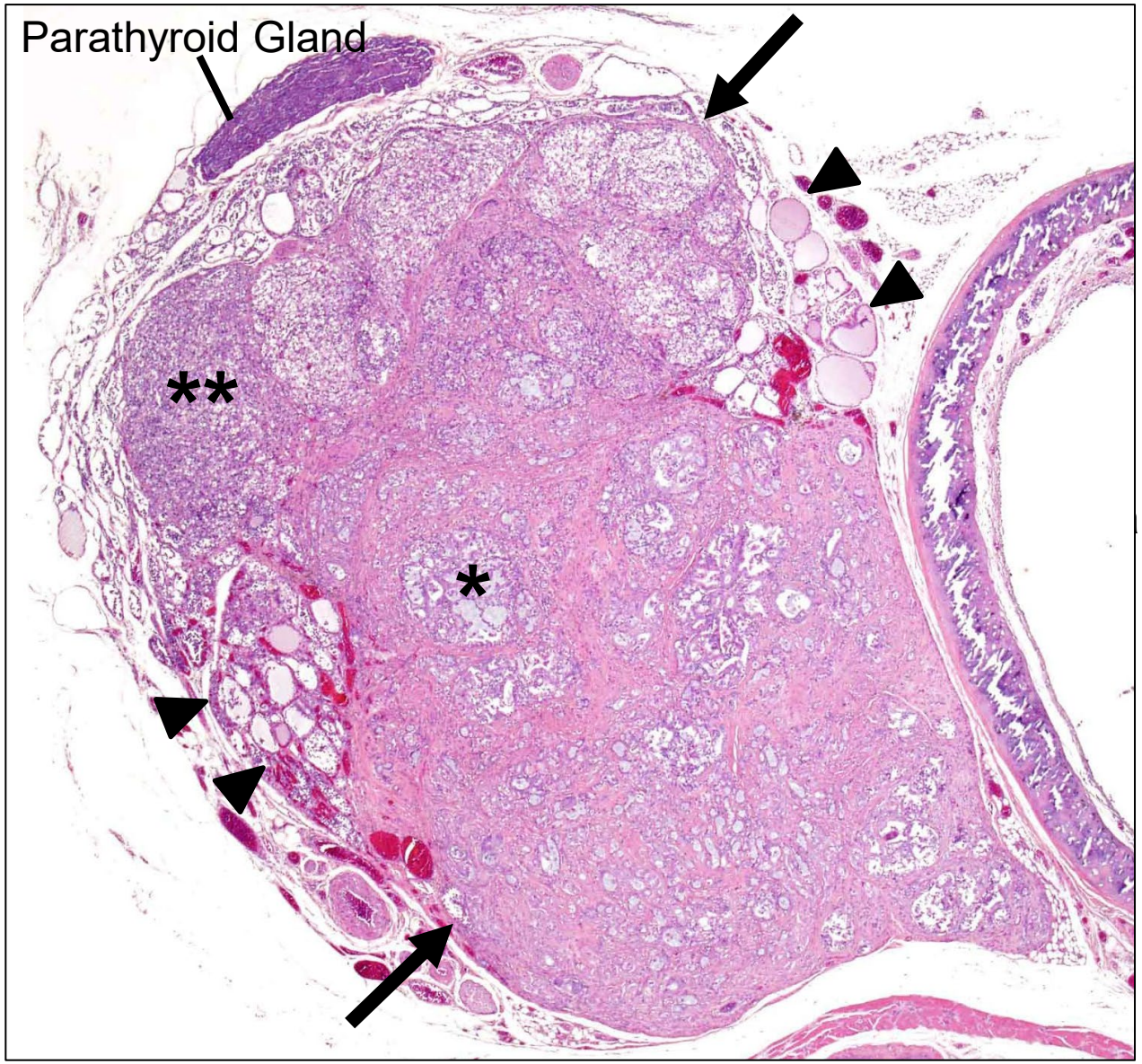
Thyroid Gland – Carcinoma, Follicular Cell

- Higher magnification of carcinoma from previous slide
- Numerous irregular follicles containing colloid (*)
- Neoplastic cells are pleomorphic (varied in size and shape) (inset)



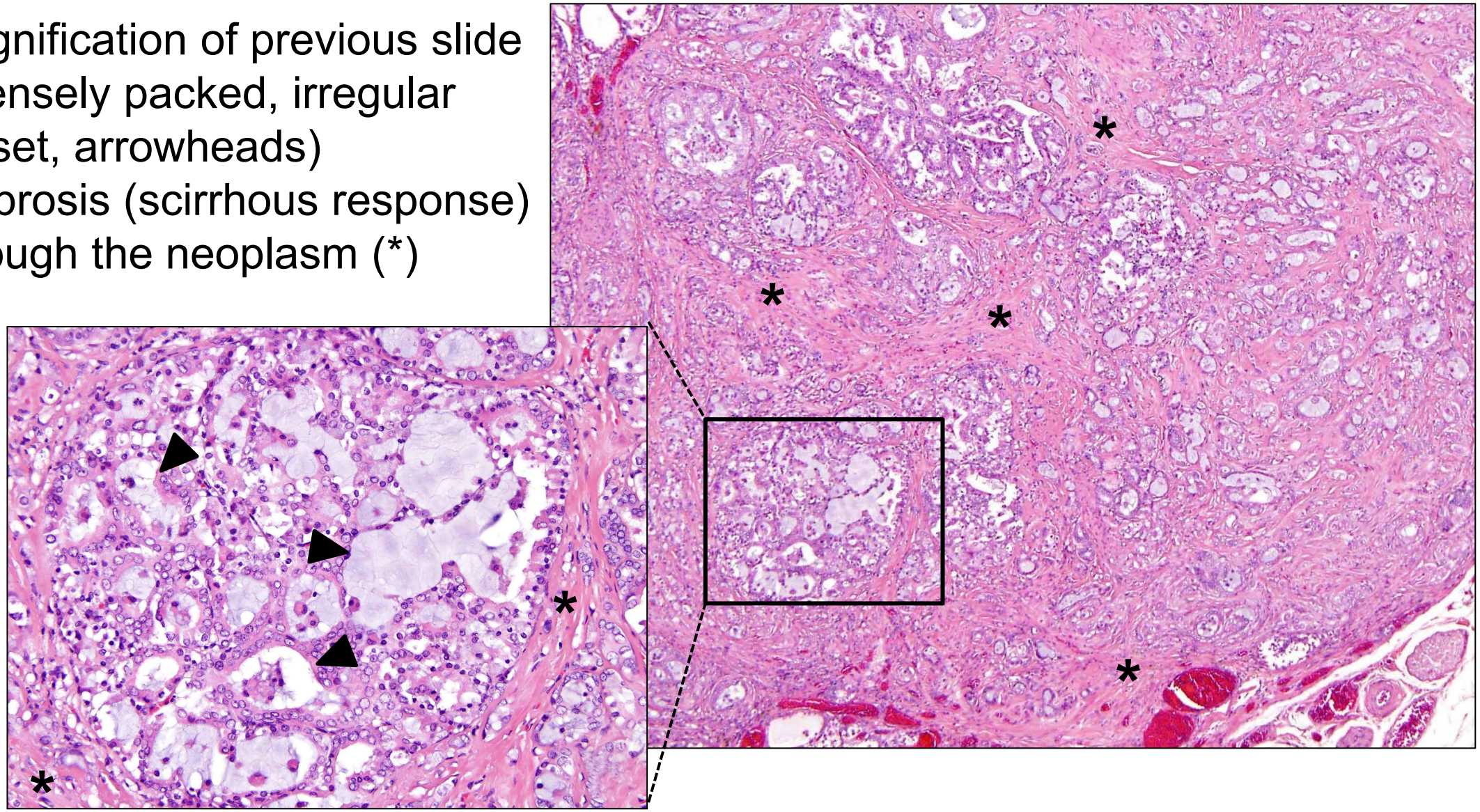
Thyroid Gland – Carcinoma, Follicular Cell

- Follicular cell carcinoma (arrows)
- Small residual foci of remaining thyroid follicles along the periphery (arrowheads)
- Mixture of follicular (*) and solid (**) growth patterns



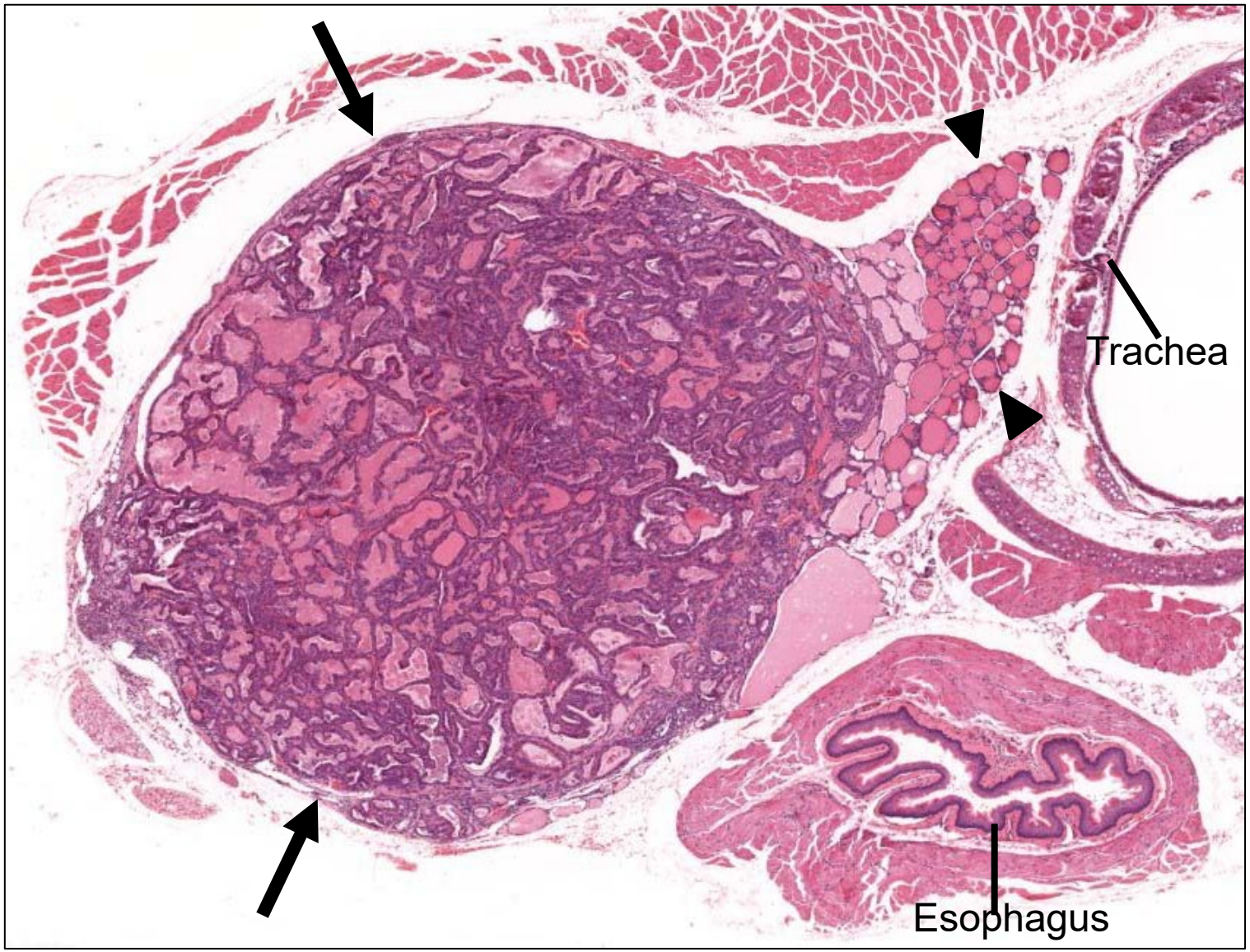
Thyroid Gland – Carcinoma, Follicular Cell

- Higher magnification of previous slide showing densely packed, irregular follicles (inset, arrowheads)
- Bands of fibrosis (scirrhous response) course through the neoplasm (*)



Thyroid Gland – Carcinoma, Follicular Cell

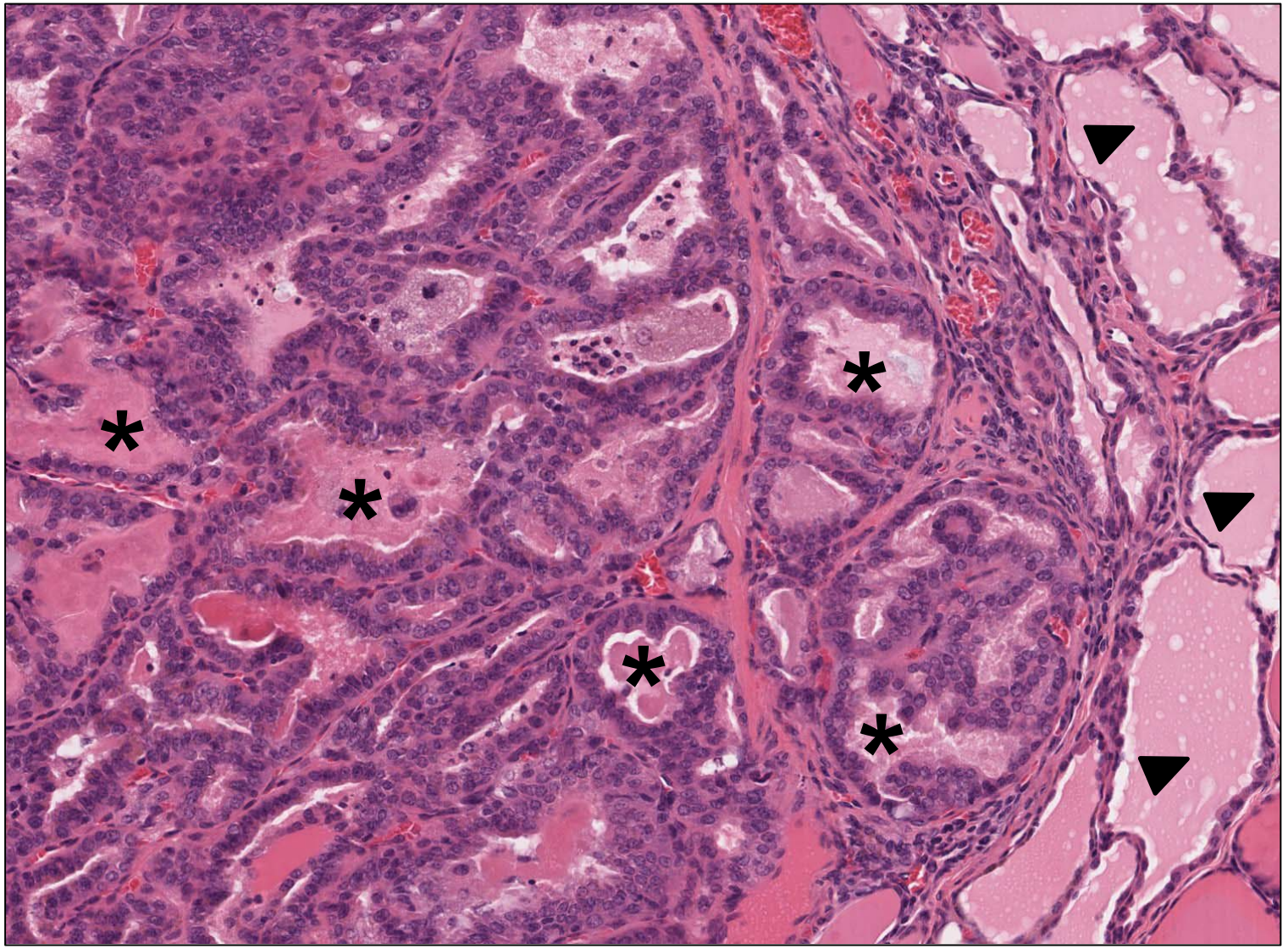
- Follicular cell carcinoma (arrows) effaces the thyroid gland
- A small residual focus of preexisting thyroid follicles remains along the periphery (arrowheads)



Thyroid Gland, Mouse

Thyroid Gland – Carcinoma, Follicular Cell

- Higher magnification showing the neoplastic cells forming densely packed, irregular follicles (*)
- Invasion of adjacent thyroid parenchyma
- Small residual focus of preexisting thyroid follicles (arrowheads) along the periphery



Thyroid Gland – Hyperplasia, C-Cell

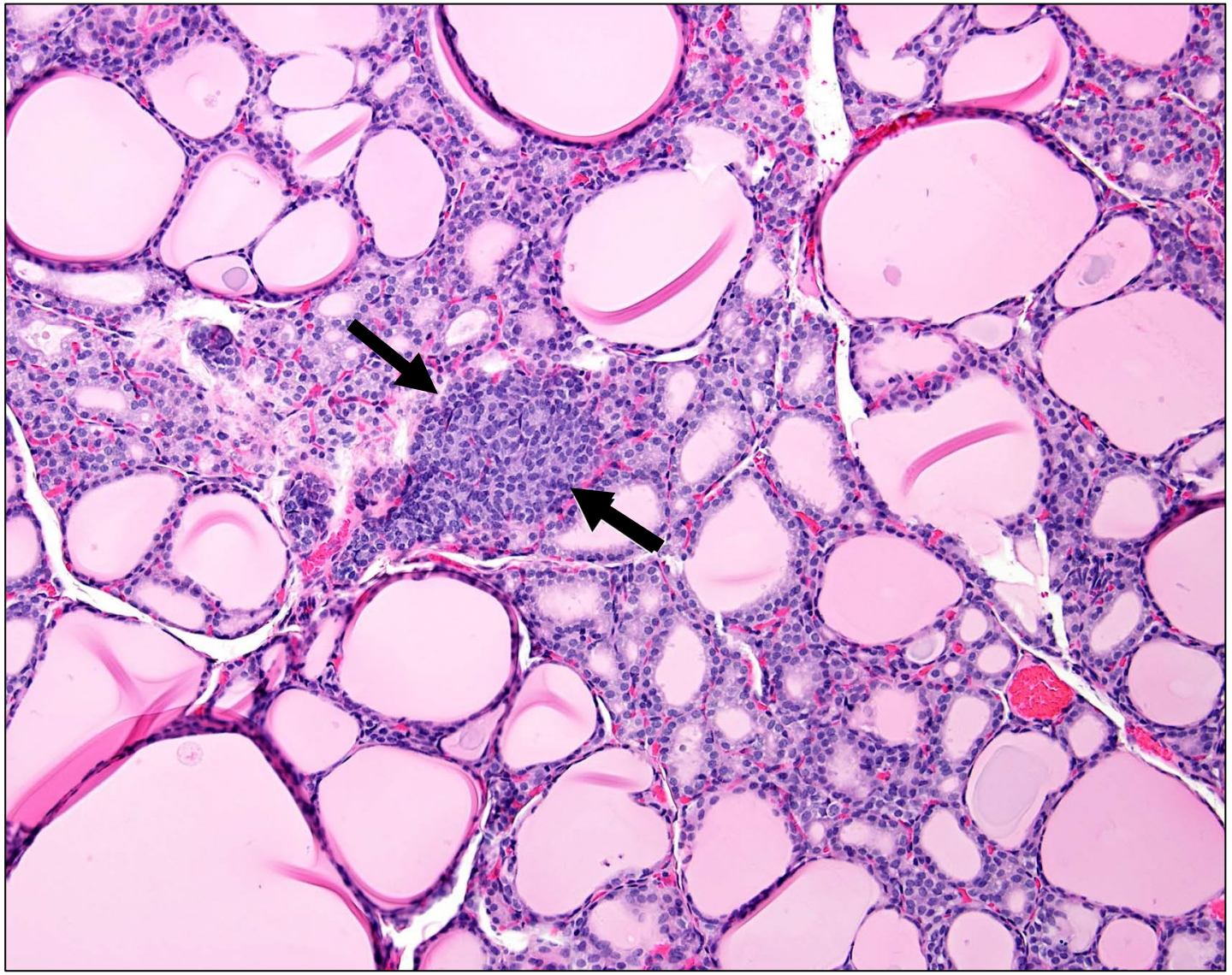
Histopathological Features

- Increased numbers of C cells (parafollicular cells)
  - C cells are polygonal cells with indistinct cell borders that produce the hormone calcitonin
- May be focal or diffuse
  - **Focal** hyperplasia is preneoplastic (may progress to adenoma, then carcinoma)
  - **Diffuse** hyperplasia is not considered preneoplastic and is a response to C cell stimulation, such as with chronic hypercalcemia
- **Focal**
  - Small nodular accumulation of C cells
  - Smaller than the area of 5 average follicles
  - No capsule and no compression of adjacent tissue
  - **Complex** is a rare type of focal hyperplasia that also contains ganglion cells (seen only in rats)
- **Diffuse**
  - Diffuse increase in numbers of C cells involving most follicles with no discrete nodule
  - No compression of adjacent tissue
  - Compare with age- and sex-matched controls to differentiate from normal aging change in rat
- Occurs in rats and mice; note that C cell numbers normally increase in aged rats

Thyroid Gland – Hyperplasia, C-Cell

Hyperplasia, C-Cell, Focal

Focal, nodular accumulation of C cells (arrows) that is smaller than the area of 5 average contiguous thyroid follicles

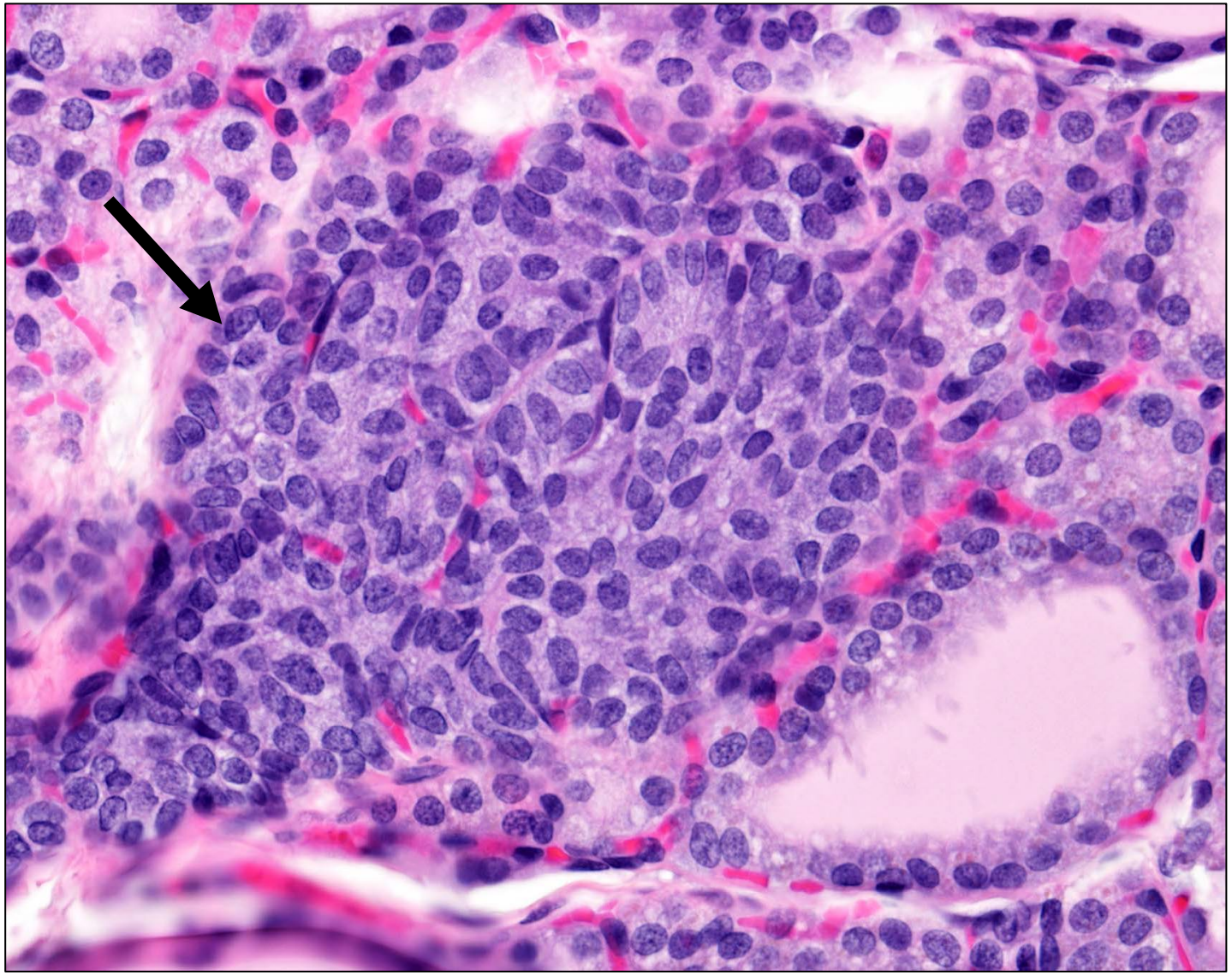


Thyroid Gland, Rat

Thyroid Gland – Hyperplasia, C-Cell

Hyperplasia, C-Cell, Focal

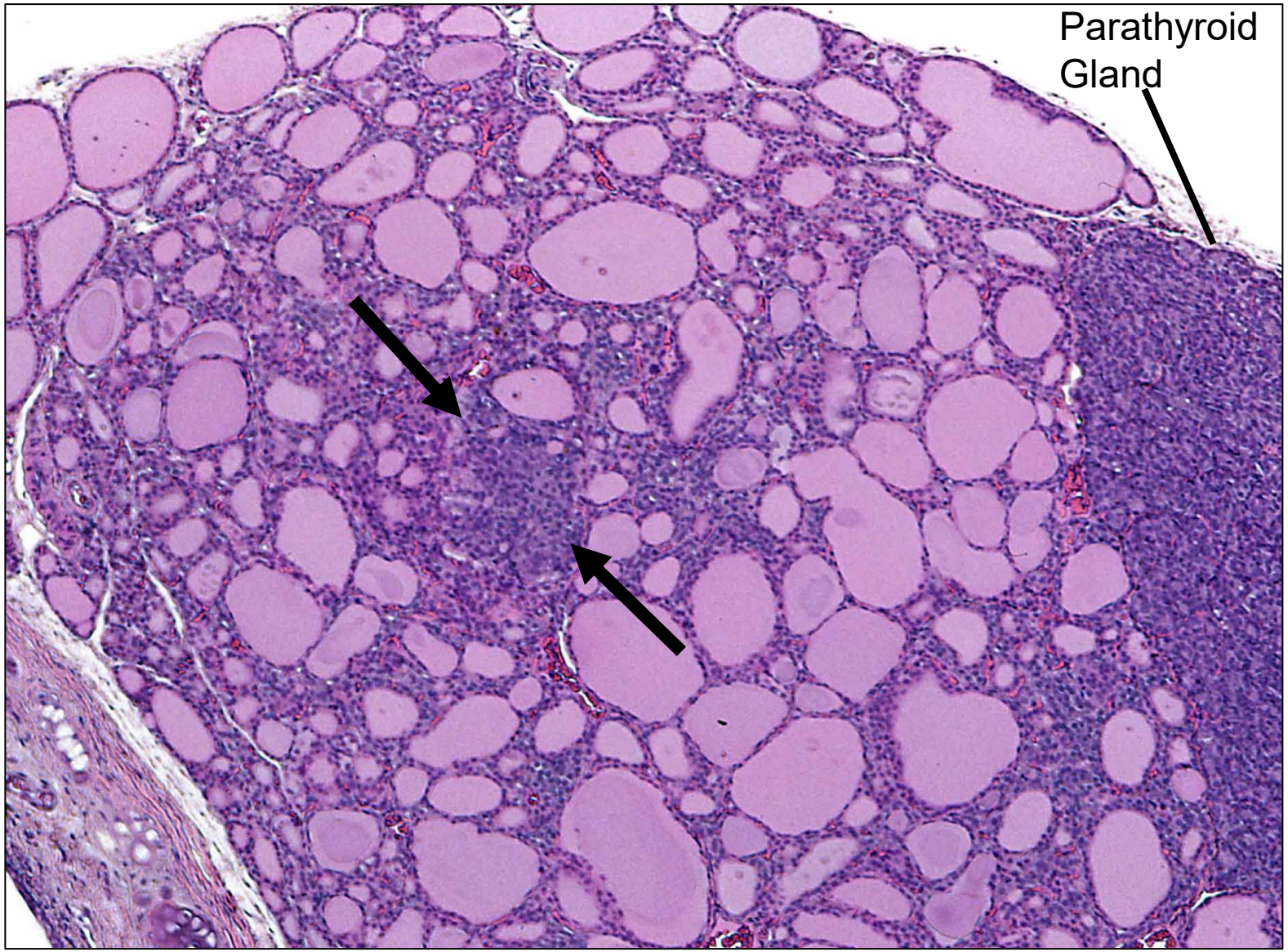
- Higher magnification of focal C-cell hyperplasia (arrow) from the previous slide
- Solid nest of C cells with indistinct cell borders, oval nuclei, and amphophilic (purple) cytoplasm



Thyroid Gland – Hyperplasia, C-Cell

Hyperplasia, C-Cell, Focal

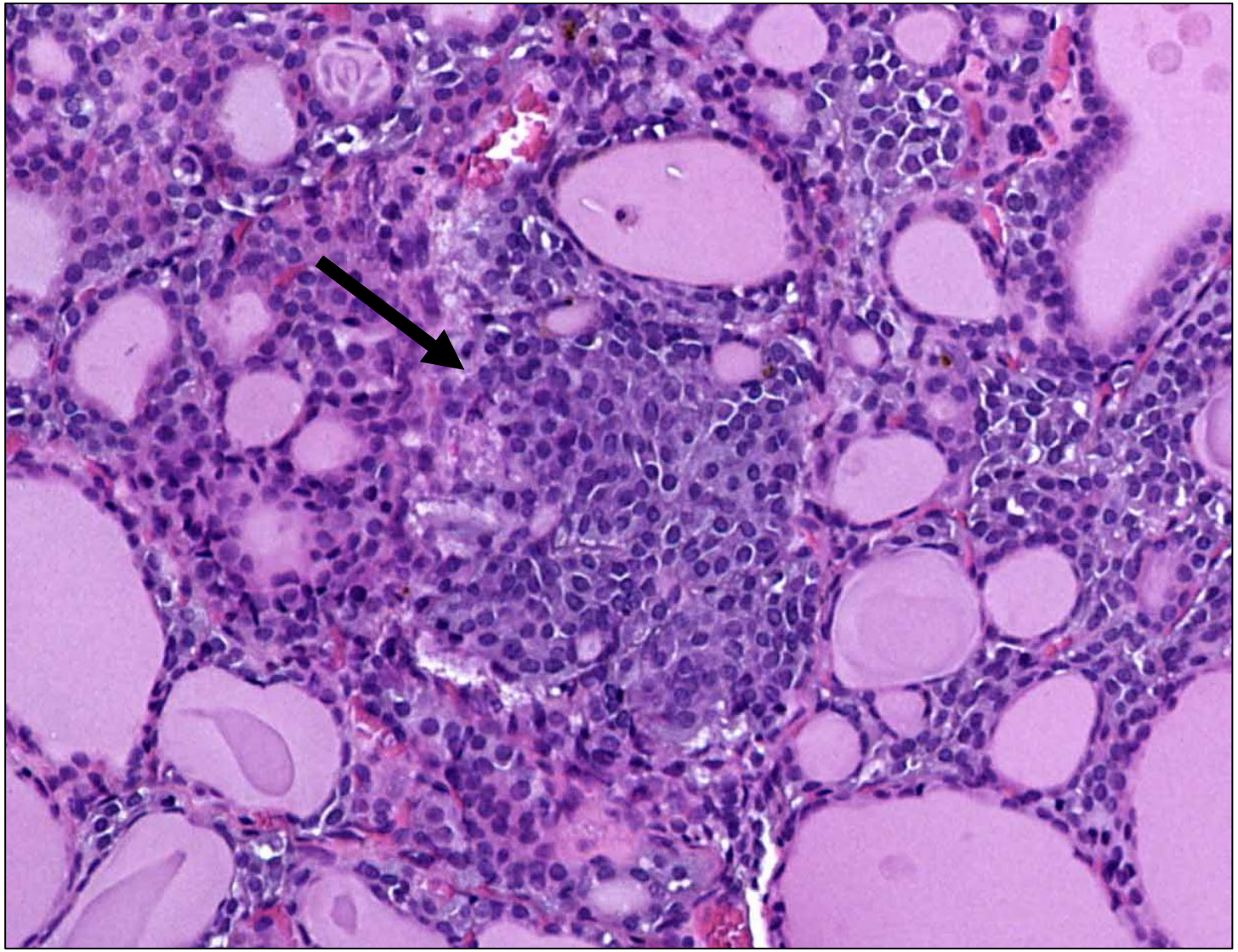
- Focal C-cell hyperplasia (arrows)
- Focal increase in the number of C cells that is smaller than the area of 5 average contiguous thyroid follicles



Thyroid Gland – Hyperplasia, C-Cell

Hyperplasia, C-Cell, Focal

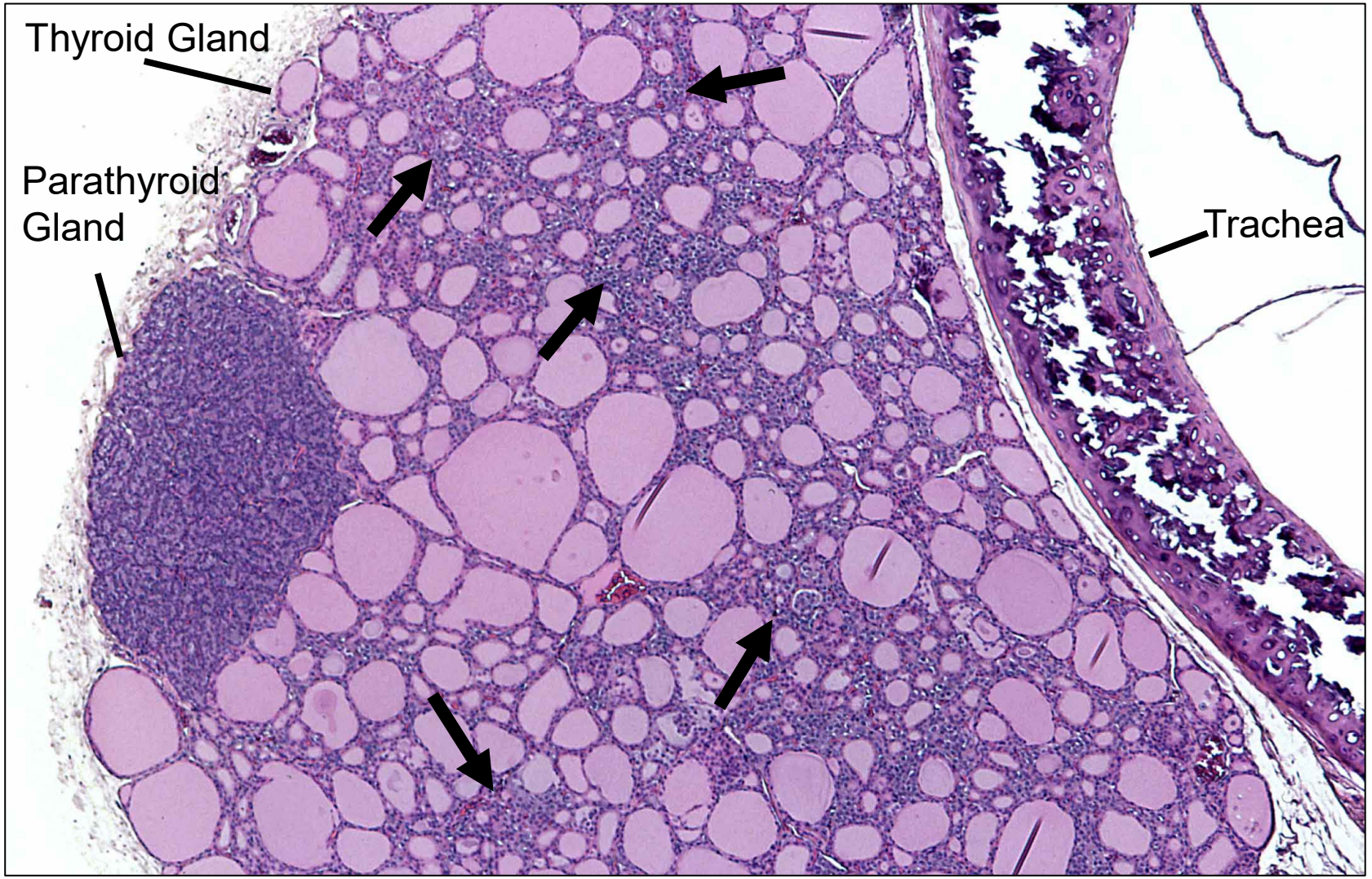
- Higher magnification of focal C-cell hyperplasia (arrow) from the previous slide
- Solid nest of C cells with indistinct cell borders, oval nuclei, and amphophilic to basophilic cytoplasm



Thyroid Gland – Hyperplasia, C-Cell

Hyperplasia, C-Cell, Diffuse

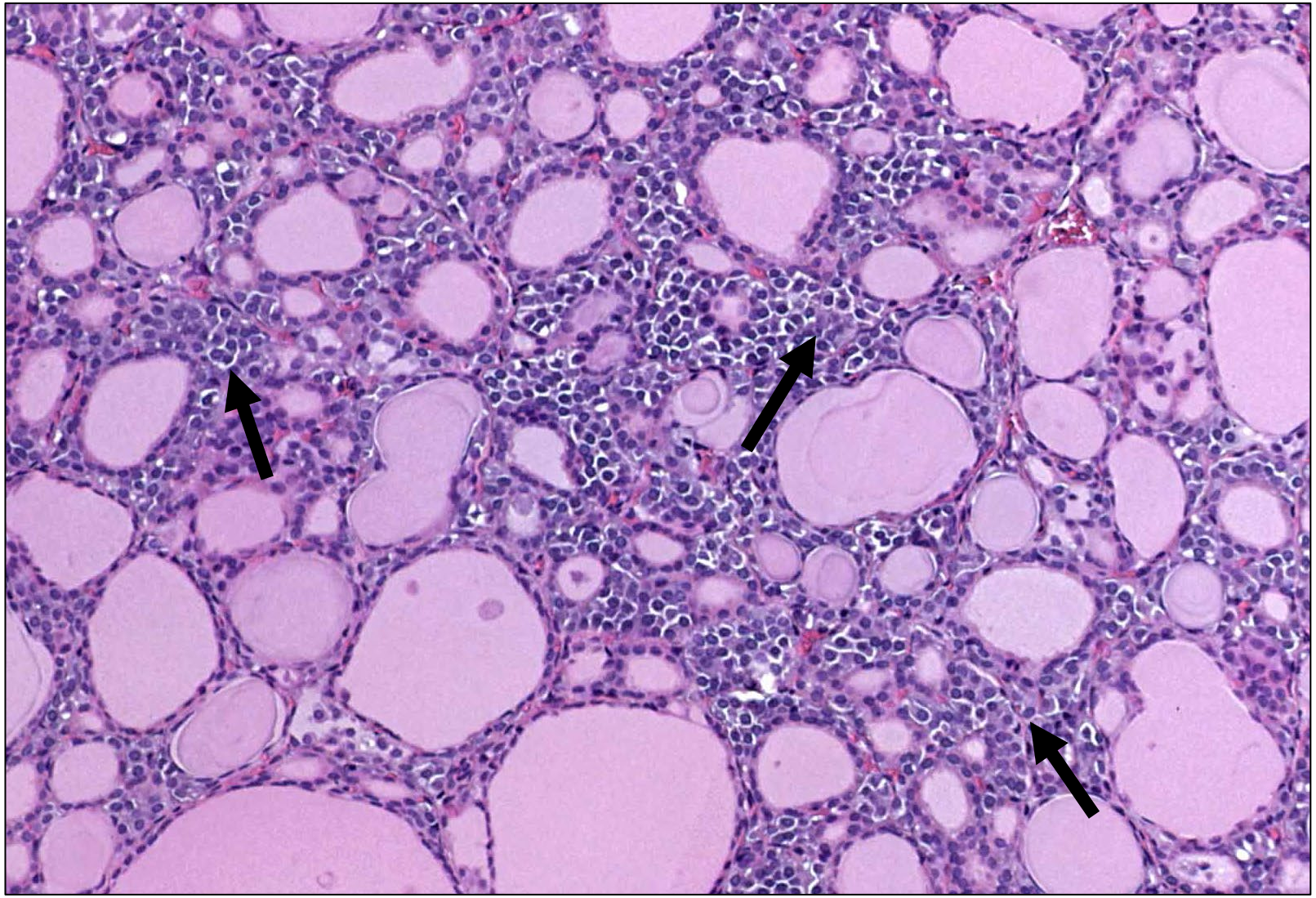
Increased numbers of C cells are present throughout the thyroid gland (arrows)



Thyroid Gland – Hyperplasia, C-Cell

Hyperplasia, C-Cell, Diffuse

- Higher magnification of diffuse C-cell hyperplasia (arrows) from the previous slide
- Increased numbers of C cells expand the parafollicular region (between the follicles)



Thyroid Gland – Adenoma, C-Cell

Histopathological Features

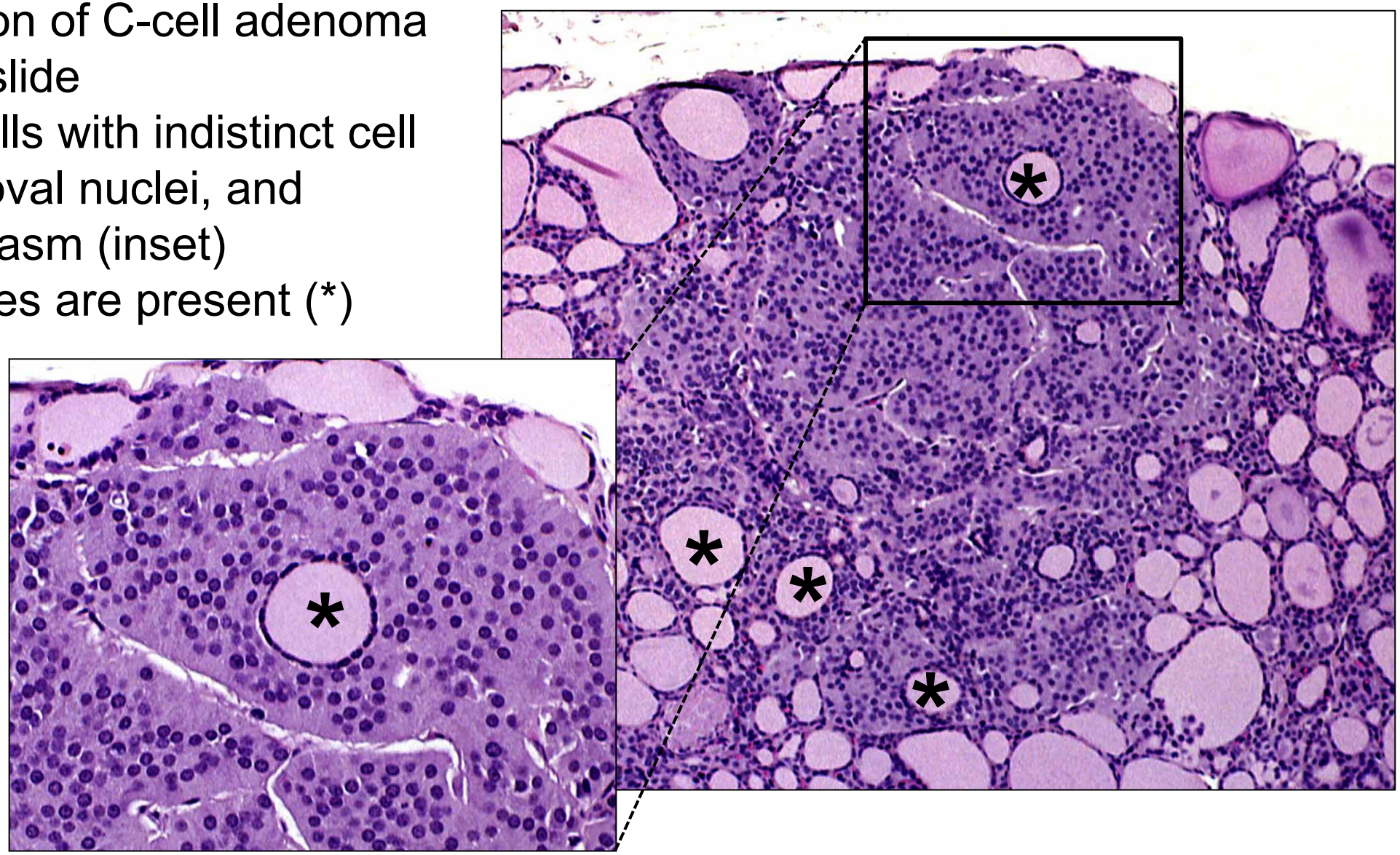
- Benign, well-demarcated, discrete mass of C cells larger than the area of 5 average follicles
- May compress surrounding follicles and may have a thin capsule
- Polygonal cells with indistinct borders arranged in solid nests with neuroendocrine packeting (nests of cells separated by delicate fibrovascular stroma)
- Stroma may contain amyloid or fibrous septa
- May resemble solid follicular cell adenomas
  - Small colloid-containing follicles are often present in follicular cell adenomas, but follicle remnants also may be present in C-cell adenomas
  - In C-cell adenomas, immunohistochemistry for calcitonin is positive, and thyroglobulin is negative
  - Electron microscopy may identify membrane-bound intracytoplasmic granules characteristic of C cells
- Occurs in rats; rare in mice

Thyroid Gland – Adenoma, C-Cell

- C-cell adenoma (arrows) in the thyroid gland
- Discrete mass that is larger than the area of 5 average contiguous thyroid follicles

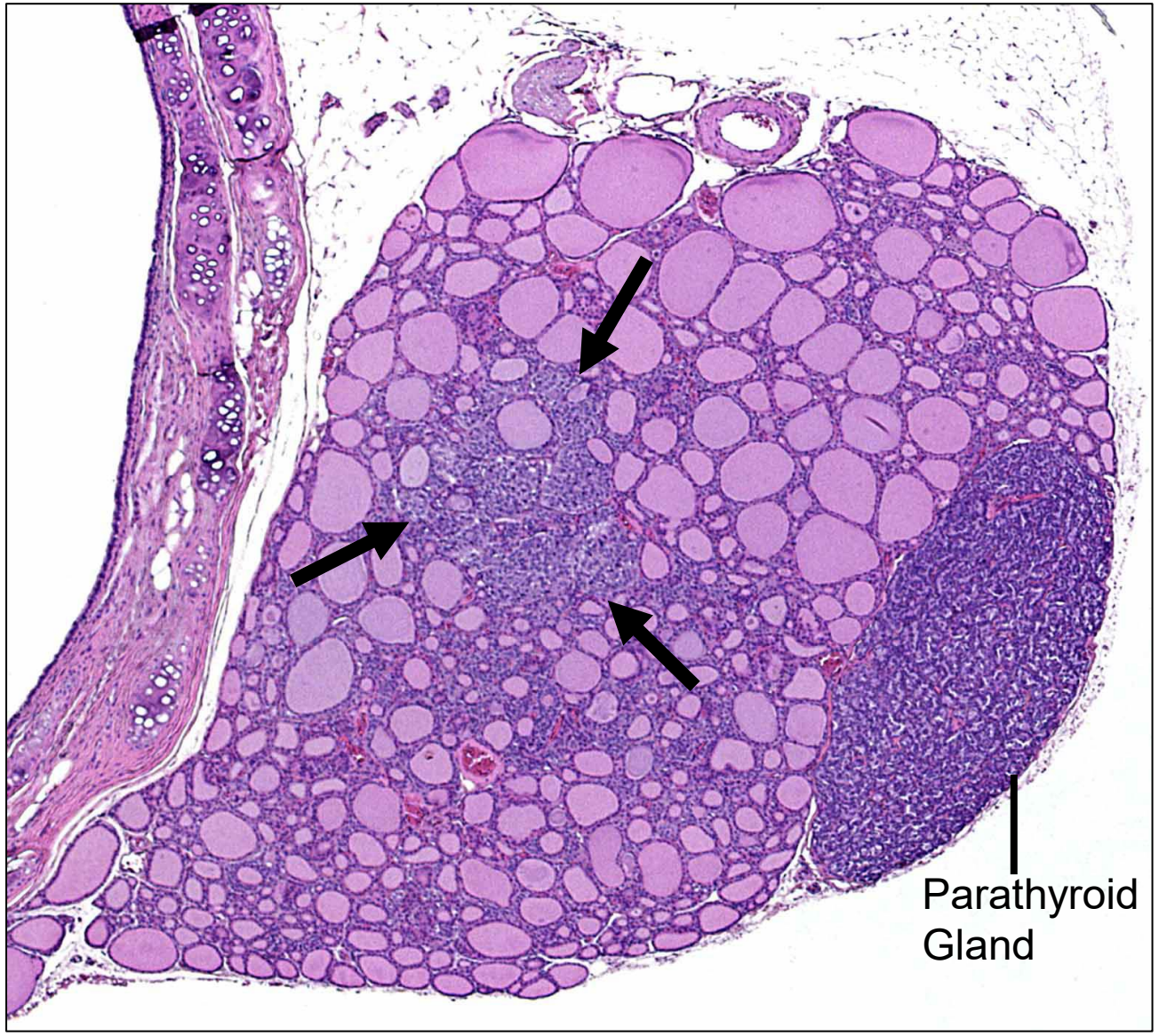
Thyroid Gland – Adenoma, C-Cell

- Higher magnification of C-cell adenoma from the previous slide
- Solid nests of C cells with indistinct cell borders, round to oval nuclei, and amphophilic cytoplasm (inset)
- Remnants of follicles are present (*)



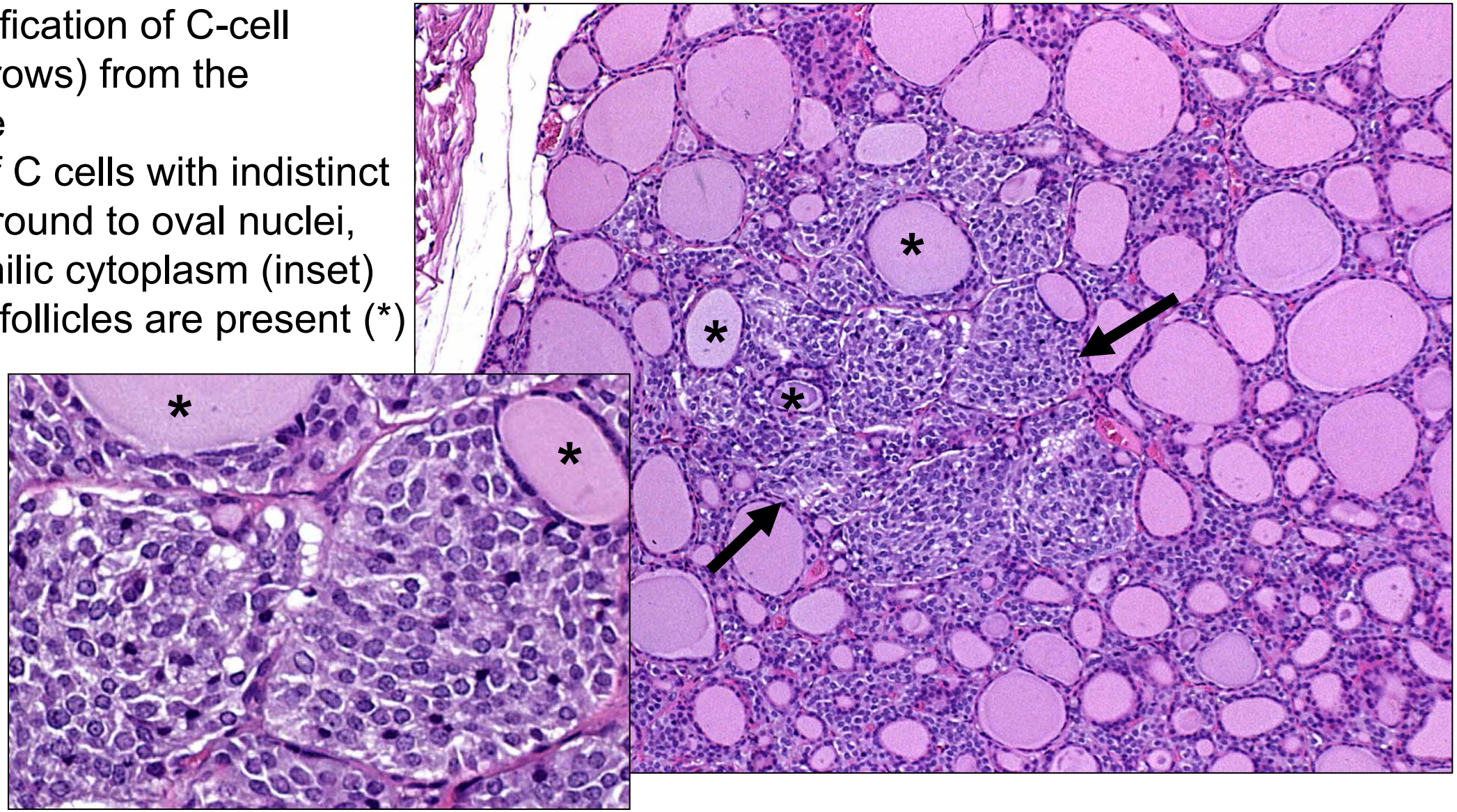
Thyroid Gland – Adenoma, C-Cell

- C-cell adenoma (arrows) in the thyroid gland
- Discrete mass that is larger than the area of 5 average contiguous follicles



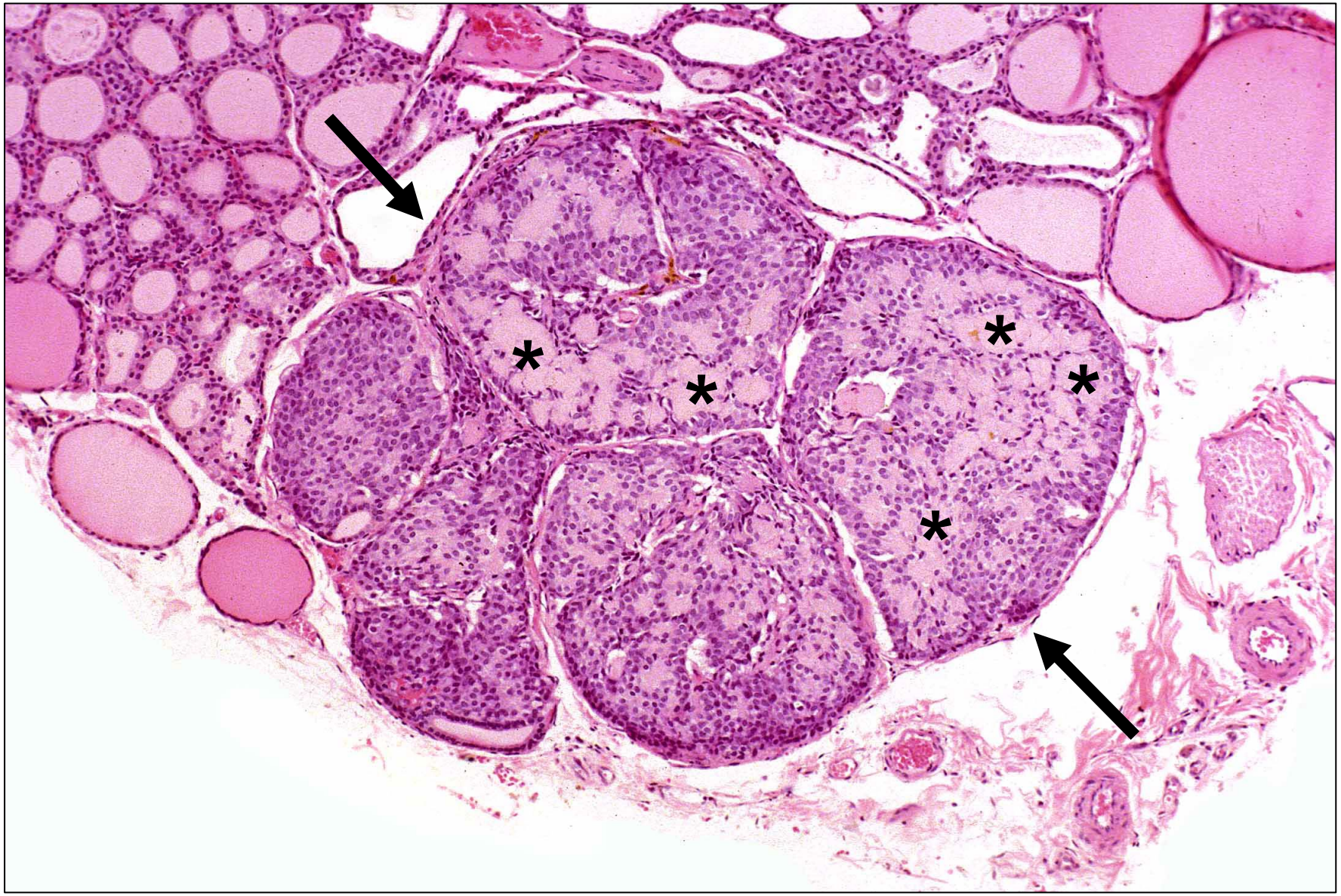
Thyroid Gland – Adenoma, C-Cell

- Higher magnification of C-cell adenoma (arrows) from the previous slide
- Solid nests of C cells with indistinct cell borders, round to oval nuclei, and amphophilic cytoplasm (inset)
- Remnants of follicles are present (*)



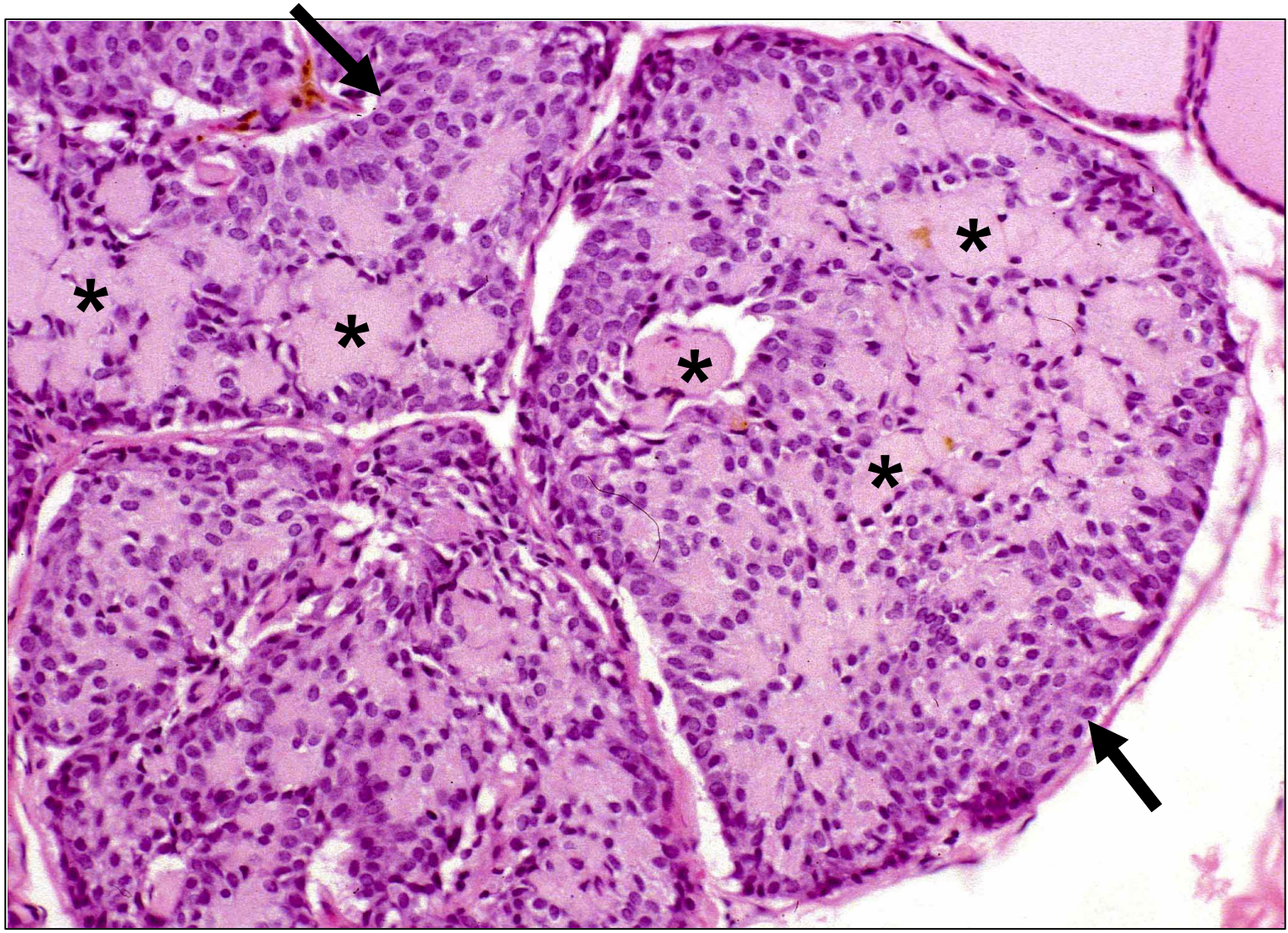
Thyroid Gland – Adenoma, C-Cell

- C-cell adenoma (arrows) in the thyroid gland
- Amorphous eosinophilic material consistent with amyloid deposits (*)



Thyroid Gland – Adenoma, C-Cell

- Higher magnification of C-cell adenoma with amyloid
- Solid nests of neoplastic C cells (arrows) with indistinct cell borders, oval nuclei, and amphophilic cytoplasm
- Amyloid (*) is present in the tumor stroma



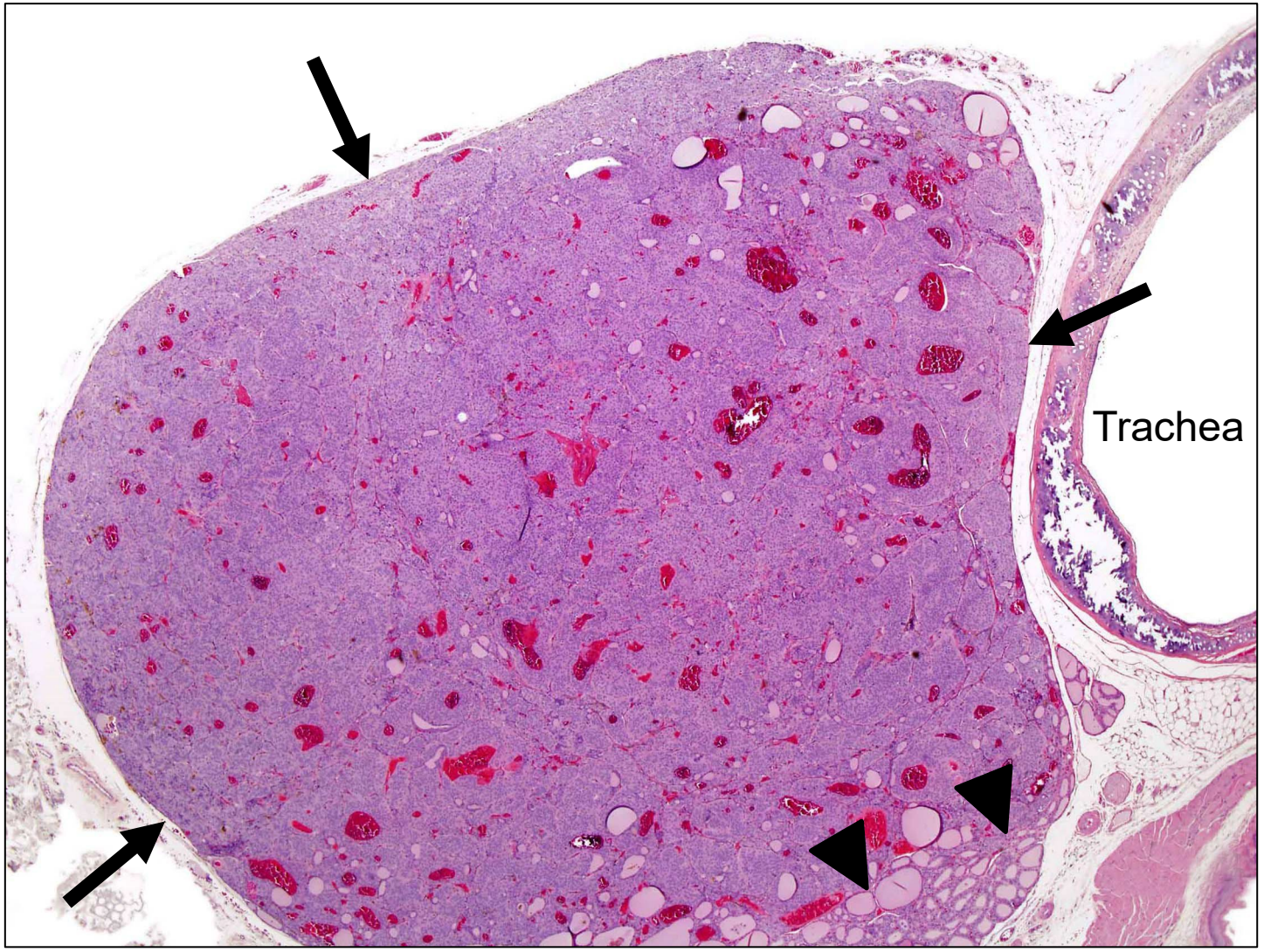
Thyroid Gland – Carcinoma, C-Cell

Histopathological Features

- Malignant proliferation of nests and sheets of C cells that effaces the thyroid gland and invades the thyroid capsule and adjacent tissues or vessels
  - Metastasis may occur
  - May contain central necrosis and hemorrhage
  - Amyloid may be present
- Cellular pleomorphism (varied in size and shape) and mitotic figures may be present
- May resemble solid type of follicular cell carcinoma
  - Small colloid-containing follicles are often present in solid follicular cell carcinomas, but entrapped follicles also may be present in C-cell carcinomas
  - In C-cell tumors, immunohistochemistry for calcitonin is positive, and thyroglobulin is negative
- Occurs in rats; rare in mice

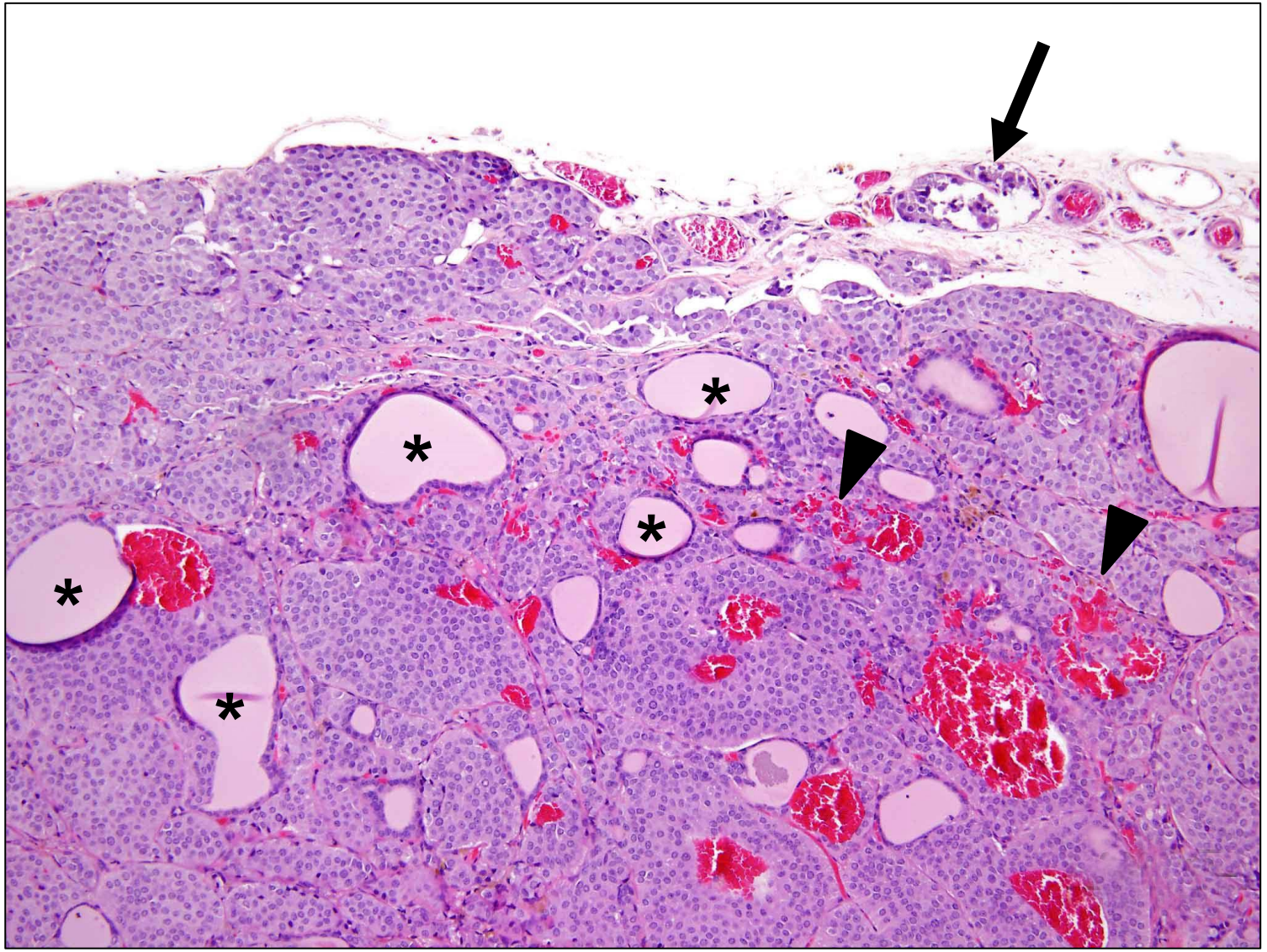
Thyroid Gland – Carcinoma, C-Cell

- C-cell carcinoma (arrows) in the thyroid gland
- Neoplastic cells have effaced most of the thyroid gland except for residual thyroid tissue along one edge (arrowheads)



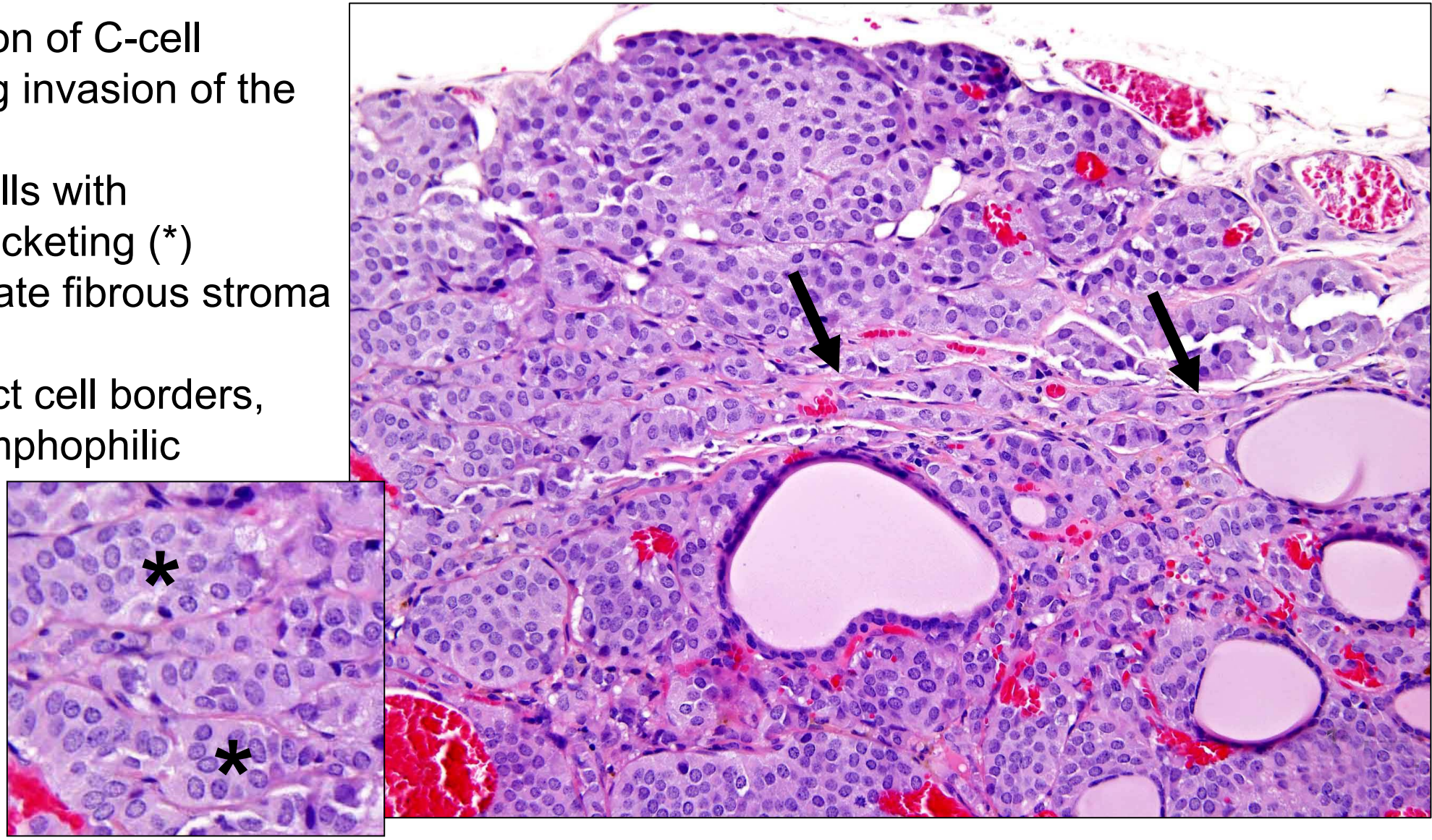
Thyroid Gland – Carcinoma, C-Cell

- Higher magnification of C-cell carcinoma from the previous slide
- Remnant follicles are present (*)
- Small areas of hemorrhage (arrowheads)
- Vascular invasion (arrow)



Thyroid Gland – Carcinoma, C-Cell

- Higher magnification of C-cell carcinoma showing invasion of the capsule (arrows)
- Solid nests of C cells with neuroendocrine packeting (*) separated by delicate fibrous stroma (inset)
- Cells have indistinct cell borders, oval nuclei, and amphophilic cytoplasm (inset)



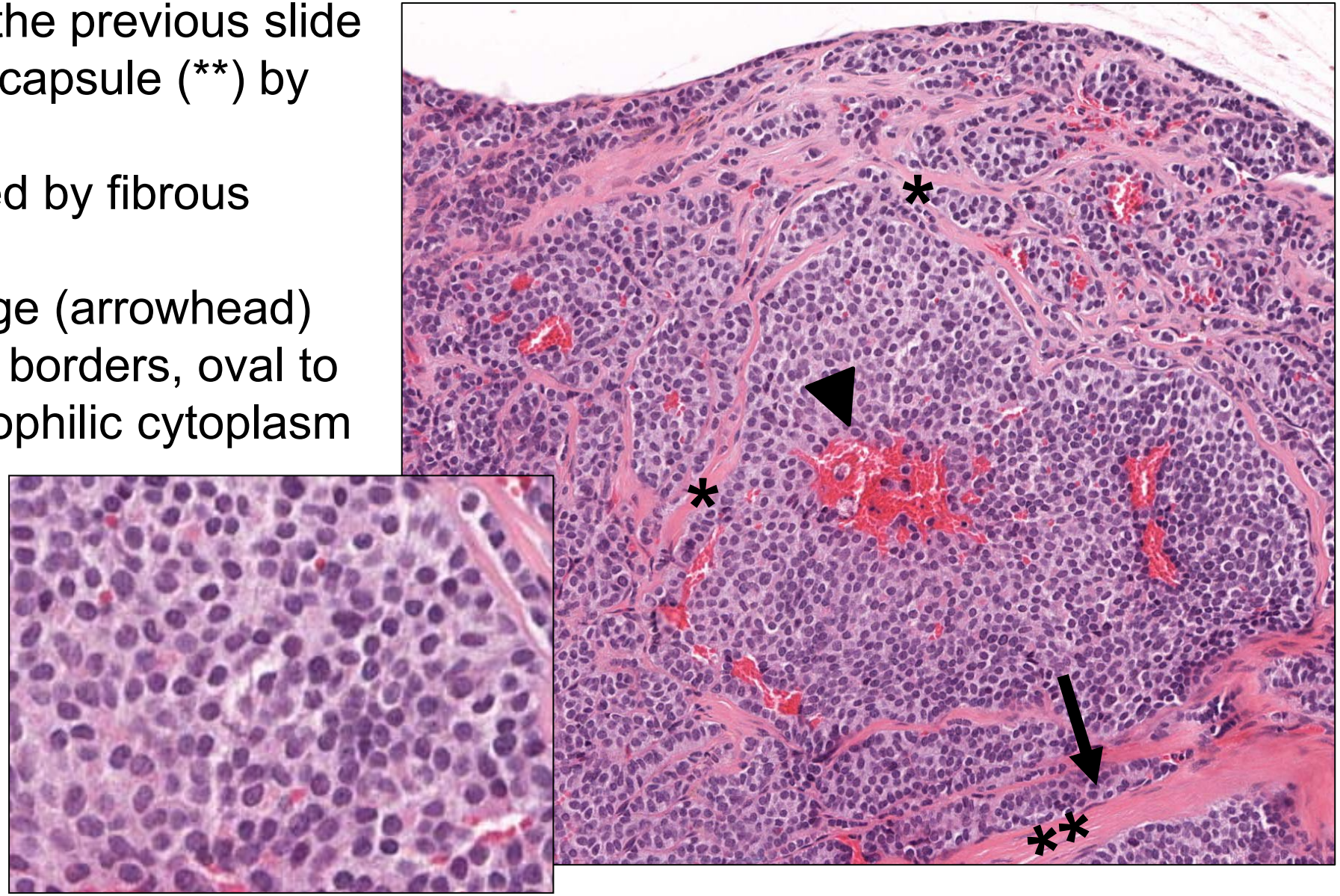
Thyroid Gland – Carcinoma, C-Cell

- C-cell carcinoma (arrows)
- Neoplastic cells have effaced the thyroid gland

Thyroid Gland, Mouse

Thyroid Gland – Carcinoma, C-Cell

- Higher magnification of the previous slide showing invasion of the capsule (**) by tumor cells (arrow)
- Solid nests are separated by fibrous stroma (*)
- Small area of hemorrhage (arrowhead)
- Cells have indistinct cell borders, oval to round nuclei, and amphophilic cytoplasm (inset)



References

- Brandli-Baiocco A, Balme E, Bruder M, Chandra S, Hellmann J, Hoenerhoff MJ, Kambara T, Landes C, Lenz B, Mense M, Rittinghausen S, Satoh H, Schorsch F, Seeliger F, Tanaka T, Tsuchitani M, Wojcinski Z, Rosol TJ. (2018). Nonproliferative and proliferative lesions of the rat and mouse endocrine system. Toxicol Pathol 31 (3 Suppl): 1S-95S https://doi.org/10.1293/tox.31.1S
- goRENI: https://www.goreni.org
- Hardisty JF, Boorman GA (1999). Thyroid and Parathyroid Glands. In Maronpot RR (ed.) *Pathology of the Mouse,* pp. 537 – 554. Cache River Press. Vienna, IL.
- Maronpot RR, Brix A. 2014. Thyroid Gland. In: Cesta MF, Herbert RA, Brix A, Malarkey DE, Sills RC (Eds.), National Toxicology Program Nonneoplastic Lesion Atlas. Available: https://ntp.niehs.nih.gov/atlas/nnl/endocrine-system/thyroid-gland.
- Mense MG, Rosol TJ (2018). Thyroid Gland. In Suttie AW (ed.) *Boorman's Pathology of the Rat,* pp. 669 – 686. Academic Press. Cambridge, MA.

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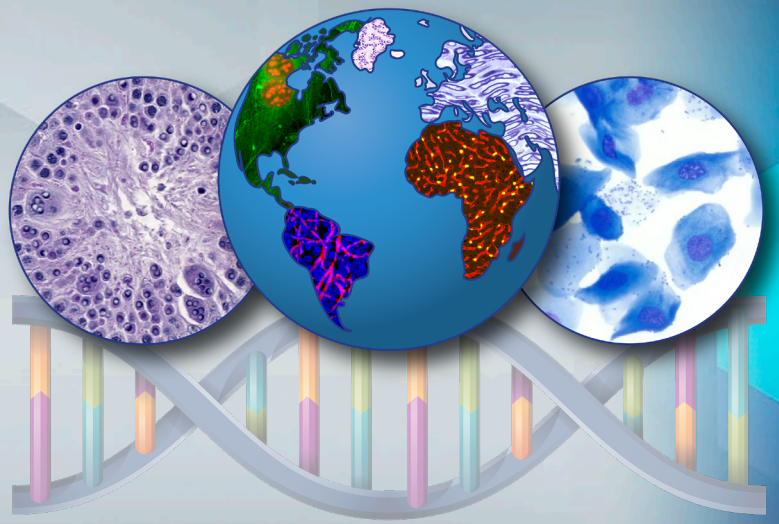

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