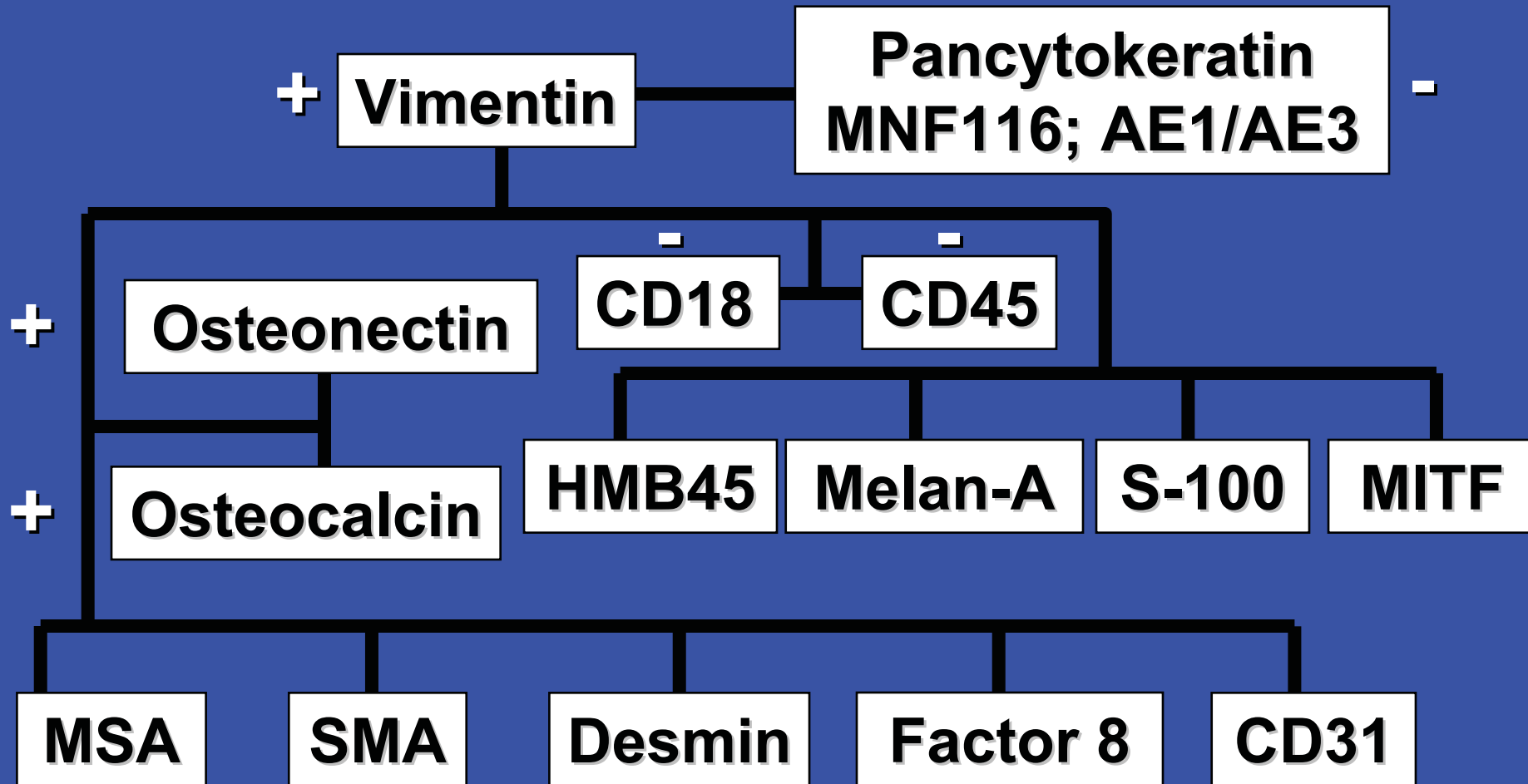


Osteonectin

What's your Diagnosis



Osteosarcoma



Osteosarcoma



- **Most markers used in human pathology have not been extensively tested in domestic animals**
- **Vimentin: 100%**
- **Osteocalcin: Mainly in osteoblasts**
 - **Osteosarcomas: 70% (very specific)**
- **Osteonectin: Osteosarcomas: 90%**
 - **Specificity: <55% (endothelium, pericytes, fibroblasts, nerves, epithelium, chondrocytes)**
- **RANKL: osteoclast differentiation, not validated in dogs**
- **Osteopontin and Bone Sialoprotein**
 - **Markers for risk of bone metastasis in carcinomas**
- **Ezrin: Potential marker for prognosis (metastatic risk, relapse)**



Osteosarcoma

This histological image shows a dense population of spindle-shaped cells, characteristic of osteosarcoma. The cells are arranged in a disorganized pattern, with many showing hyperchromatic nuclei and pleomorphism. The background is a pale, eosinophilic matrix, likely representing osteoid or bone tissue. The overall appearance is that of a highly cellular, malignant neoplasm.

p53

Osteosarcoma

A high-magnification histological image of an osteosarcoma. The tissue is stained with hematoxylin and eosin (H&E), showing a dense population of malignant cells with hyperchromatic, pleomorphic nuclei. Several large, multinucleated osteoclast-like giant cells are visible, characterized by their foamy or vacuolated cytoplasm. The overall architecture is disorganized, with areas of necrosis and hemorrhage. The brown staining represents E-cadherin immunohistochemistry, which is positive in the tumor cells.

Ezrin

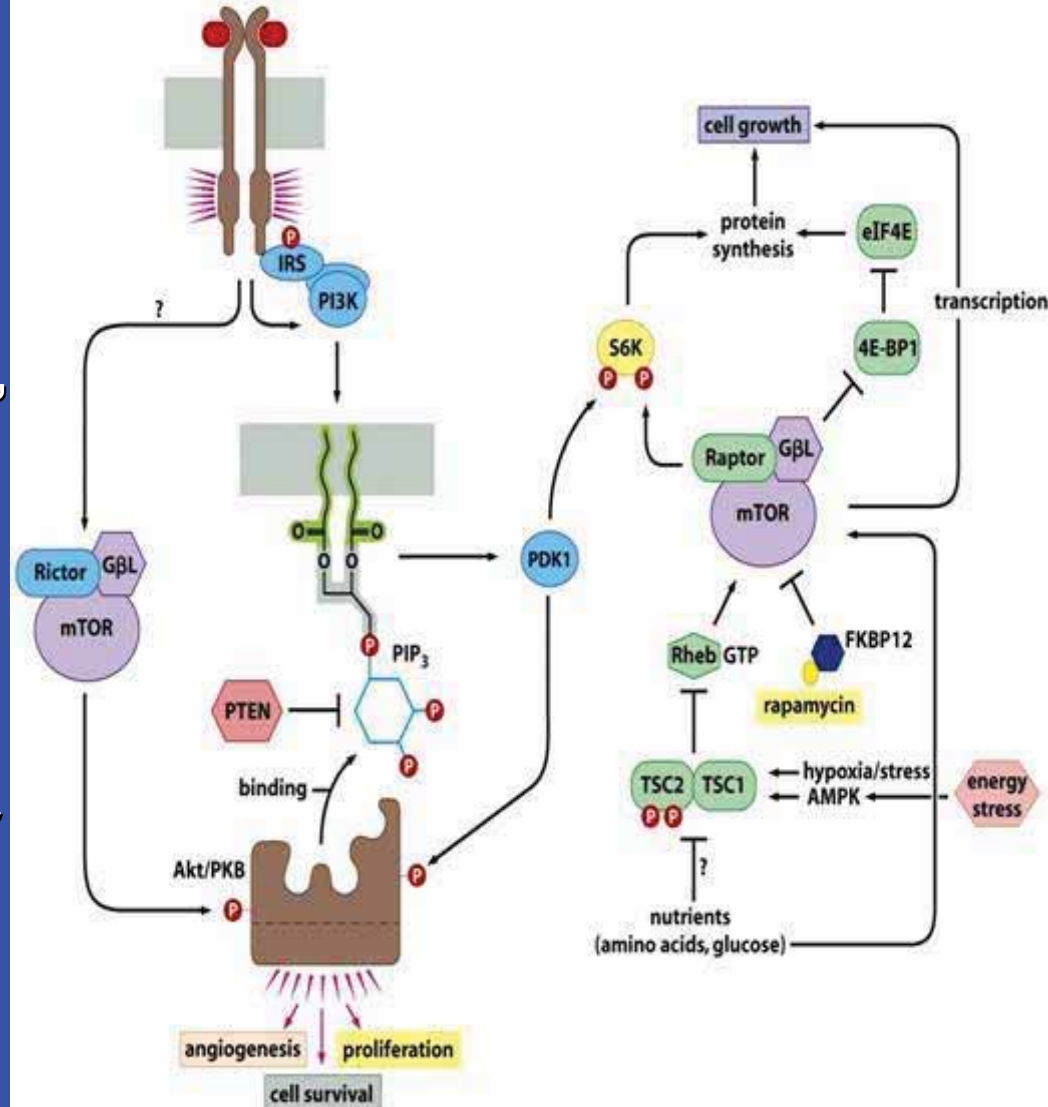


Osteosarcoma

PTEN

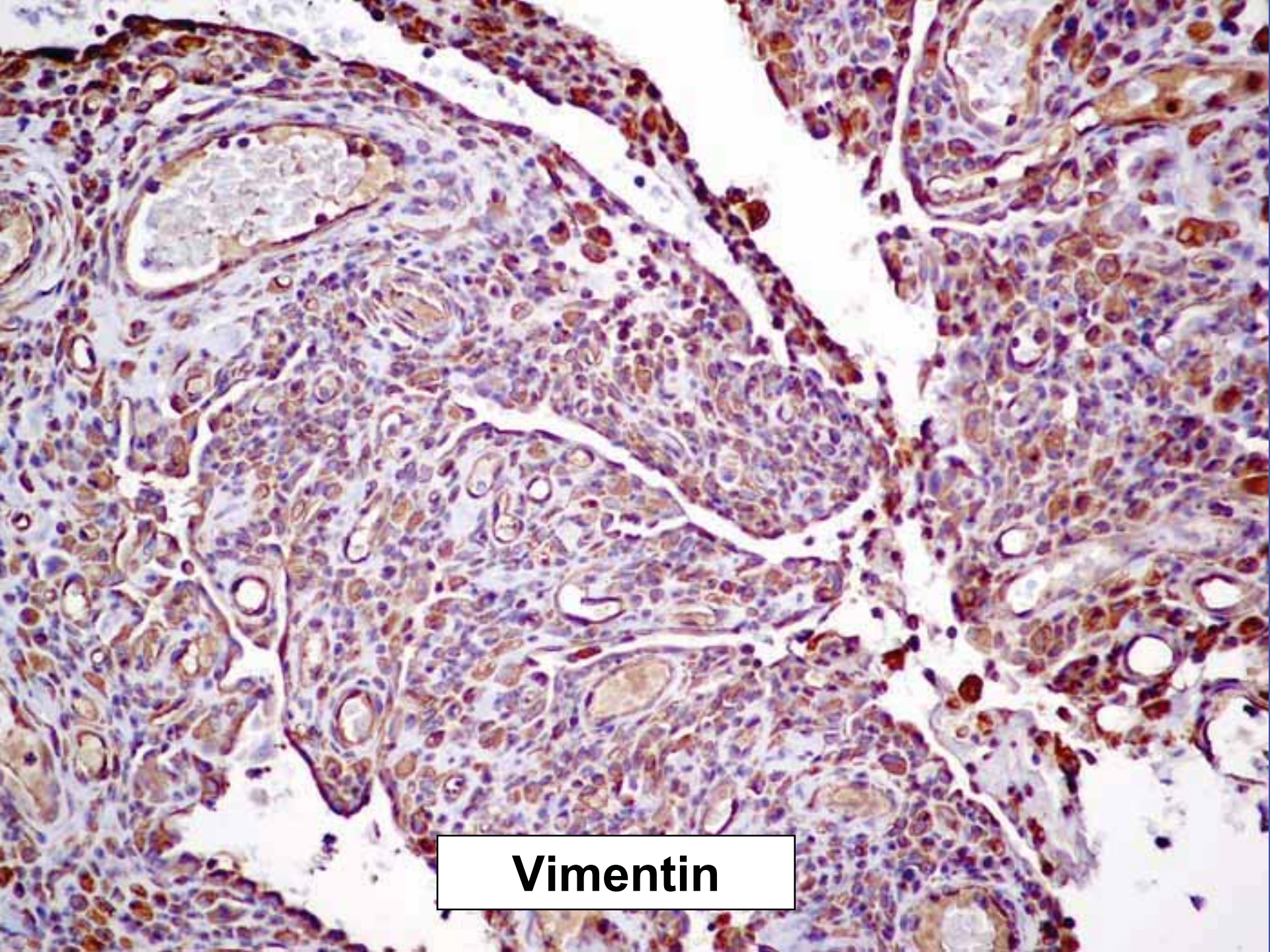
Rapamycin and the mTOR circuit

- mammalian target of rapamycin
- signals: nutrients, oxygen, ATP, mitogenic signals
- responses: cell proliferation, protein synthesis, angiogenesis, anti-apoptotic, ribosome biogenesis, cell motility
- exists in alternative complexes:
 - Rictor > activity of Akt/PKB
 - Raptor > activates protein synthesis
- rapamycin blocks mTOR-Raptor
- also shuts down mTOR-Rictor
- primary effect is inhibition of Akt/PKB signaling (carcinomas with loss of PTEN)

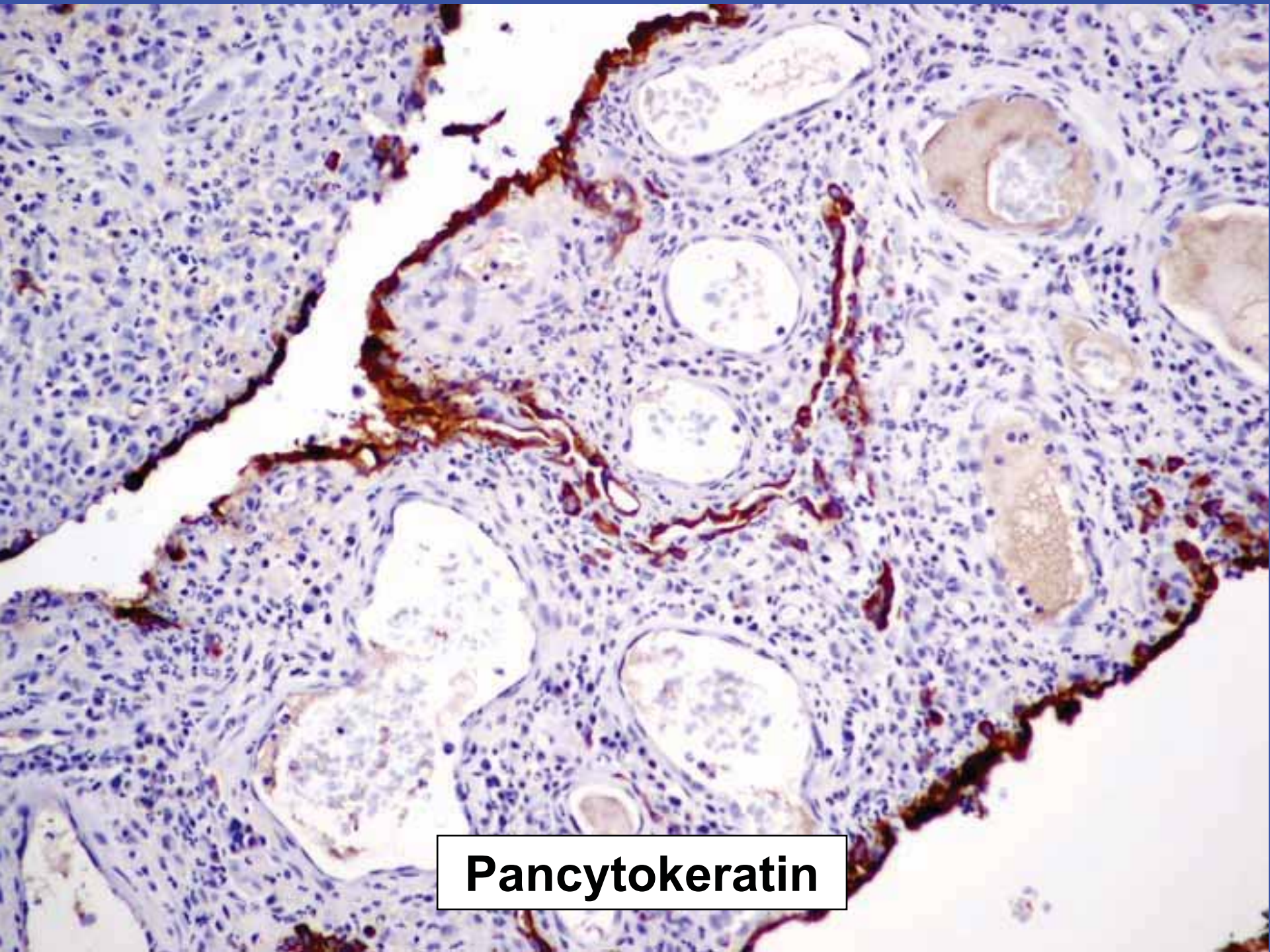


Abdominal Mass

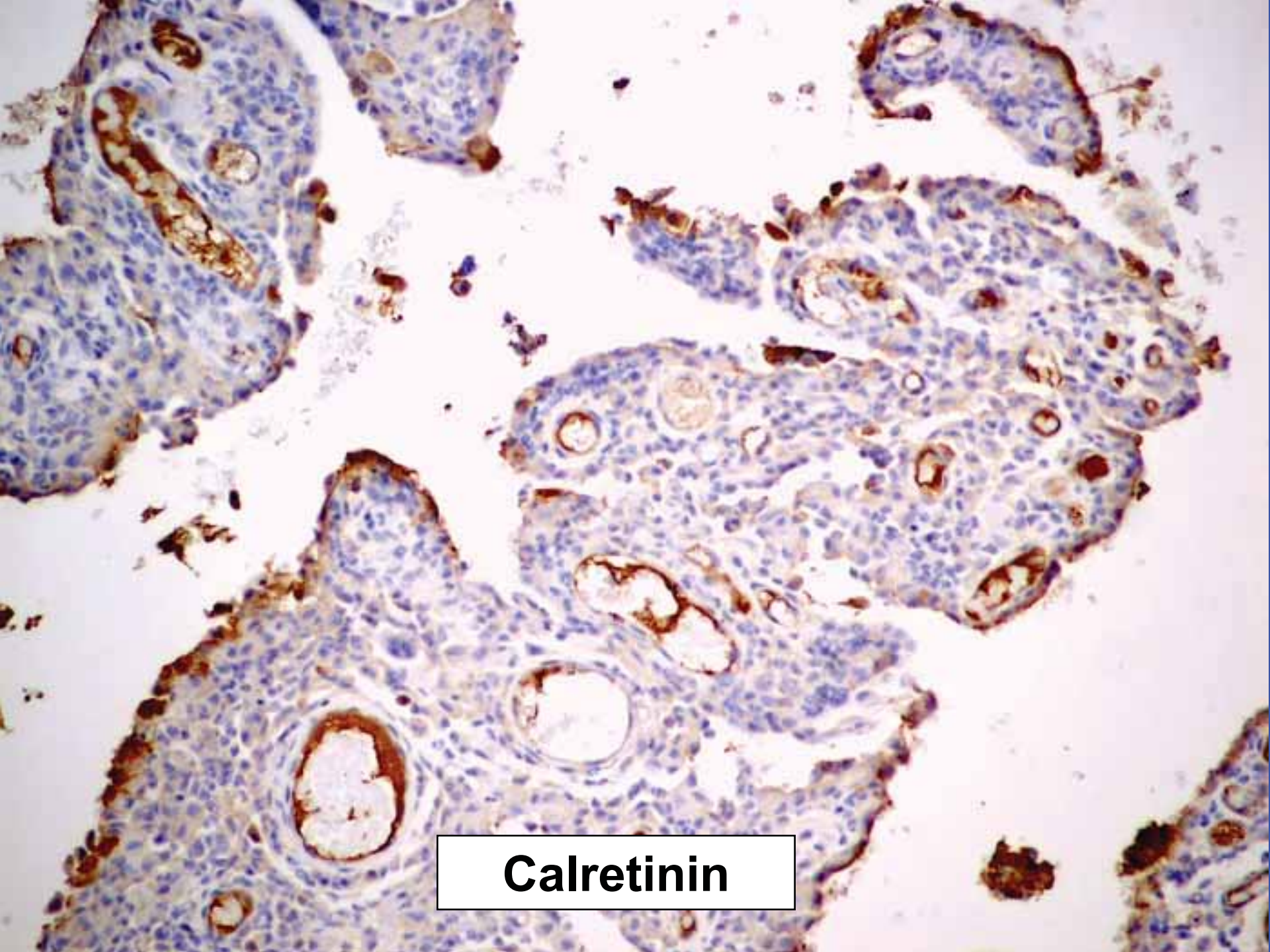




Vimentin



Pancytokeratin

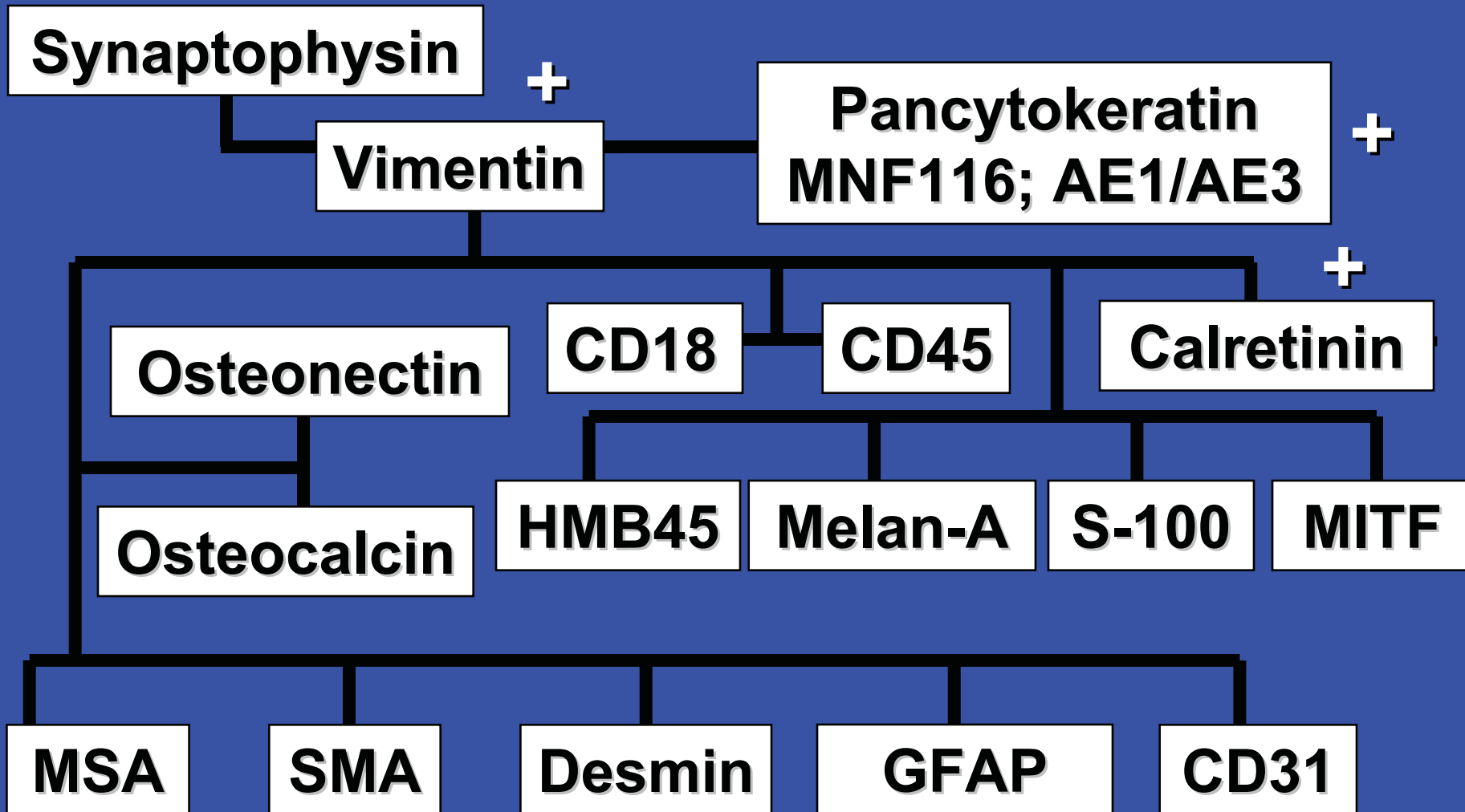


Calretinin

A long-haired white cat with a grumpy expression, looking slightly to the right. The cat has long, straight white fur and green eyes. It is standing on a wooden floor.

**What's
your
Diagnosis**

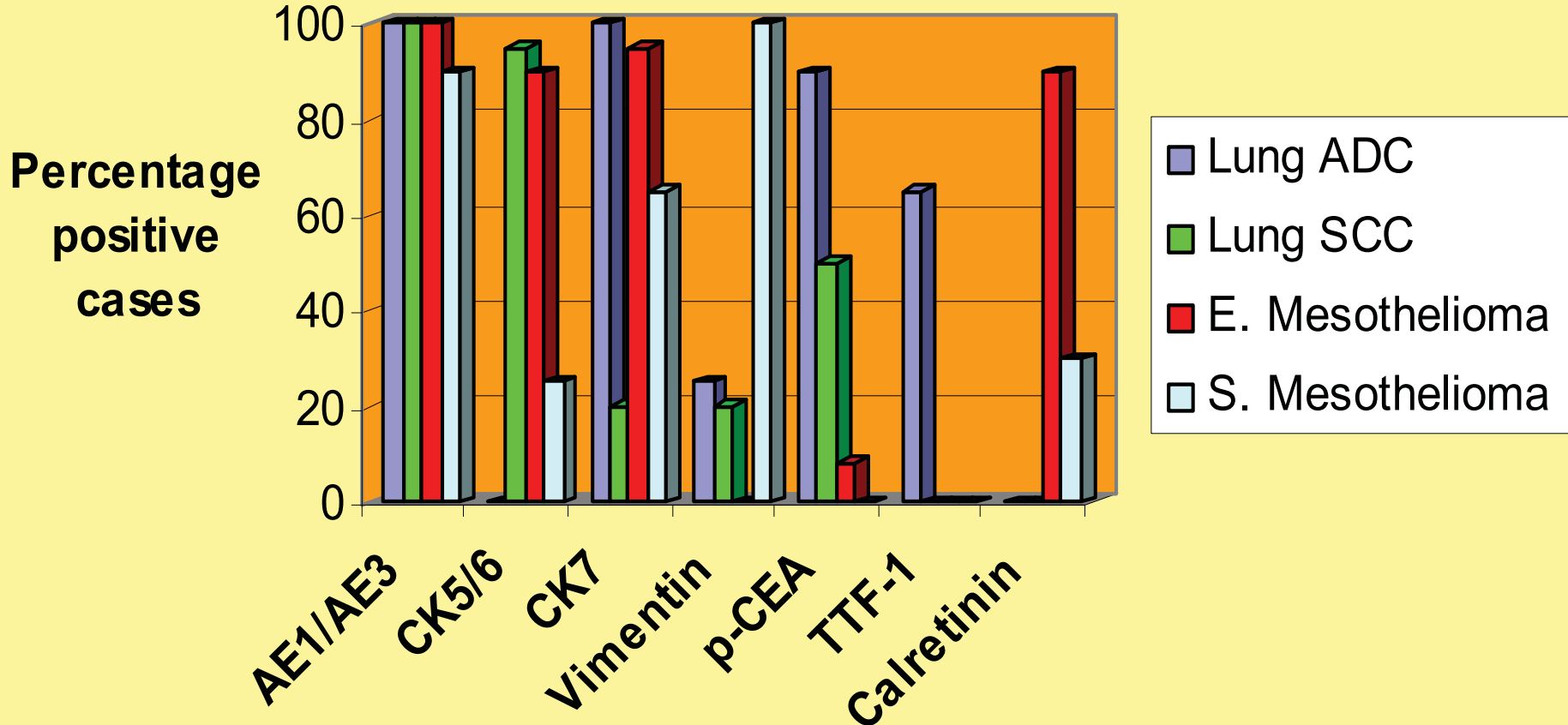
Mesothelioma



Mesothelioma Markers

- **Positive markers:**
 - Calretinin
 - Wilms tumor gene product (WT1)
 - Cytokeratin 5
 - Thrombomodulin
 - Mesothelin (frozen)
 - Vimentin
- **Negative markers:**
 - Carcinoembryonic antigen
 - Tumor glycoprotein (BerEp4)
 - CD15 (LeuM1)
 - Epithelial glycoproteins Bg8 & B72.3

Pulmonary Carcinoma vs. Mesothelioma



Cytokeratins

- 20 different cytokeratin polypeptides
- **Type 1 cytokeratins (acidic) and type 2 cytokeratins (basic), majority paired together as acidic and basic types**
- Numbered in each group consecutively
 - **type 2: cytokeratins 1-8, type 1: cytokeratins 9-20**
 - **from highest (HMW) to lowest molecular weight (LMW)**
- LMW cytokeratins in all epithelia except squamous
- HMW cytokeratins typical of squamous epithelia
- Simple epithelial keratins:
 - **appear first in embryonic development**
 - **expressed in all nonstratified (simple), ductual and pseudostratified epithelia**
- Complex (stratified) epithelial keratins:
 - **expressed in stratified epithelia, basal cells, myoepithelial cells, duct-derived epithelium**

Cytokeratins and their Tissue Distribution

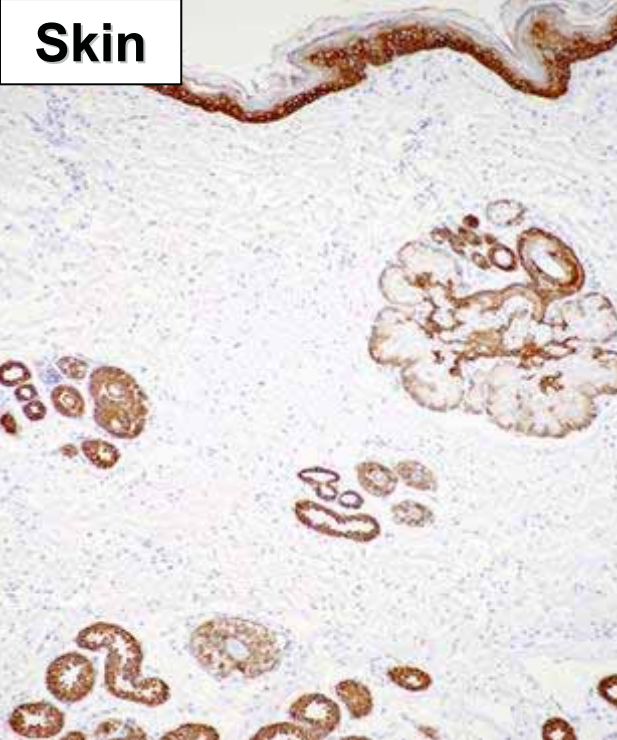
| Type II cytokeratin basic | Molecular weight kDa | Tissue distribution | Molecular weight kDa | Type I cytokeratin acidic |
|---------------------------------|----------------------------|---|----------------------------|---------------------------------|
| | | Epidermis | 64 | CK9 |
| CK1 | 67 | Keratinizing squamous epithelium | 56.5 | CK10 |
| CK2 | 65 | Epithelia, all locations | 56 | CK11 |
| CK3 | 63 | Cornea | 55 | CK12 |
| CK4 | 59 | Nonkeratinizing squamous epithelia of internal organs | 51 | CK13 |
| CK5 | 58 | Basal cells of squamous and glandular epithelia, myoepithelia, mesothelium | 50 | CK14 |
| | | Squamous epithelia | 50 | CK15 |
| CK6 | 56 | Squamous epithelia, hyperproliferative | 48 | CK16 |
| CK7 | 54 | Simple epithelia | 46 | CK17 |
| CK8 | 52 | Basal cells of glandular epithelia, myoepithelia | 45 | CK18 |
| | | Simple epithelia, most glandular and some squamous epithelia (basal) | 40 | CK19 |
| | | Simple epithelia of intestines and stomach, Merkel cells | 46 | CK20 |

Pancytokeratin MNF116

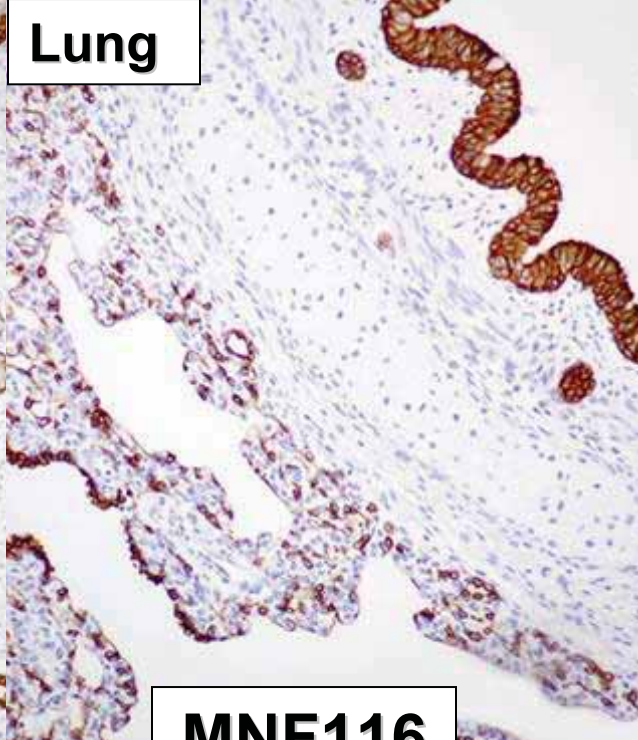


- Clon MNF116 recognizes the 58, 56 and 52 kD keratins of the basic subfamily and the 46 and 40 kD keratins of the acidic subfamily (CK 5, 6, 8, 17, 19).
- **Normal tissue:** stains most epithelia:
 - skin: stratified squamous epithelium (fades to surface) apocrine glands, basal cells, sebaceous duct epithelium, outer and inner root sheath of hair follicle
 - lung, thyroid, trachea, kidney, mammary gland, bile ducts, pancreatic ducts, small and large intestine, mesothelium
- **Neoplasms:** majority of benign and malignant epithelial tumors

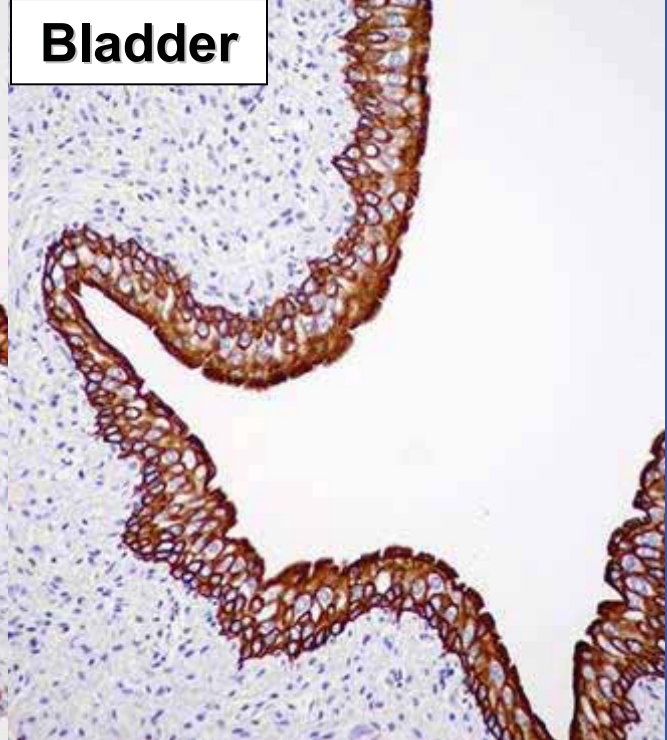
Skin



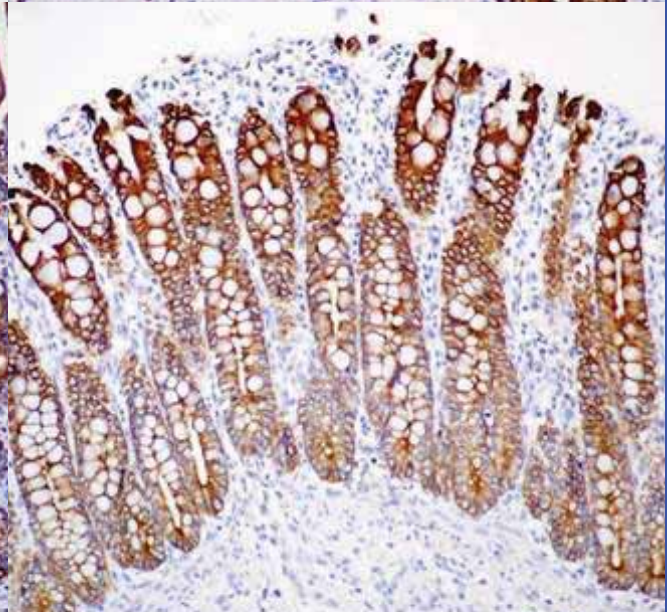
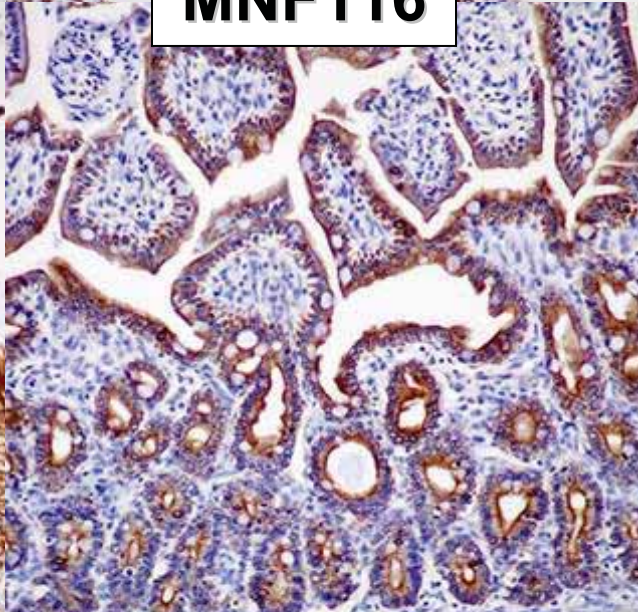
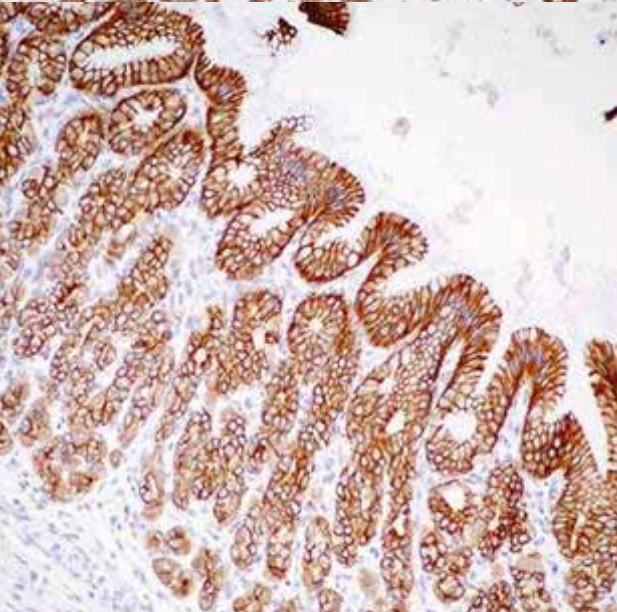
Lung



Bladder



MNF116



Stomach

Jejunum

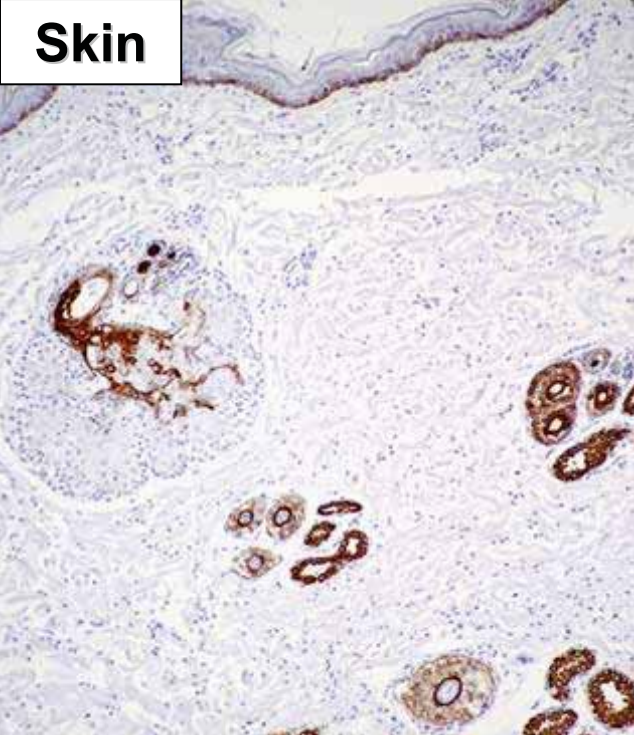
Colon

Pancytokeratin AE1/AE3

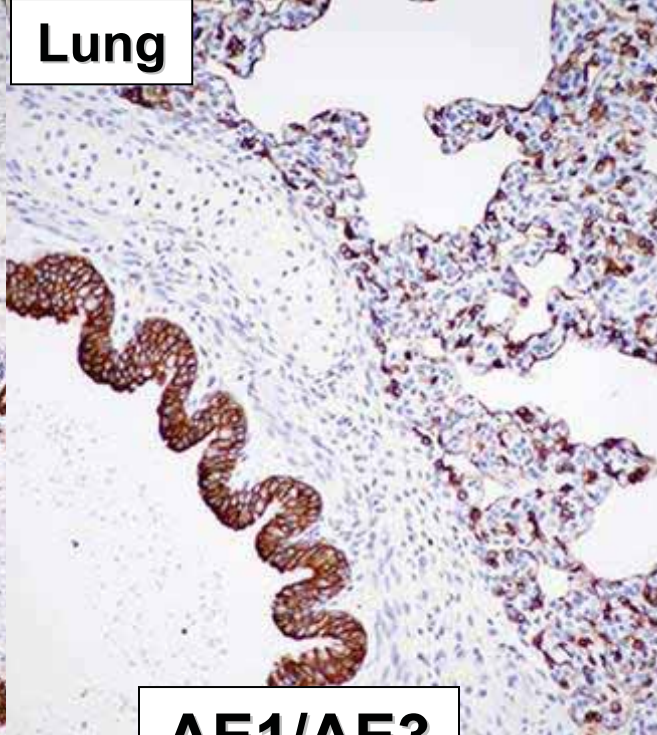


- Clon AE1 recognizes the 56.5, 50.5, 50, 48 and 40 kD keratins of the acidic subfamily, AE3 antibody recognizes the 67, 65, 58, 56, and 52 kD keratins of the basic subfamily (CK 1, 2, 5, 6, 8, 10, 14, 15, 16, 19).
- **Normal tissue:**
 - similar staining as MNF116
 - also staining of the epidermis
- **Neoplasms:** majority of benign and malignant epithelial tumors

Skin



Lung



Bladder

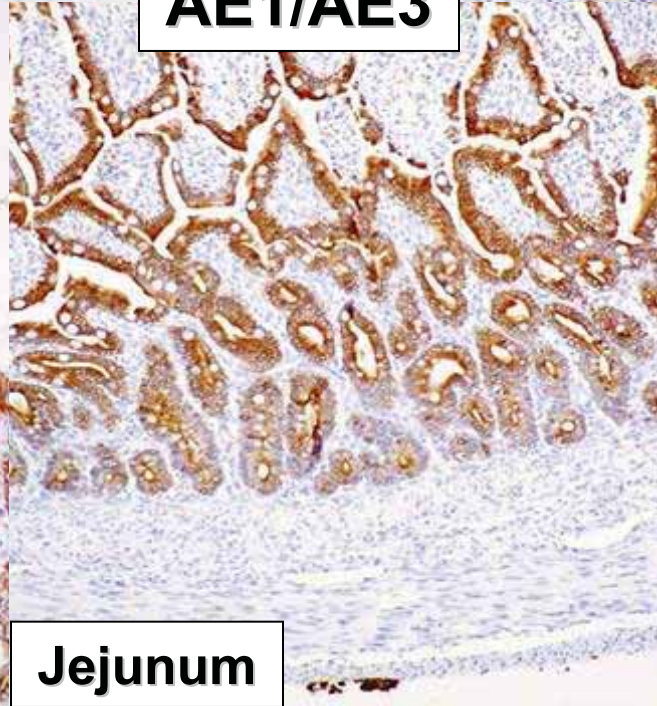


AE1/AE3

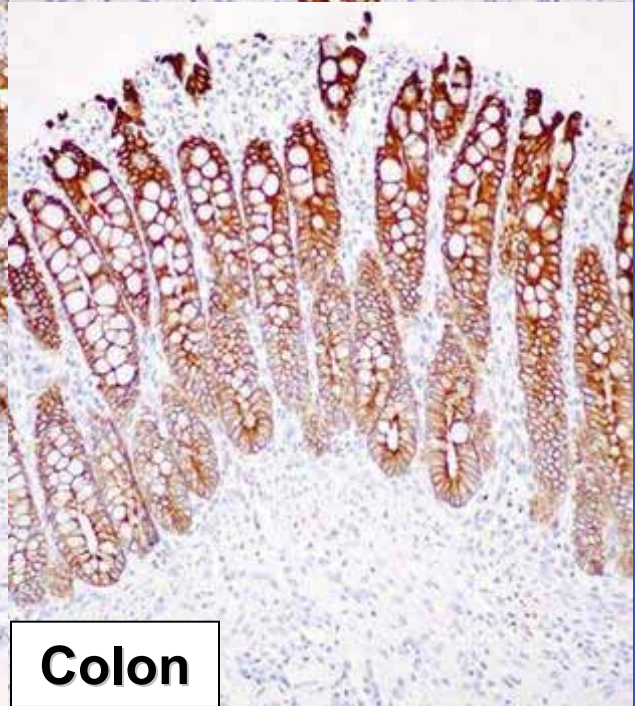
Stomach



Jejunum

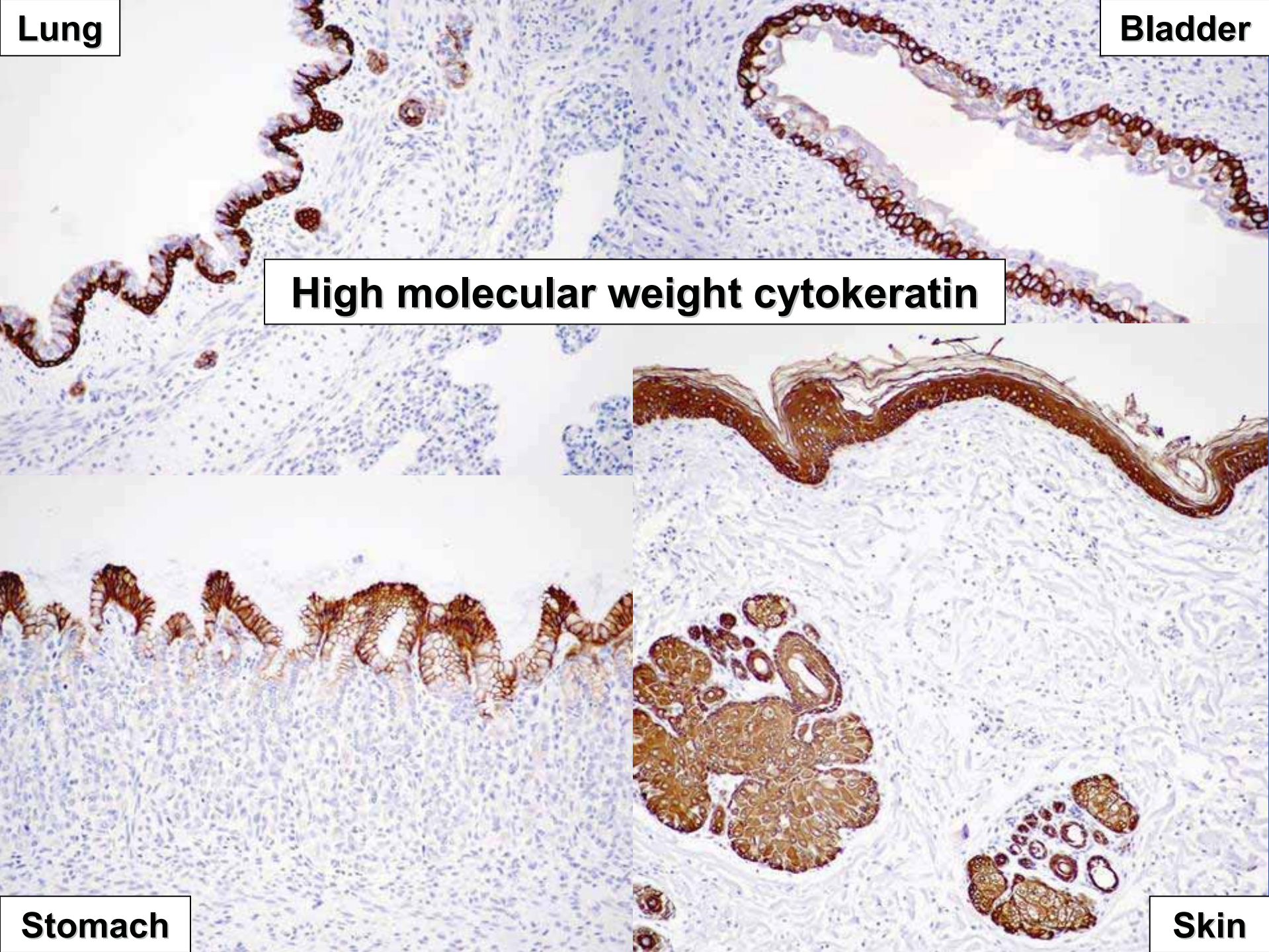


Colon



High Molecular Weight Cytokeratin

- Clon 34 β E12 recognizes 66 and 57 kD keratins of both cytokeratin families (CK 1, 5, 10, 14).
- **Normal tissue:** keratinizing epithelium
 - skin: squamous epithelium, apocrine, sebaceous glands, myoepithelia
 - stratum basale in urinary bladder, bronchiolar epithelium, superficial epithelium in small and large intestine, stomach, mesothelium
- **Neoplasms:** squamous and ductual neoplasms, does not react with most neuroendocrine neoplasms



Lung

Bladder

High molecular weight cytokeratin

Stomach

Skin

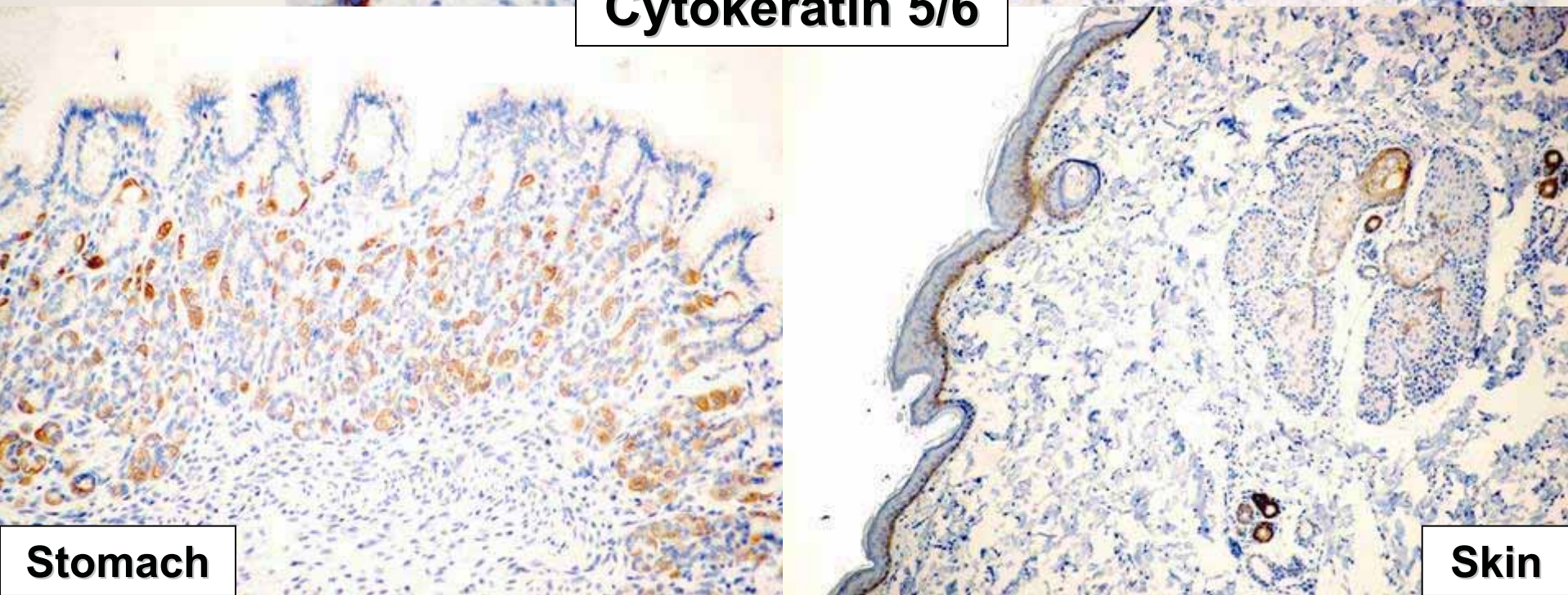
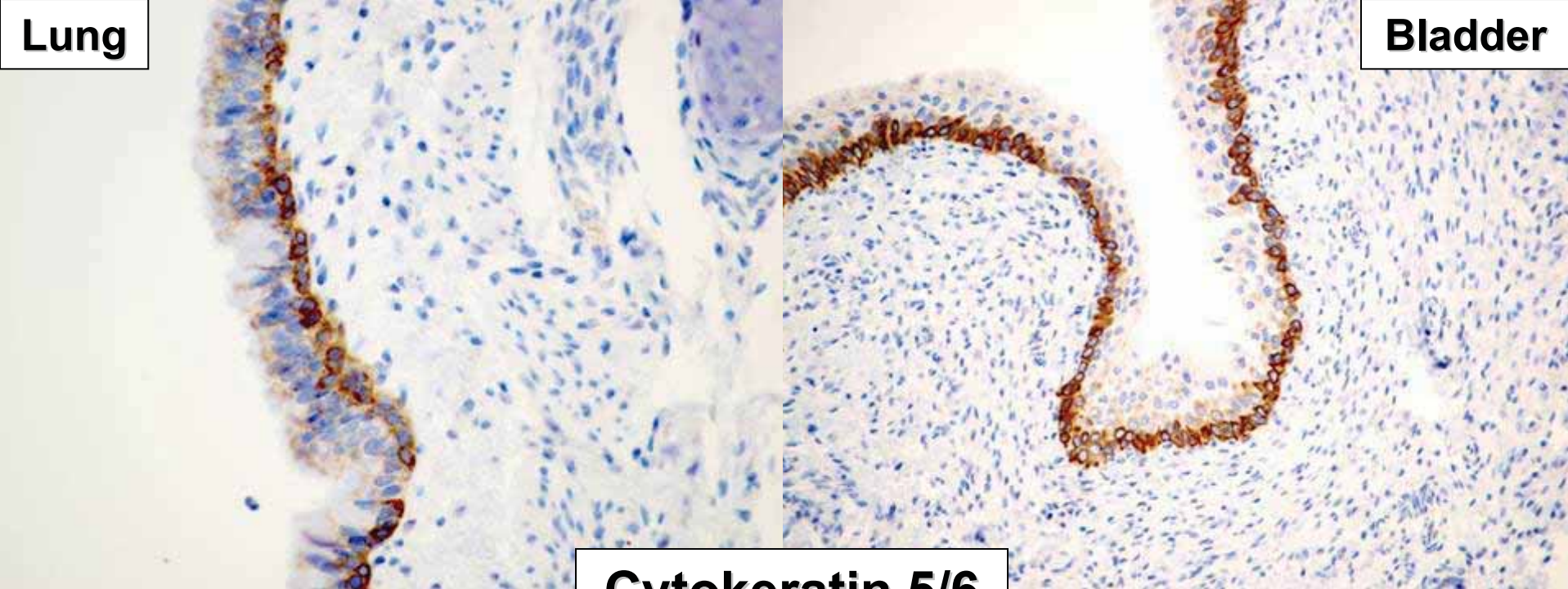
Low molecular weight cytokeratins

- Clone 5D3 recognizes 52 and 45 kD keratins of both families (CK8 and 18). Clone RCK108 recognizes a 40 kD keratin of acidic keratin family (CK19), smallest cytokeratin
- Used to identify simple epithelia does not stain stratified epithelia
- **normal tissue:** - glandular epithelium in breast, liver, thyroid, urogenital tract, respiratory tract and **GI tract (strong mucosal, moderate glandular staining)**
 - trachea, urothelium, liver
- **Neoplasms:** - adenocarcinomas of various origin including respiratory and GI tract
 - basal cell tumors, mesothelioma
 - hepatocellular carcinomas
 - useful for thyroid follicular carcinomas

Cytokeratin 5/6



- Clone D5/16 B4 recognizes 58 and 56 kD keratins of basic keratin family (CK5 and 6)
- Used to differentiate between low differentiated squamous cell carcinoma and adenocarcinoma
- **Normal tissue:**
 - stratified squamous epithelia
 - basal cells, mesothelium
 - does not stain simple epithelia
 - amnion epithelium
 - stomach: chief cells
- **Neoplasms:** - adenocarcinomas versus mesothelioma



Cytokeratin 7

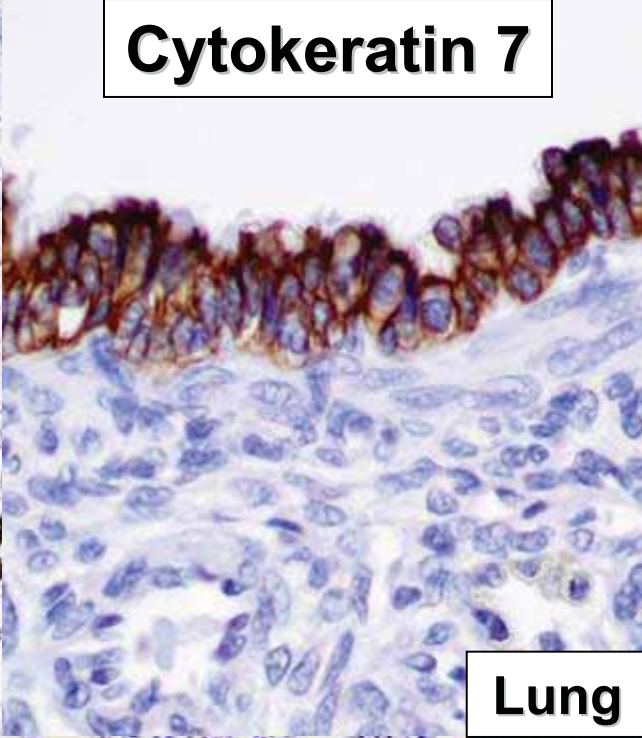


- Clone OV-TL 12/30 recognizes a 54 kD keratin of basic keratin family
- **Normal tissue:**
 - most ductual and glandular epithelia
 - transitional cell epithelium
 - does not stain stratified epithelia
 - **bronchiolar epithelium, but not intestinal epithelium**
- **Neoplasms:**
 - adenocarcinomas of ovary, mammary gland and lung
 - transitional cell carcinoma
 - **negative for GI tract carcinomas**

Cytokeratin 7



Skin



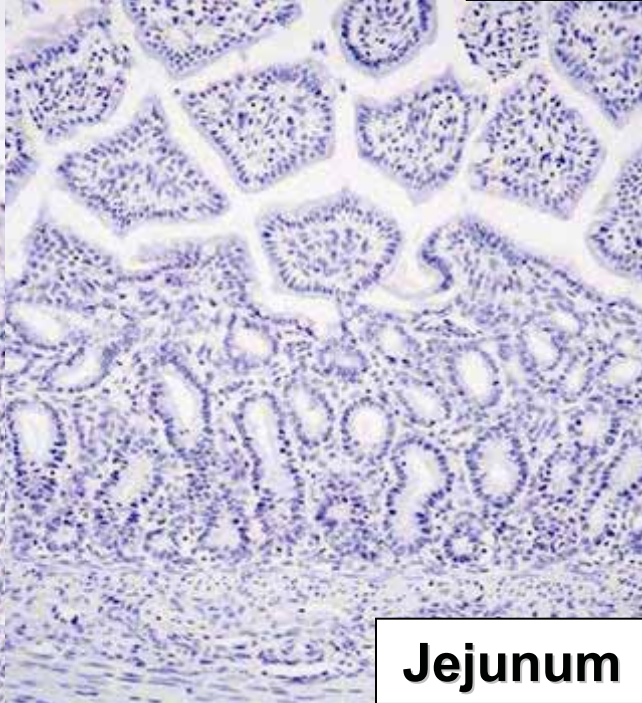
Lung



Bladder



Stomach



Jejunum

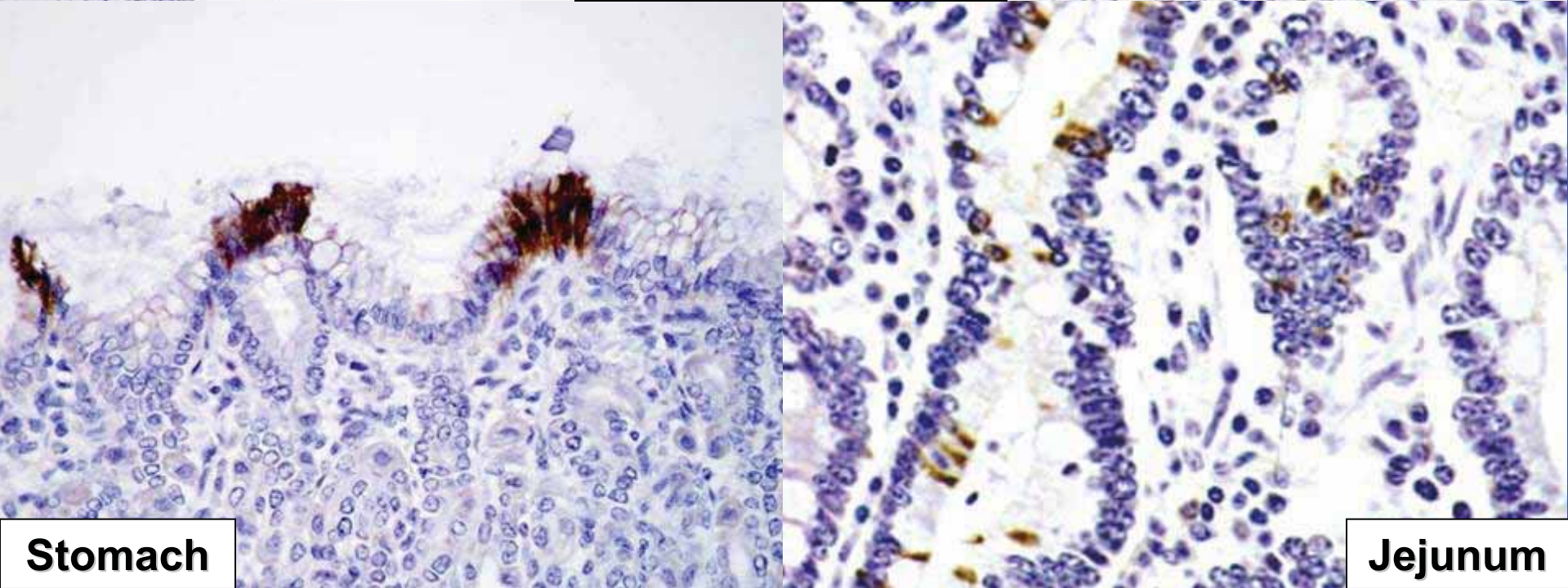
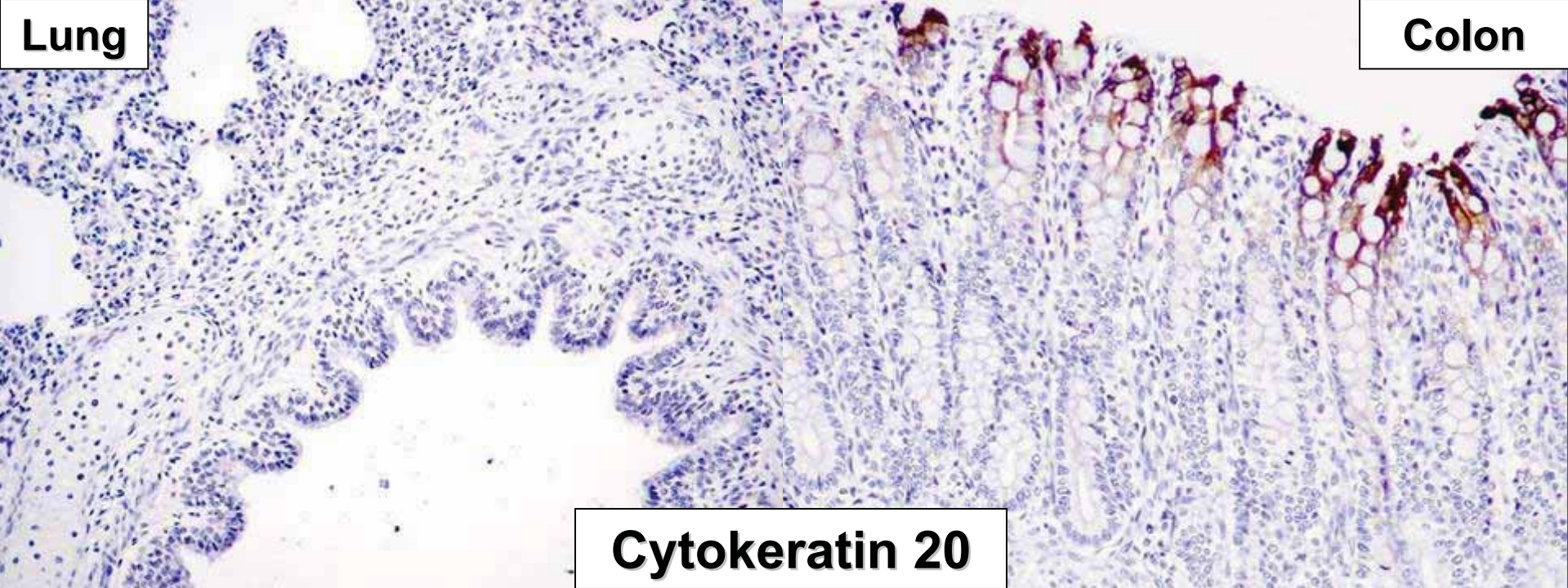


Colon

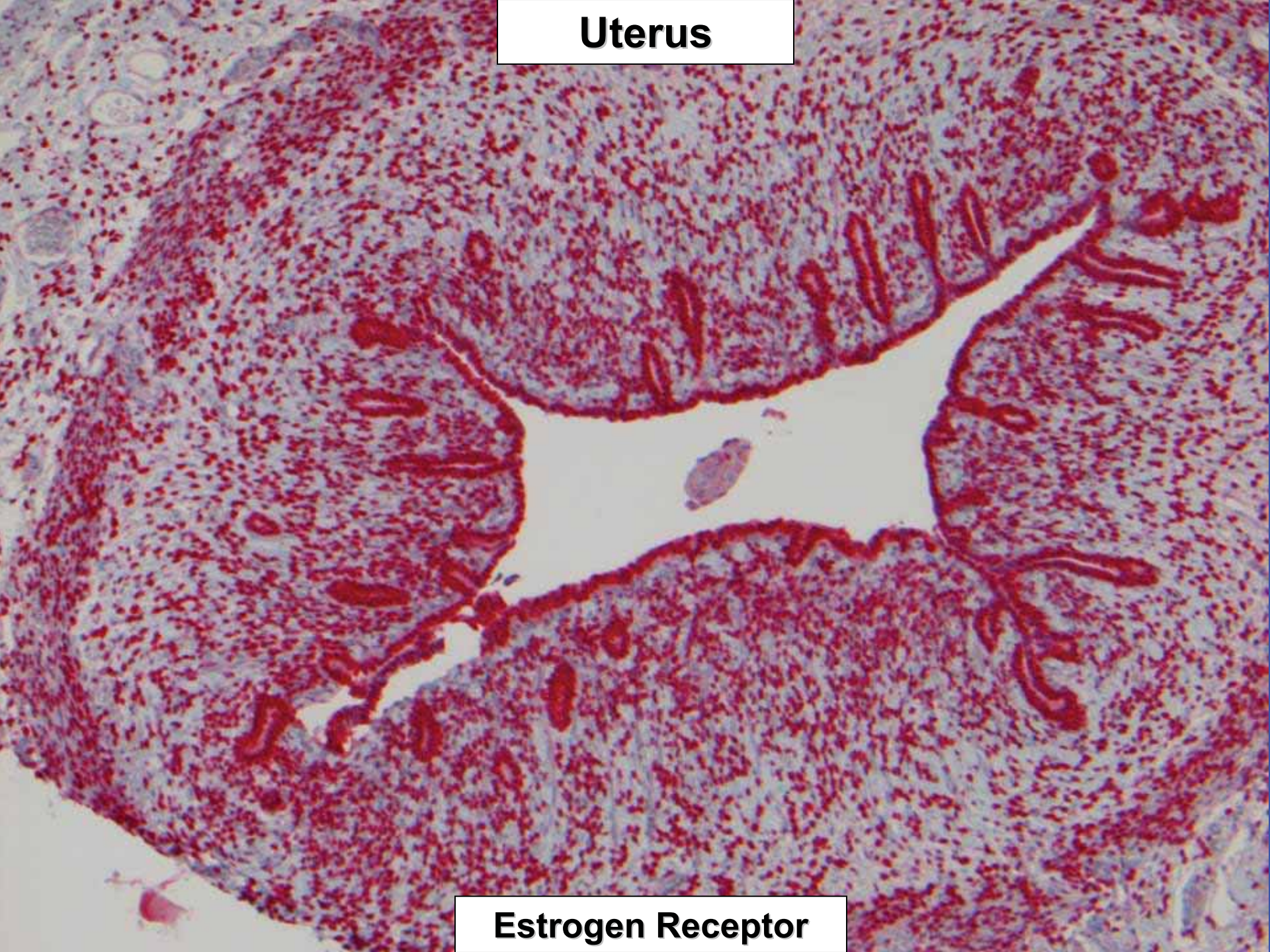
Cytokeratin 20



- Clone Ks20.8 recognizes a 46 kD keratin of acidic keratin family
- Restricted expression in tissues
- Used to identify simple epithelia
- **Normal tissue:**
 - apical intestinal and gastric epithelium
 - endocrine cells in pylorus
 - urothelium,
 - **does not stain respiratory epithelia**
- **Neoplasms:**
 - adenocarcinomas of intestinal tract
 - transitional cell carcinoma
 - **negative for respiratory tract carcinomas**

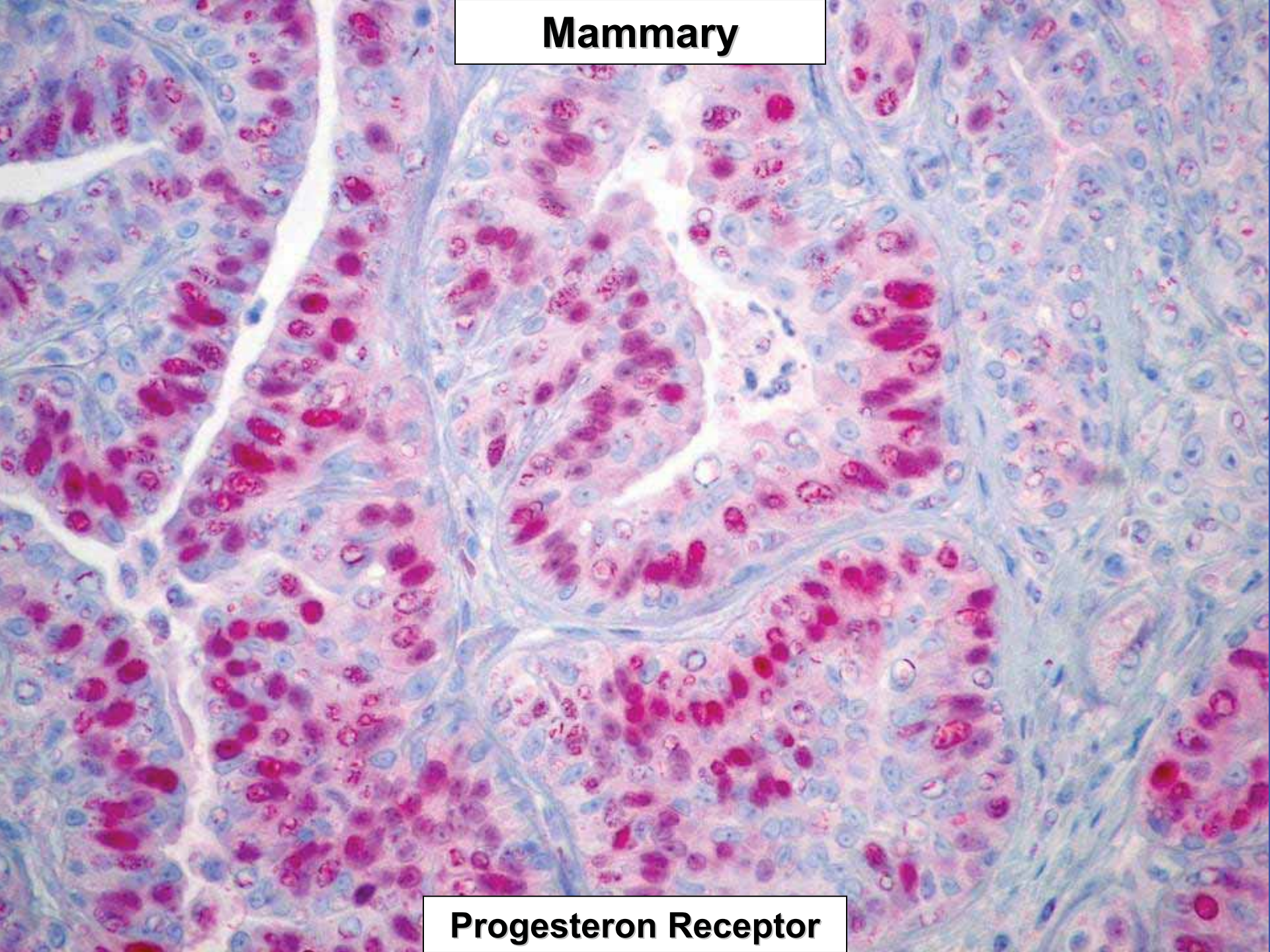


Uterus



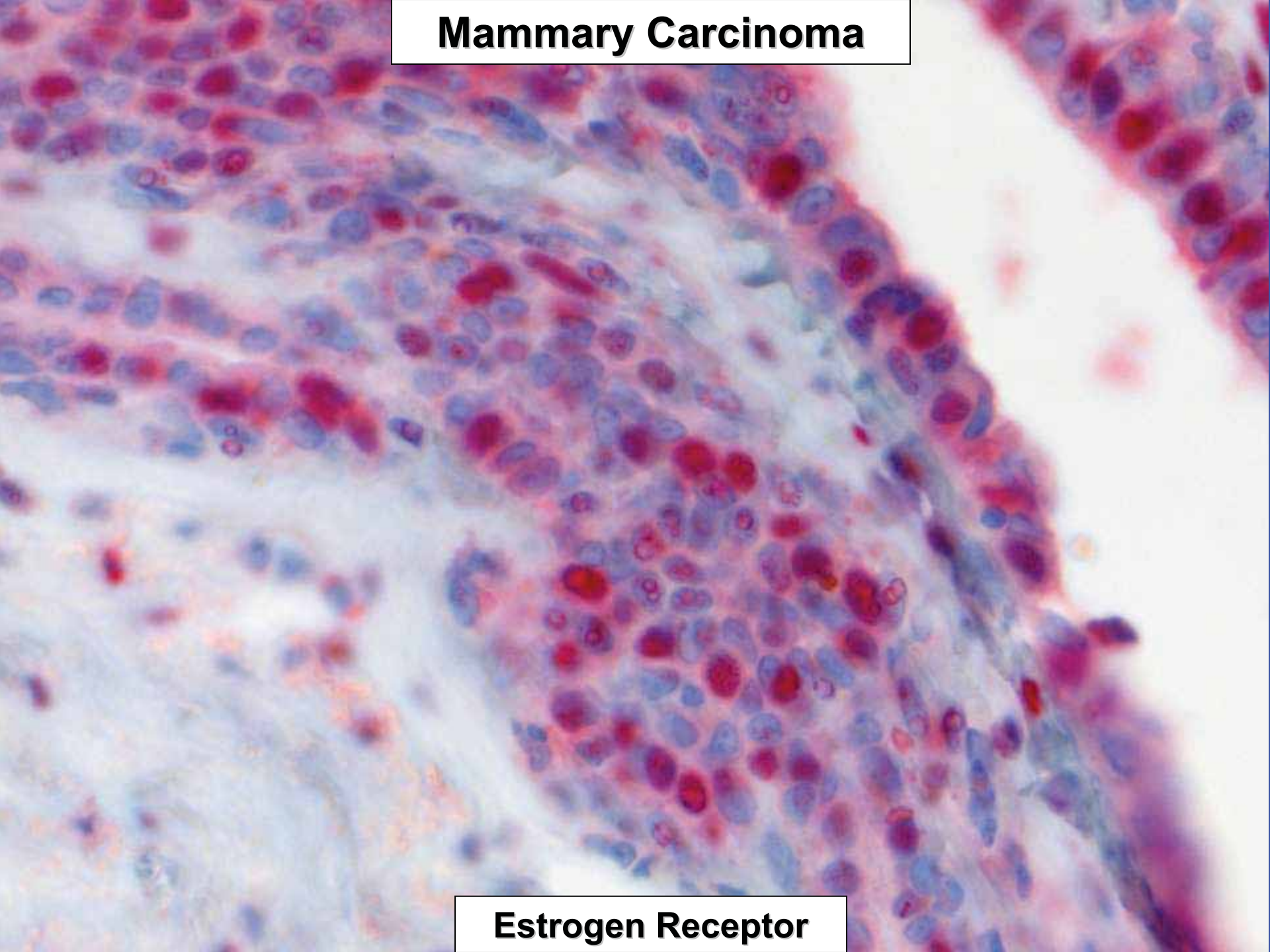
Estrogen Receptor

Mammary



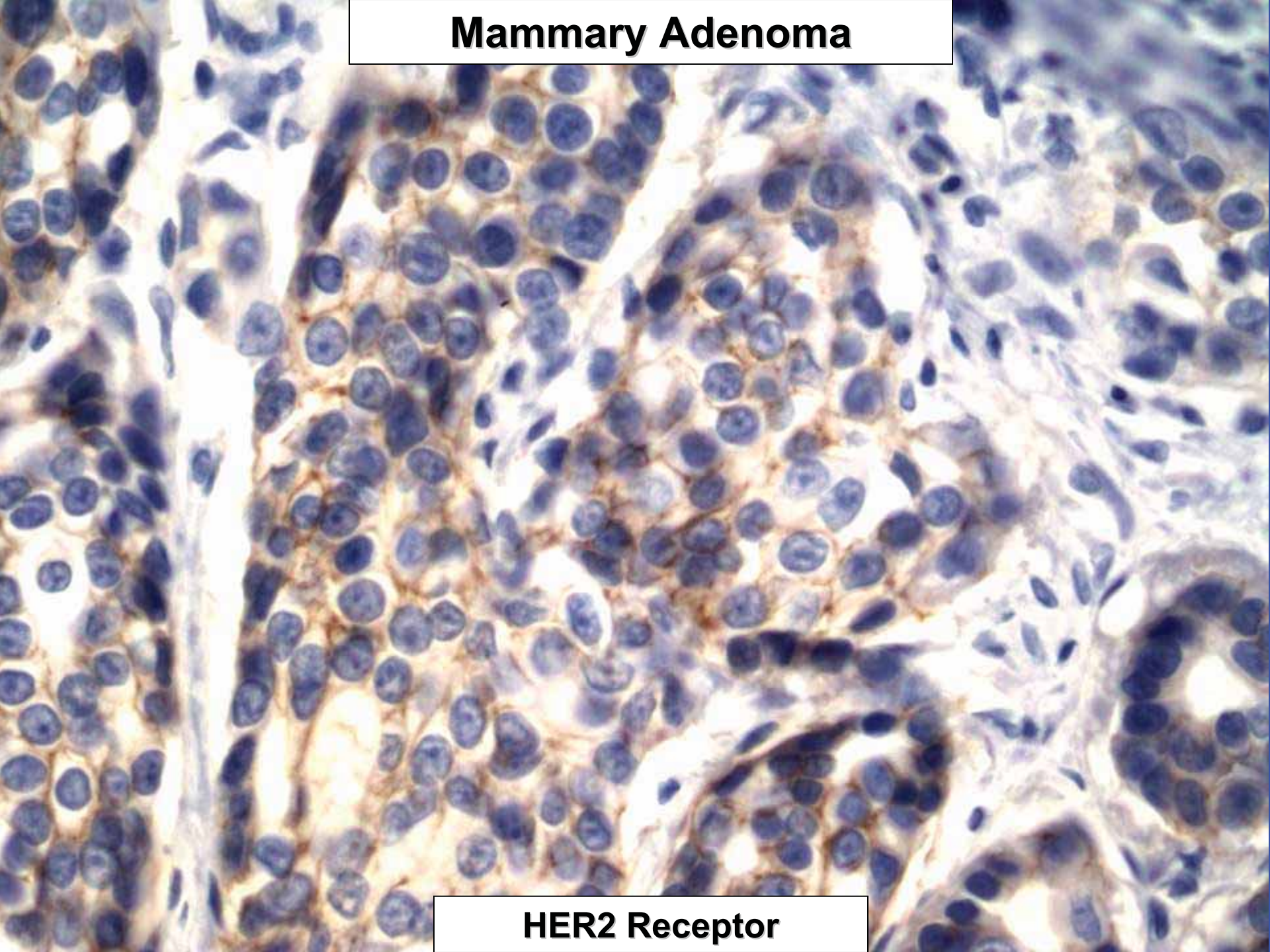
Progesteron Receptor

Mammary Carcinoma



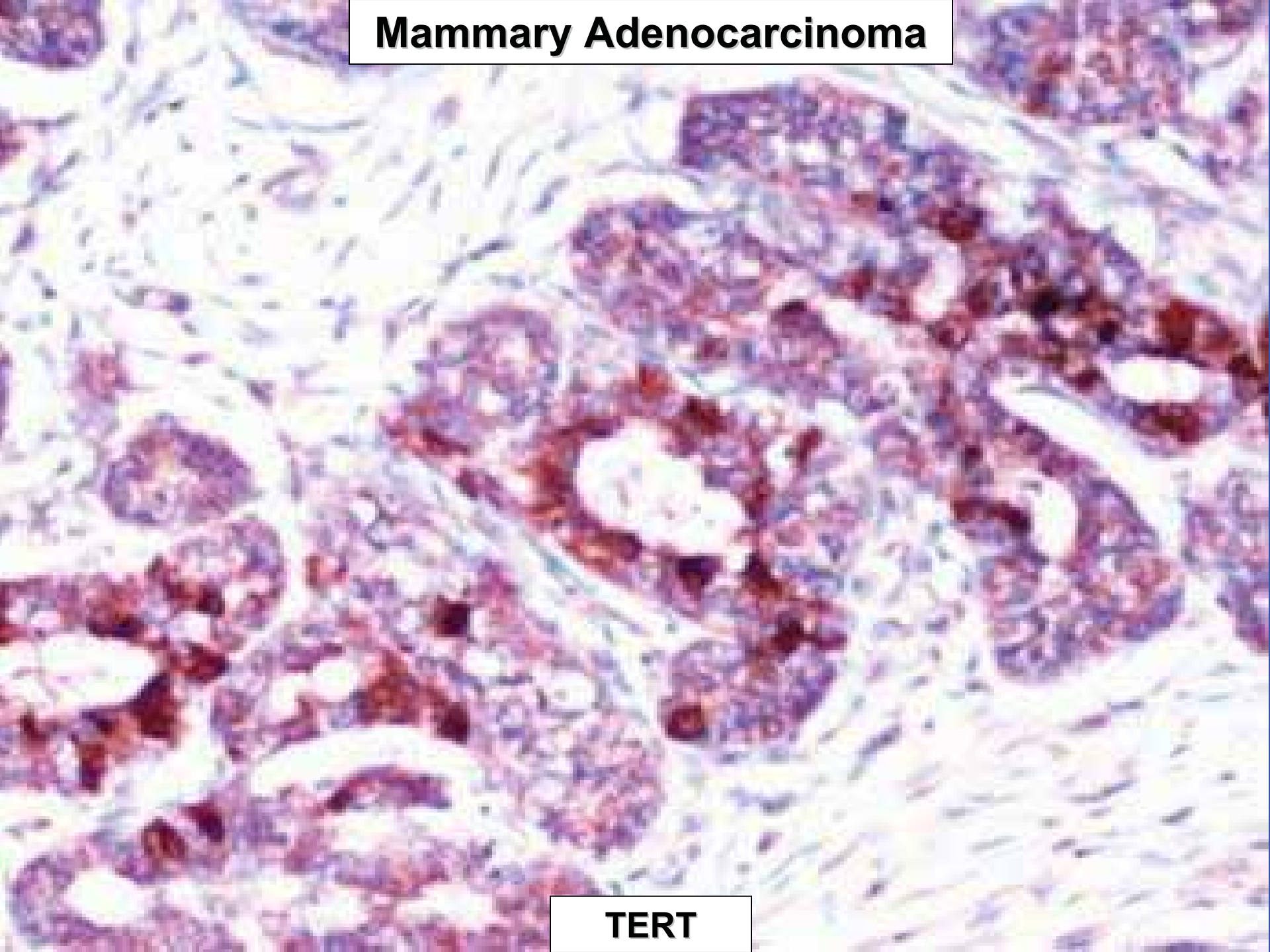
Estrogen Receptor

Mammary Adenoma



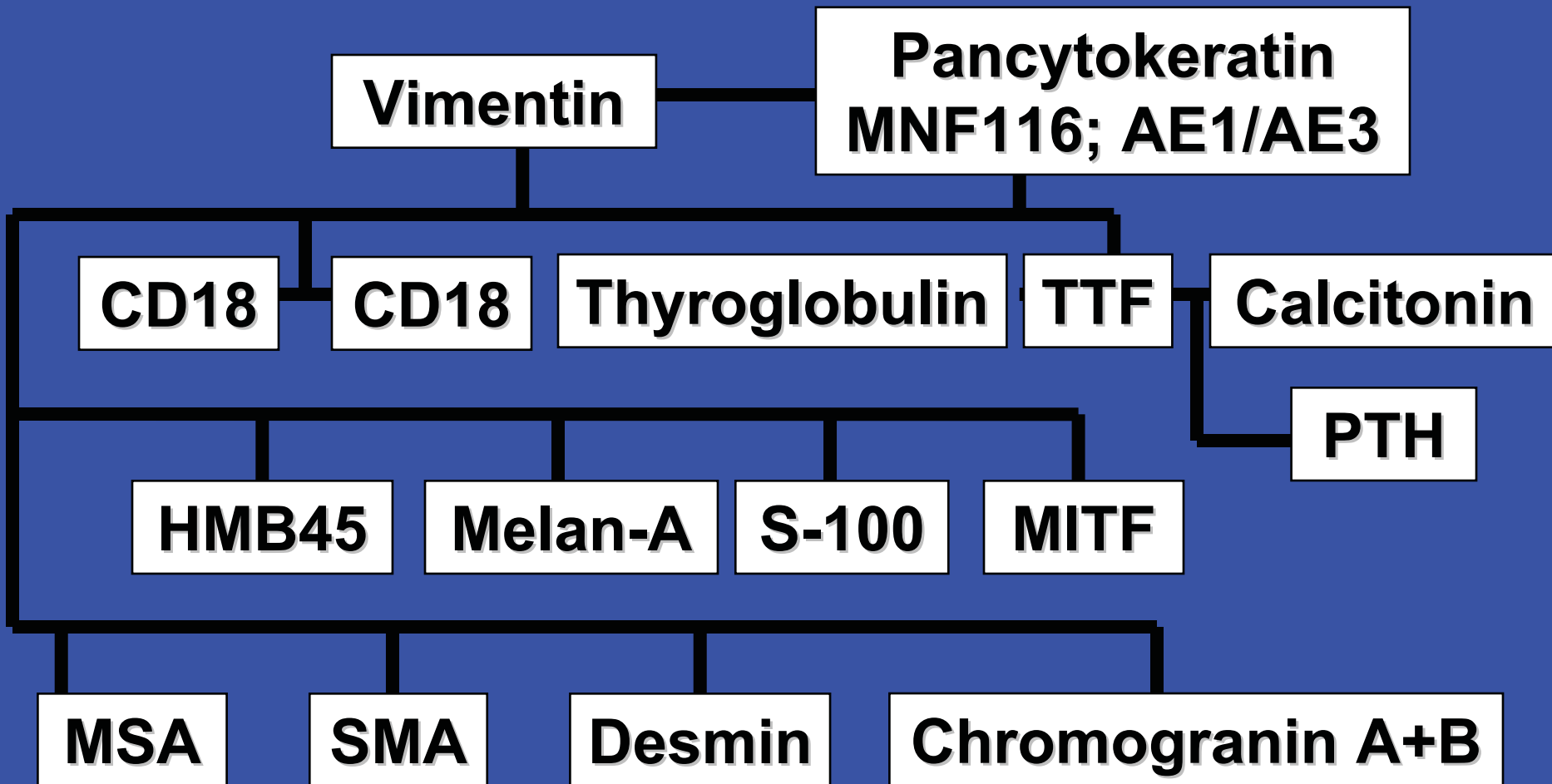
HER2 Receptor

Mammary Adenocarcinoma



TERT

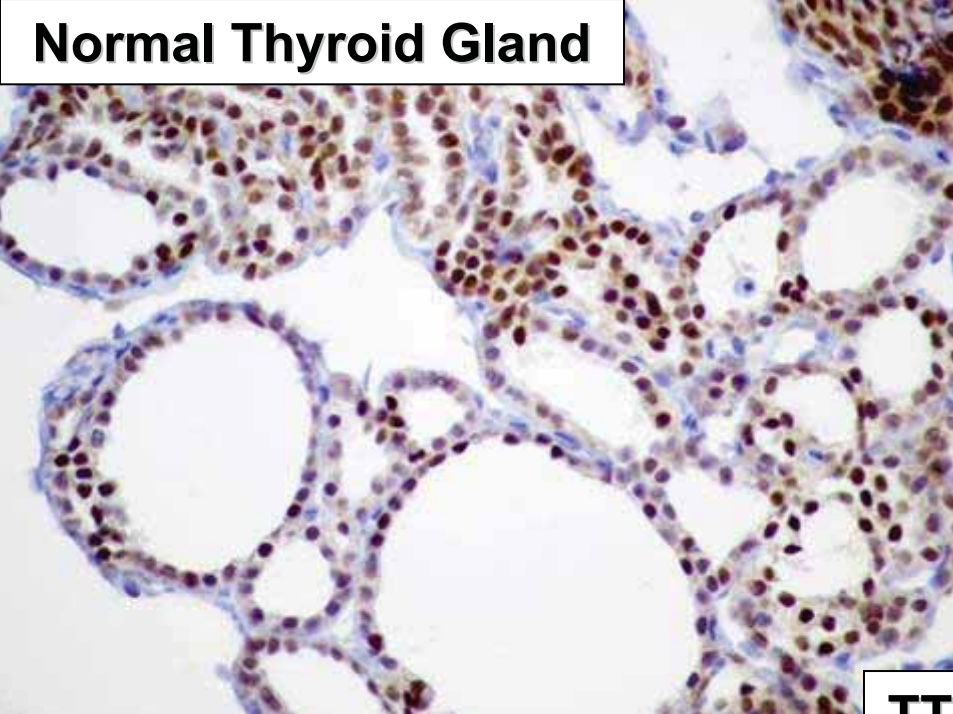
Tumors of the Neck



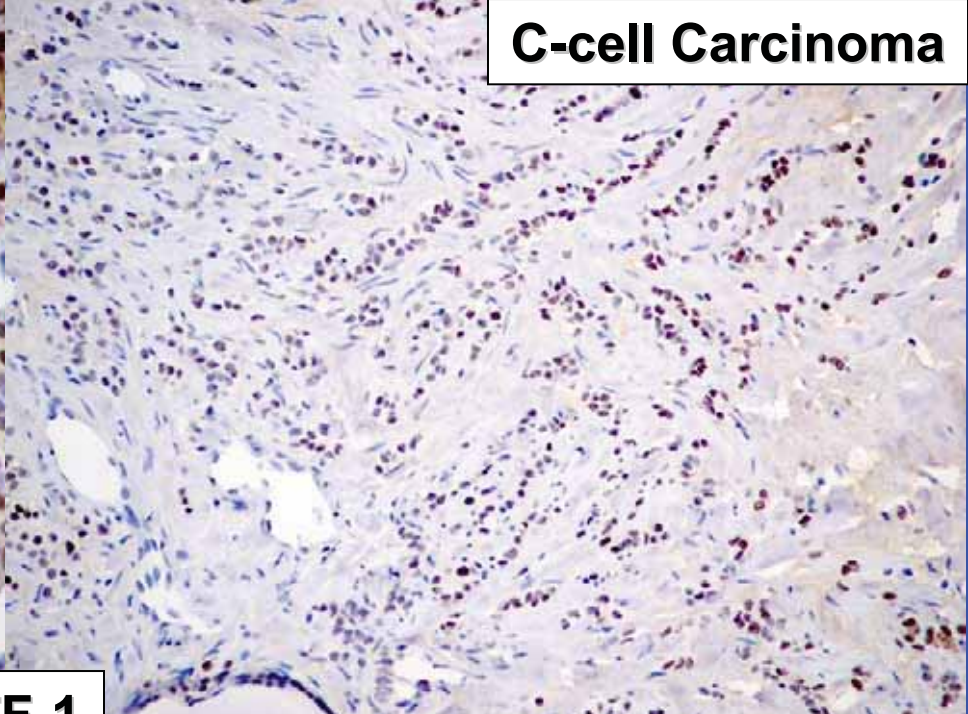
Thyroid Transcription Factor - 1 (TTF-1)

- Thyroid-specific enhancer-binding protein (NKX-2.1), NKX-2 gene family are homeodomain-containing transcription nuclear factors
- **Detected in brain, thyroid and lung during early embryogenesis, lungs and thyroid after birth**
- **In lungs: activates surfactant protein and Clara cell secretory product gene promoters**
- **In thyroid: activates thyroglobulin, thyroperoxidase, TSH receptor, thyroid peroxidase, MHC I, thyroid Na^+/I^- symporter genes transcription**
- **Detected in nuclei of normal, hyperplastic and neoplastic thyroid cells (follicular and papillary carcinomas), normal, hyperplastic and neoplastic C-cells and pulmonary carcinoma of dogs**

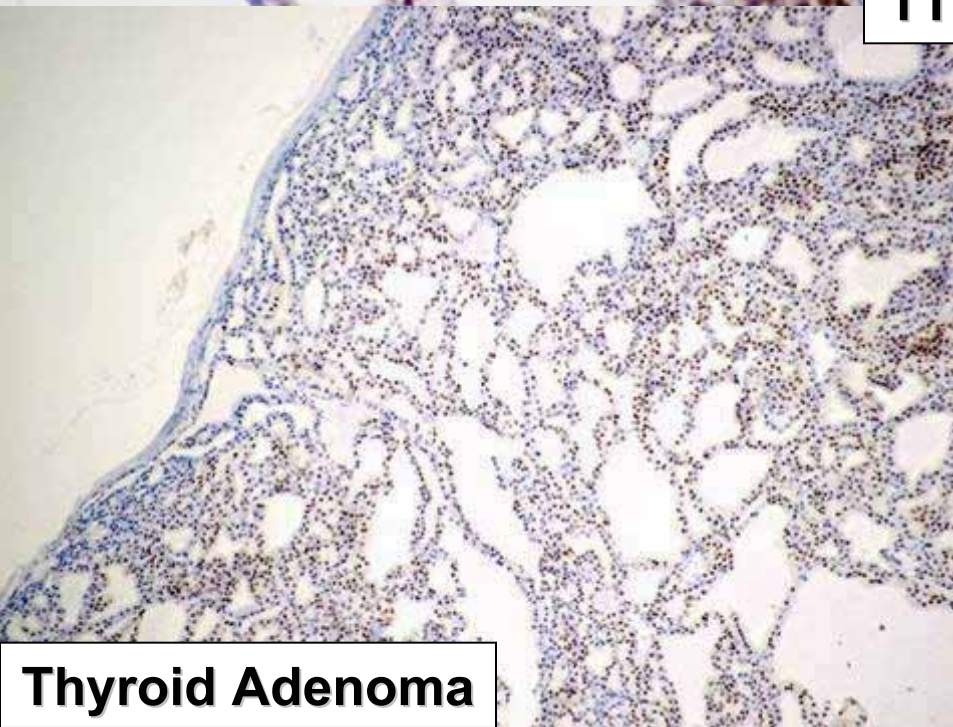
Normal Thyroid Gland



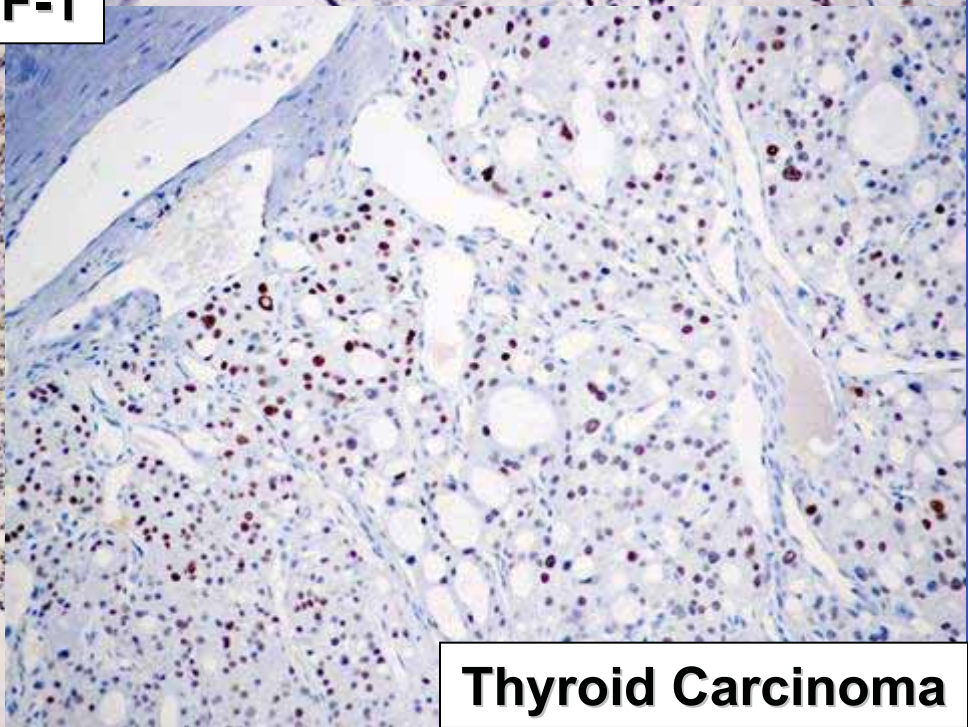
C-cell Carcinoma



TTF-1



Thyroid Adenoma



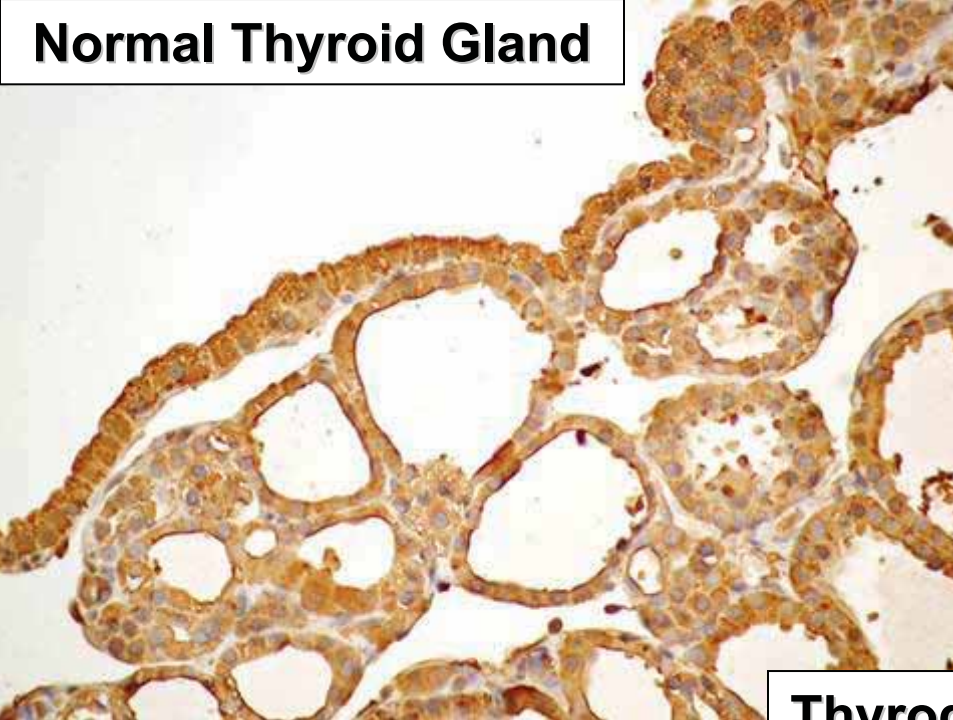
Thyroid Carcinoma

Thyroglobulin

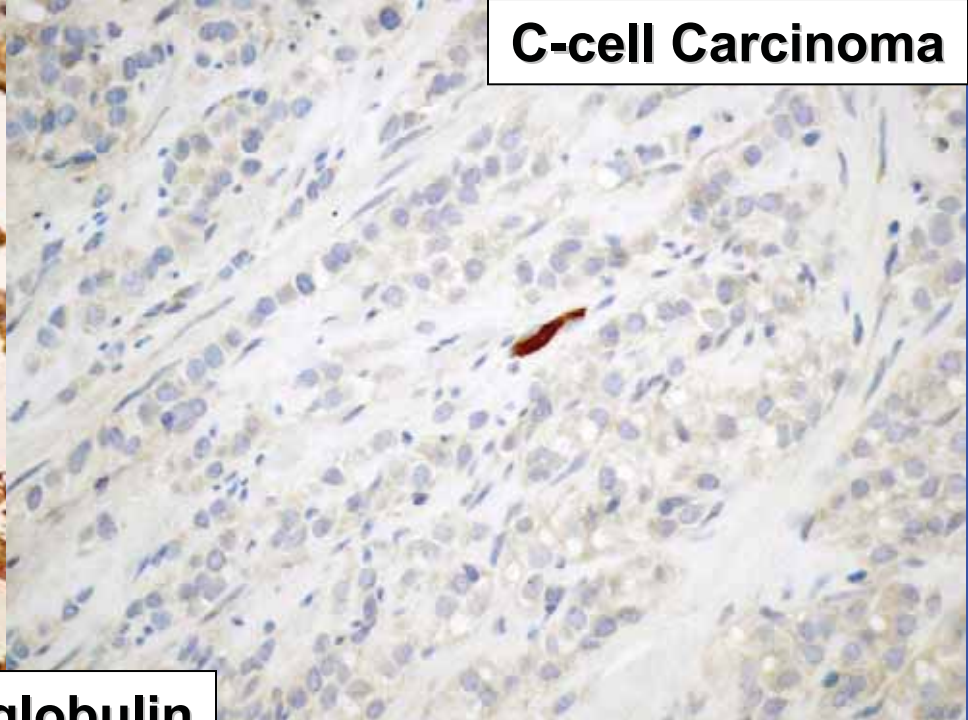


- Epithelial cells from thyroid follicles have strong granular cytoplasmic staining
- Occasional colloid is also strongly positive
- Diffusion of thyroglobulin into follicles – specific background
- C-cells are negative
- Normal (nonimmune) rabbit serum reacts strongly with thyroid follicular epithelium in a similar fashion than immune serum following treatment with proteinase K or steamer
- No staining when sections are not pre-treated

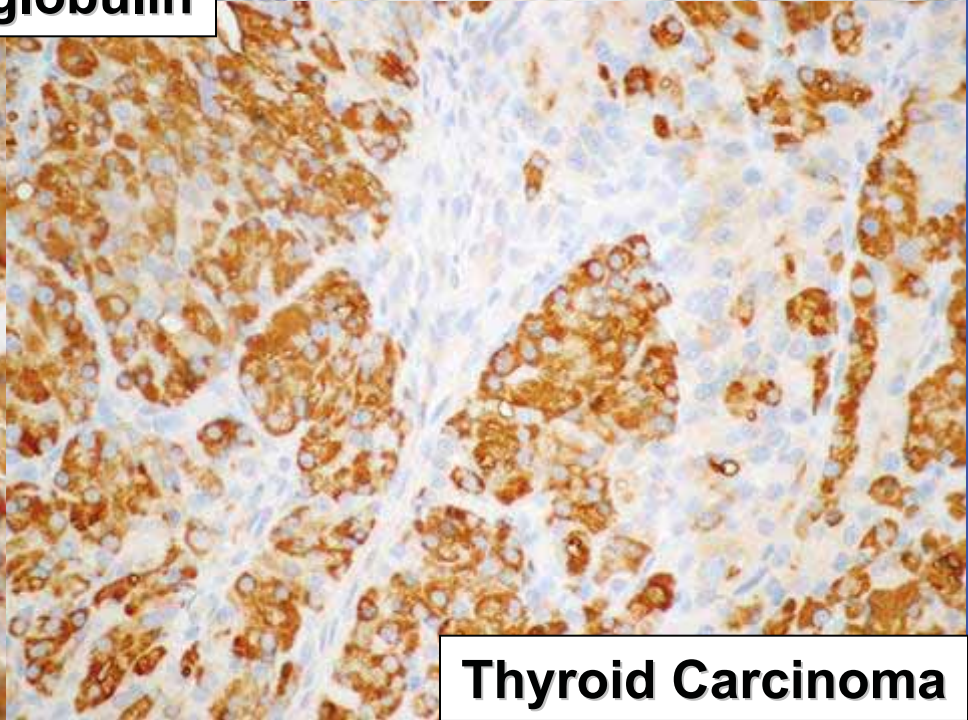
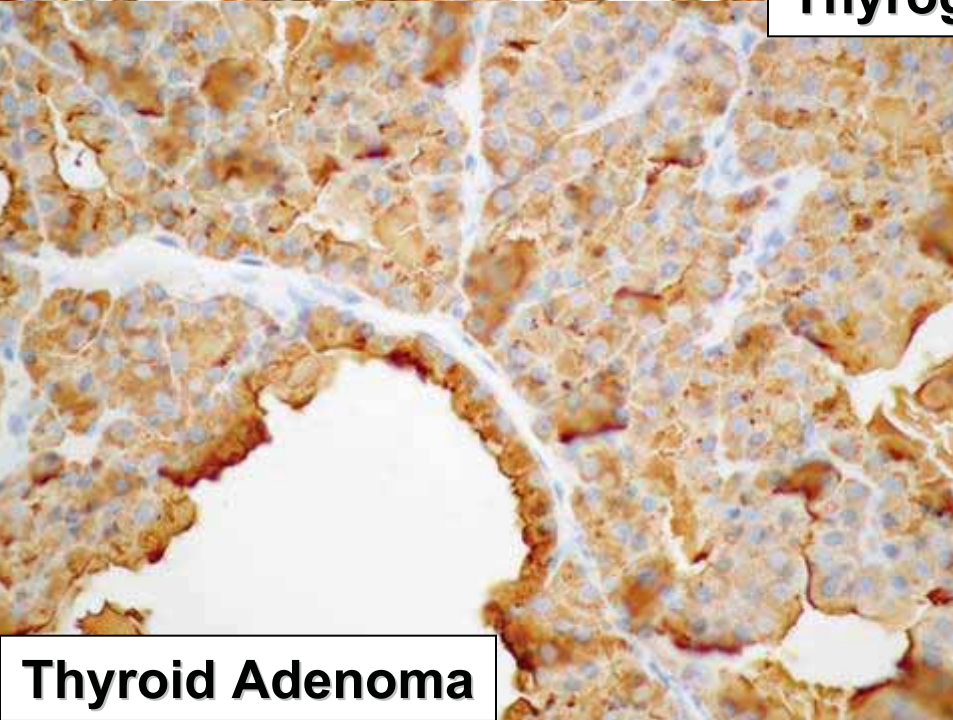
Normal Thyroid Gland



C-cell Carcinoma



Thyroglobulin



Thyroid Adenoma

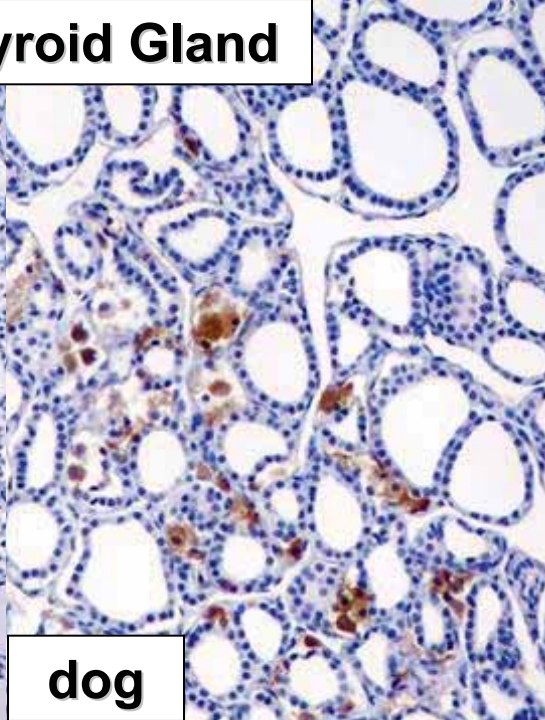
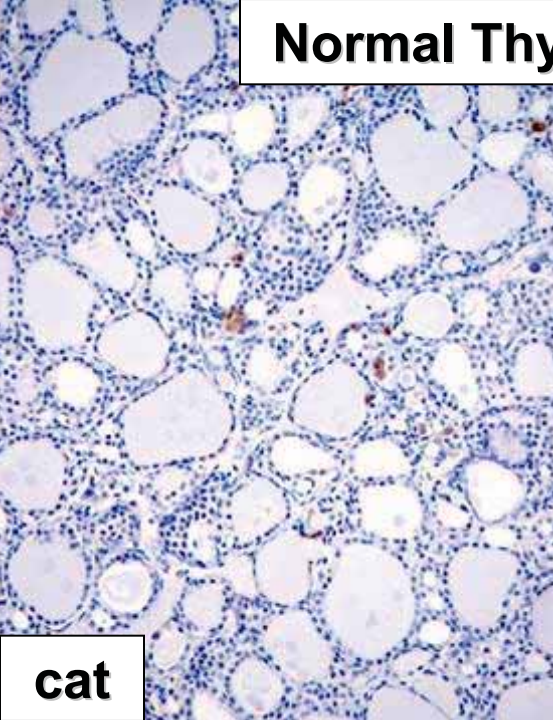
Thyroid Carcinoma

Calcitonin

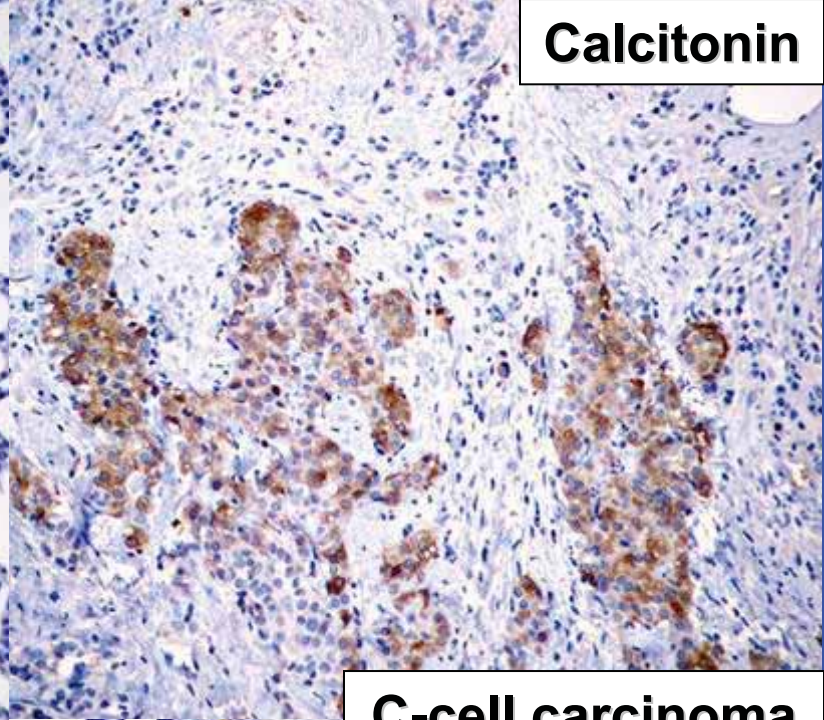


- 32 amino acid peptide
- Used to identify C-cells in thyroid
- **Normal tissue:** - C-cells of normal and hyperplastic thyroid
- **Neoplasms:** - C-cell neoplasms
 - useful for thyroid follicular carcinomas

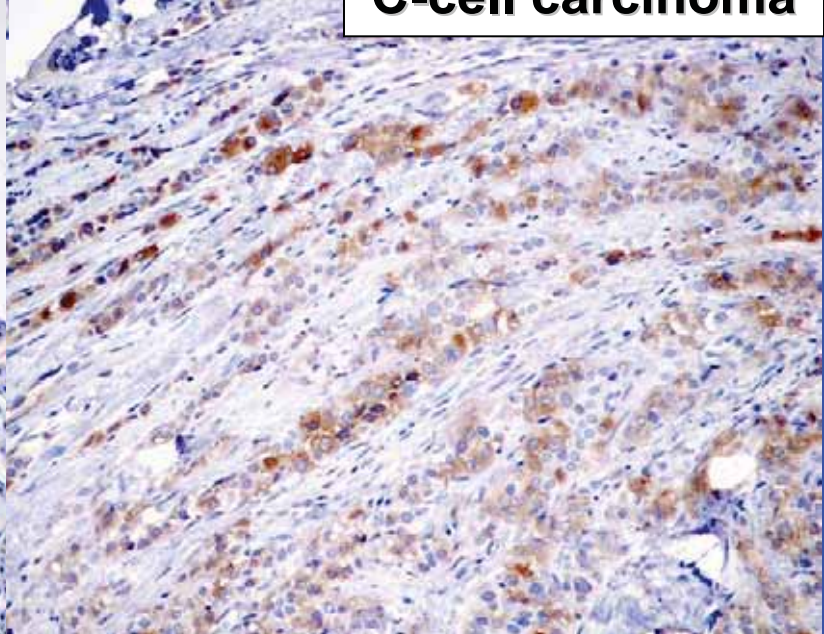
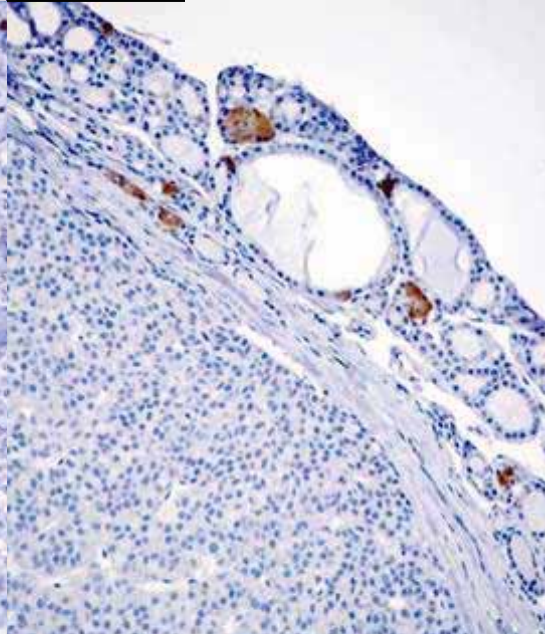
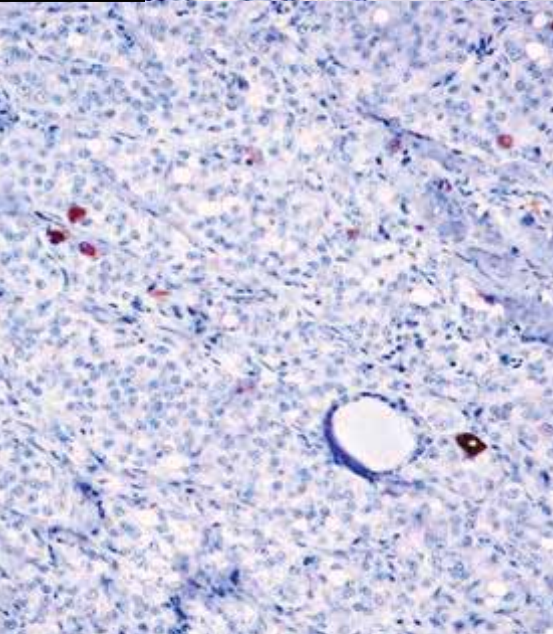
Normal Thyroid Gland



Calcitonin

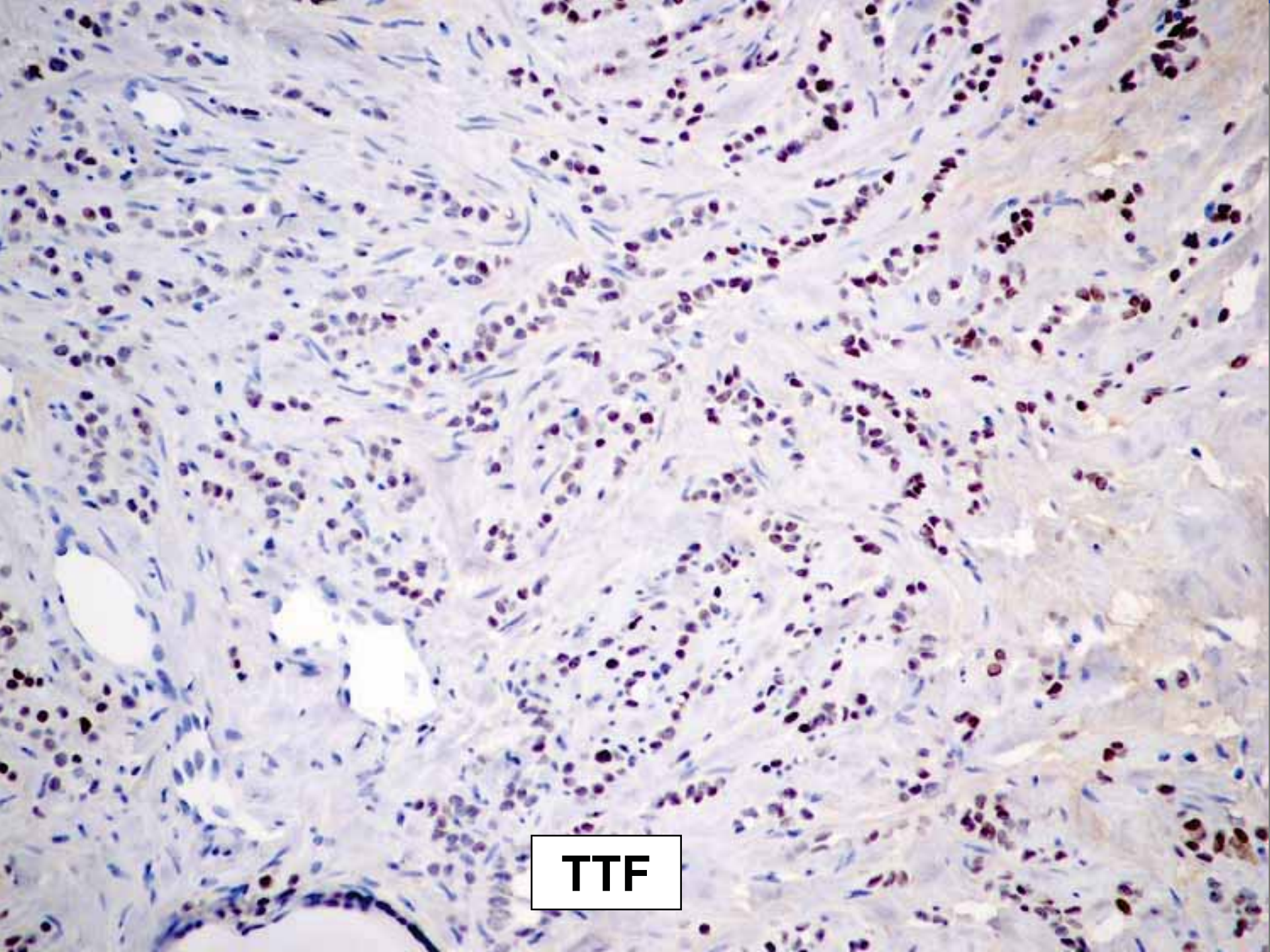


C-cell carcinoma

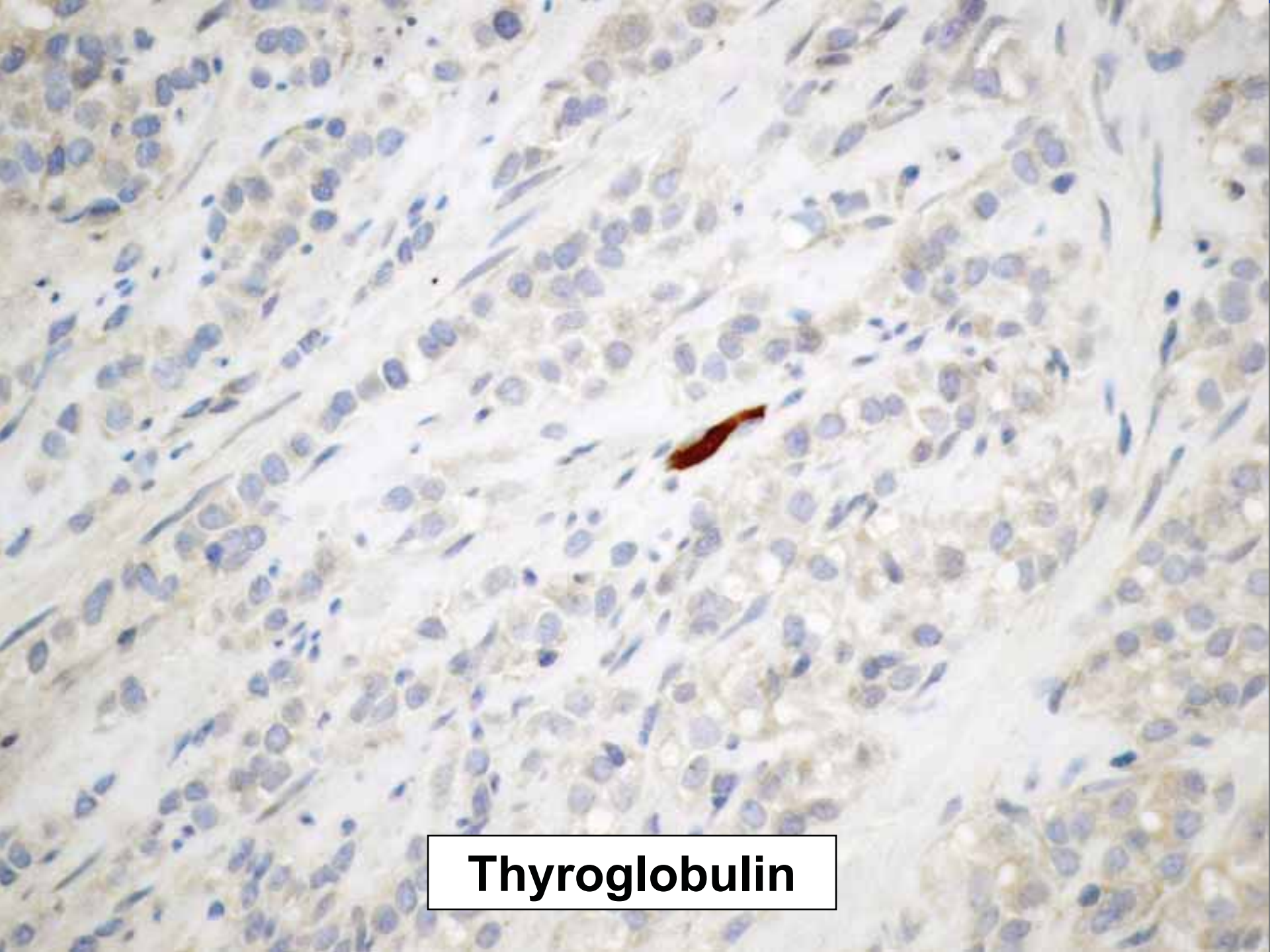


Mass in the Neck

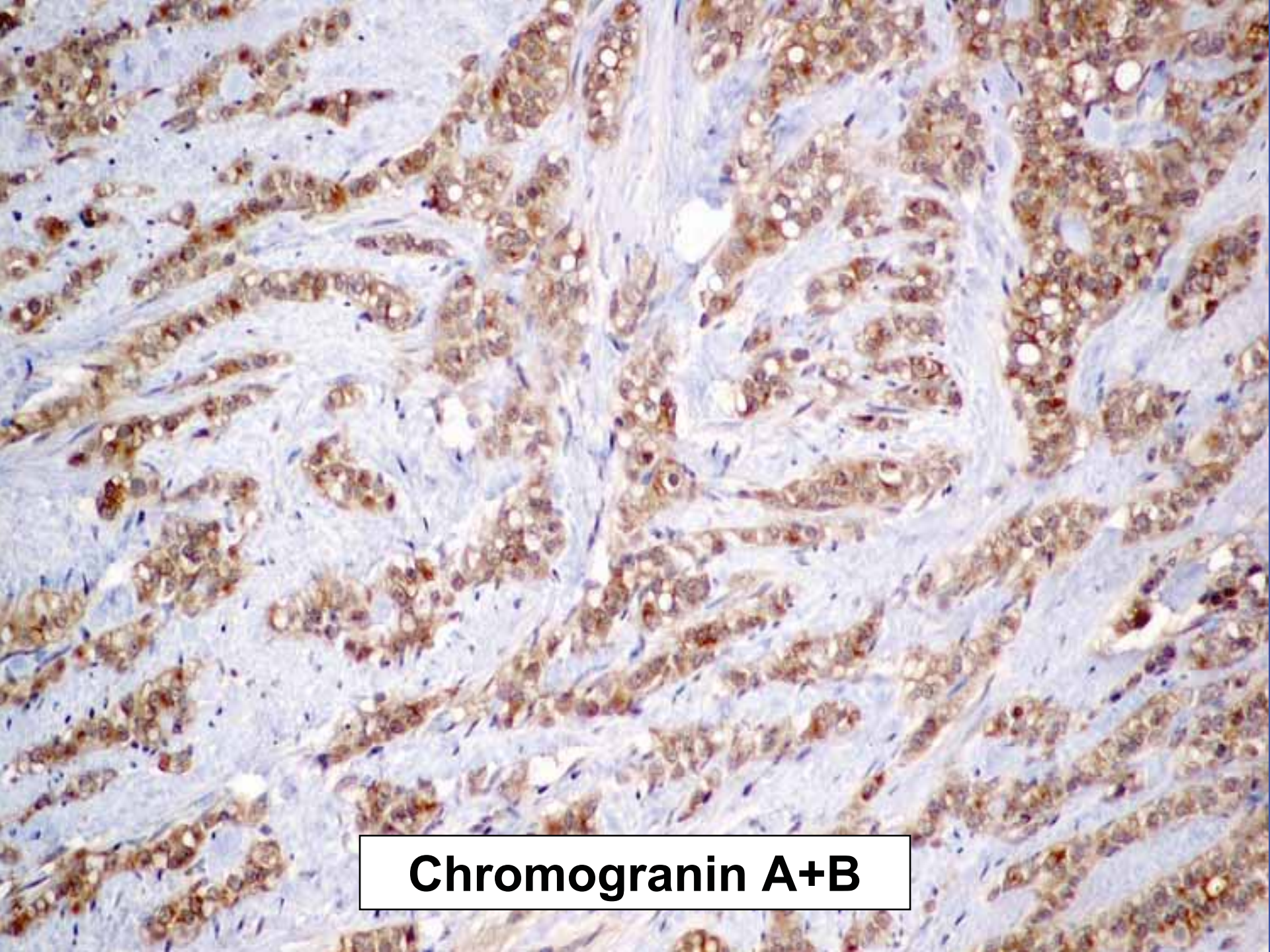




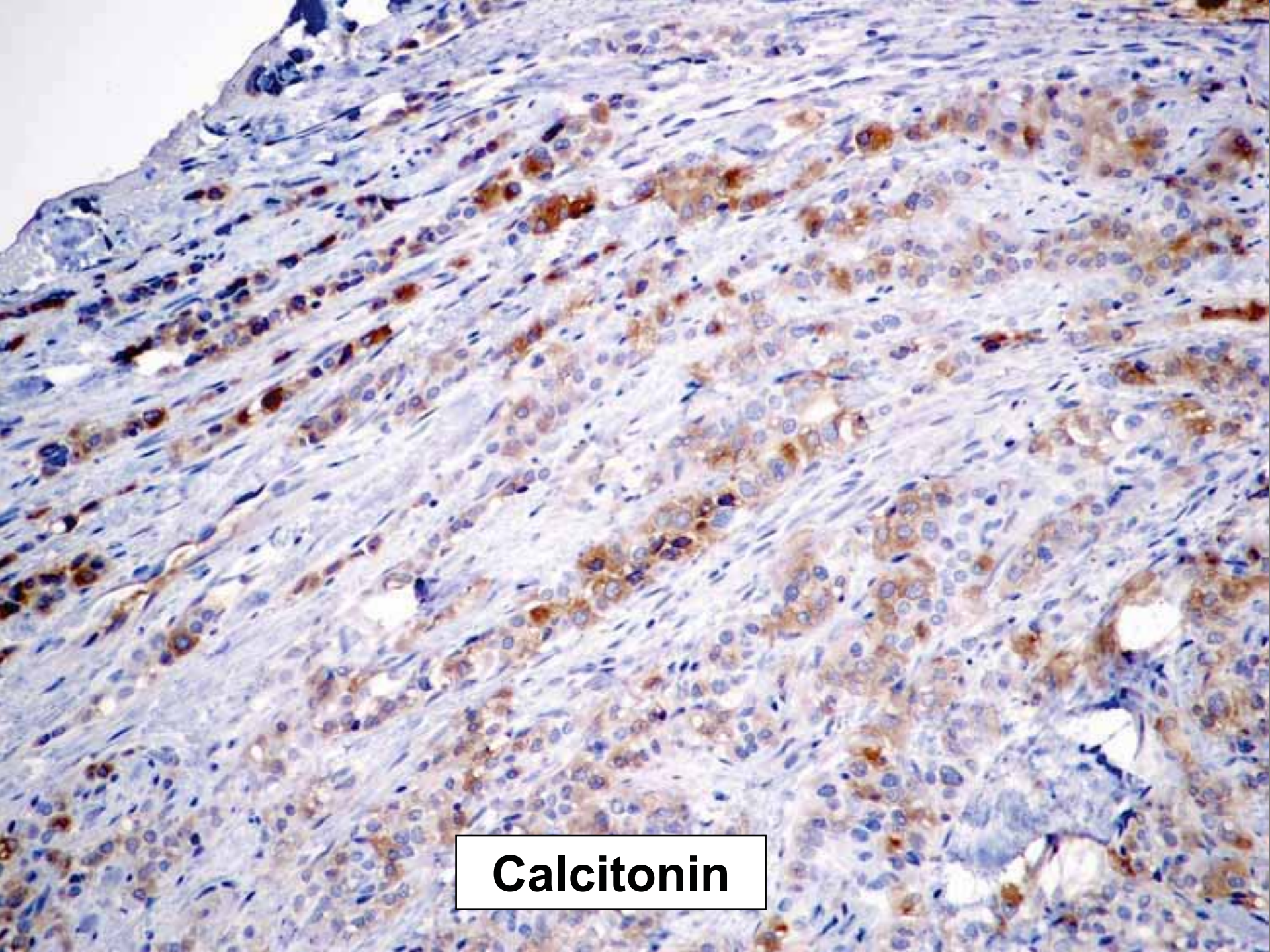
TTF



Thyroglobulin



Chromogranin A+B



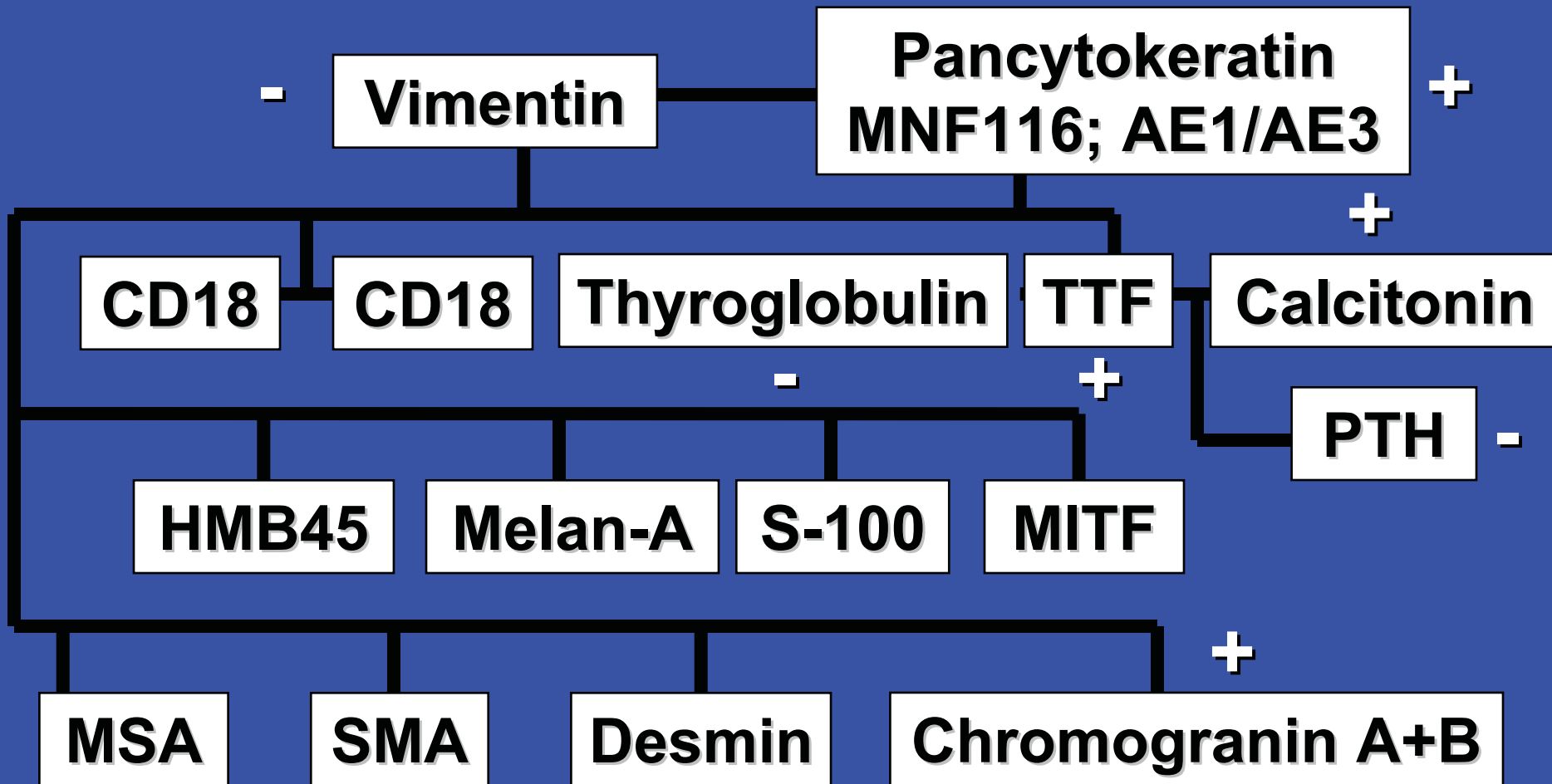
Calcitonin

A fluffy dog and three cats are sitting on a windowsill. The dog is on the left, looking happy with its tongue out. The three cats are on the right, looking serious. A thought bubble above the dog contains the text "I think there's a spy among us...".

I think there's a
spy among us...

What's your Diagnosis

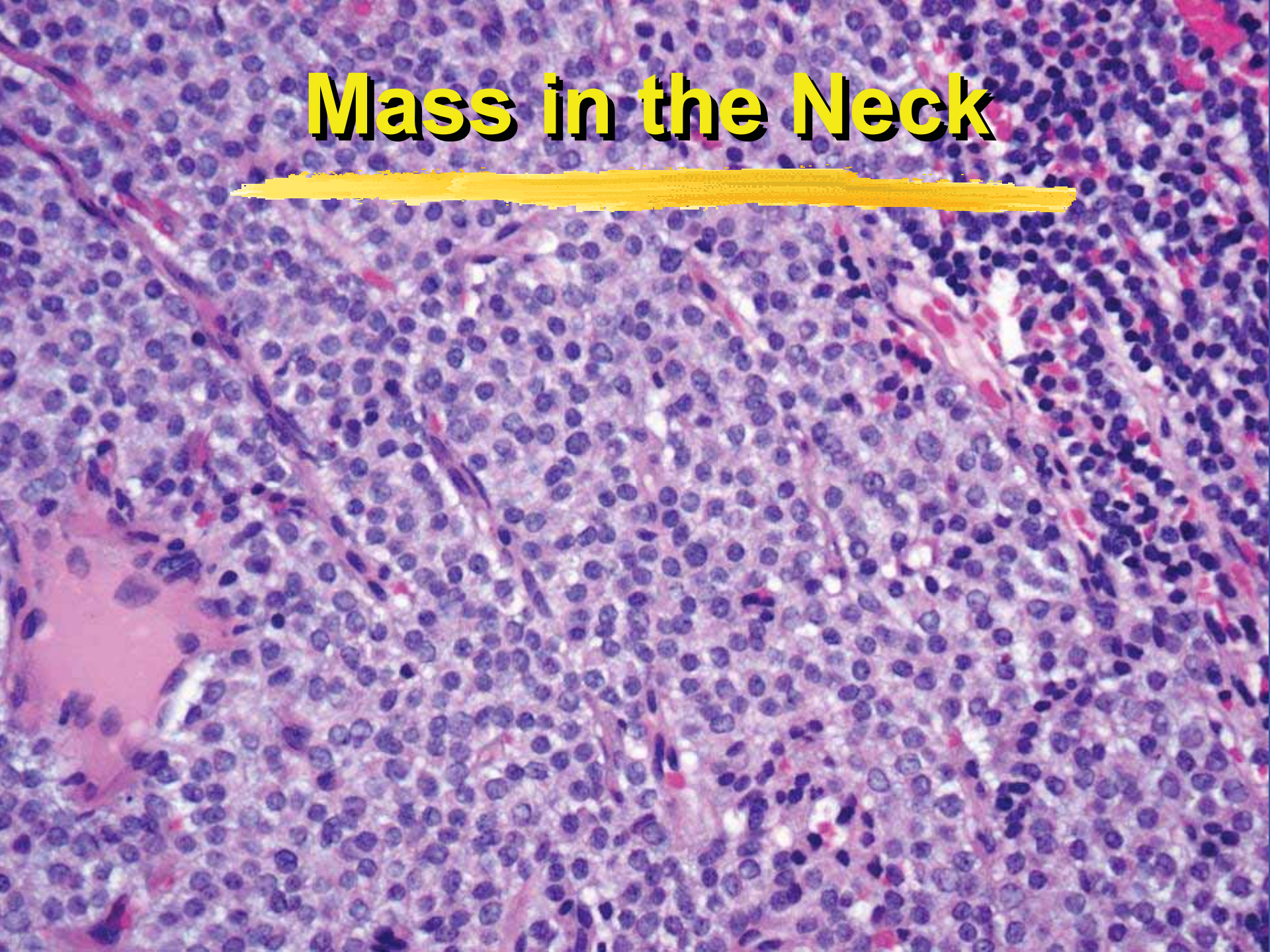
C-Cell Carcinoma

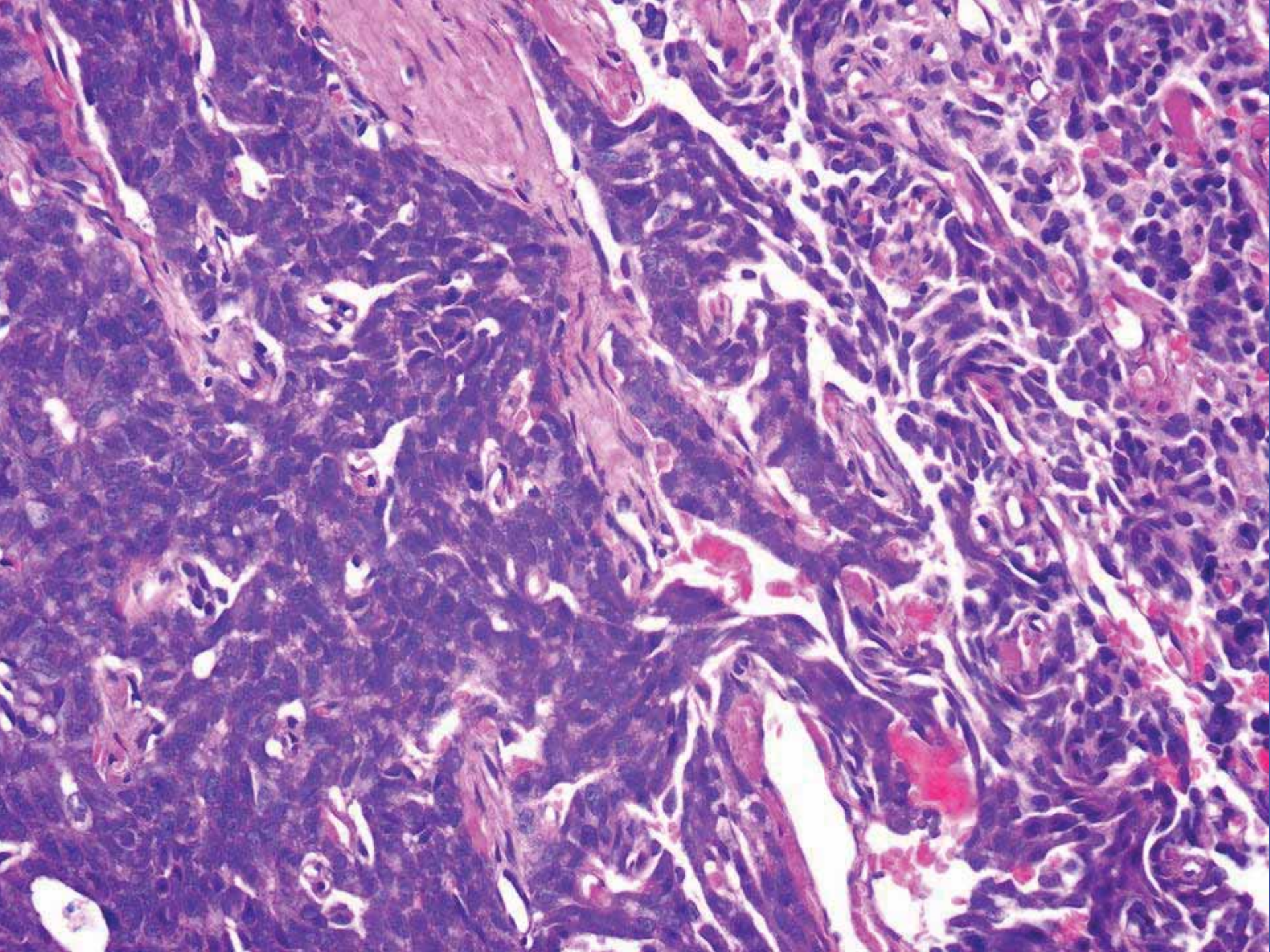


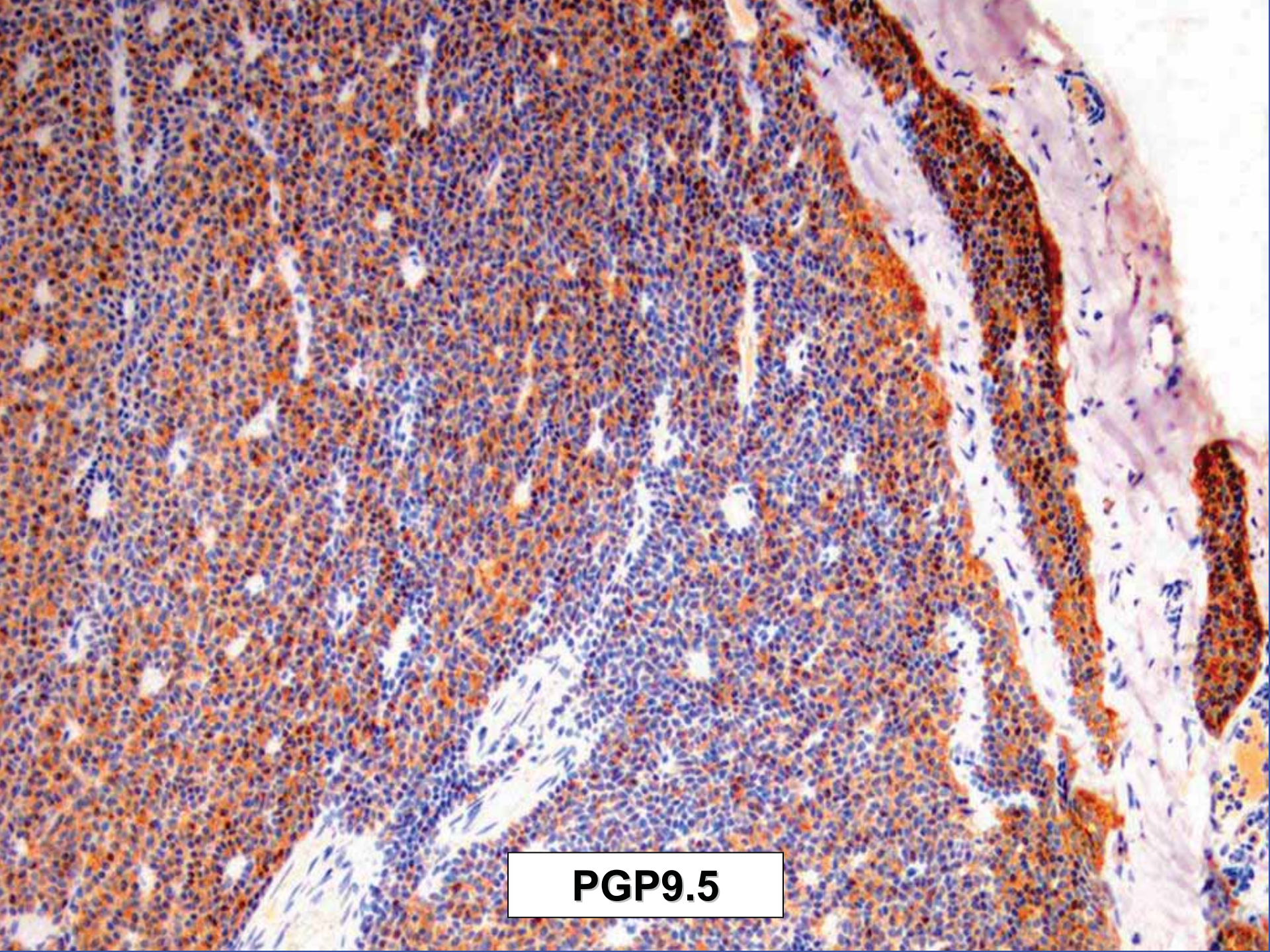
Thyroid Tumors

- TTF-1 is expressed in most thyroid neoplasms:
 - **C-cell, papillary, follicular, rarely anaplastic**
- Thyroglobulin is expressed in most papillary and follicular neoplasms, but not in C-cells
 - **less differentiated carcinomas stain poorly**
- Cytokeratins (CK 7, 8, 18, 19) and vimentin, but not CEA are expressed in most papillary and follicular neoplasms
- T3, T4, TPO expressed in differentiated thyroid tumors
- Calcitonin is expressed in most C-cell neoplasms
 - **staining not exclusive for C-cells**
- Most C-cells neoplasms stain with CEA, generic neuroendocrine markers:
 - **somatostatin, serotonin**
 - **synapthophysin, PGP 9.5**
 - **chromogranin, NSE, etc.**

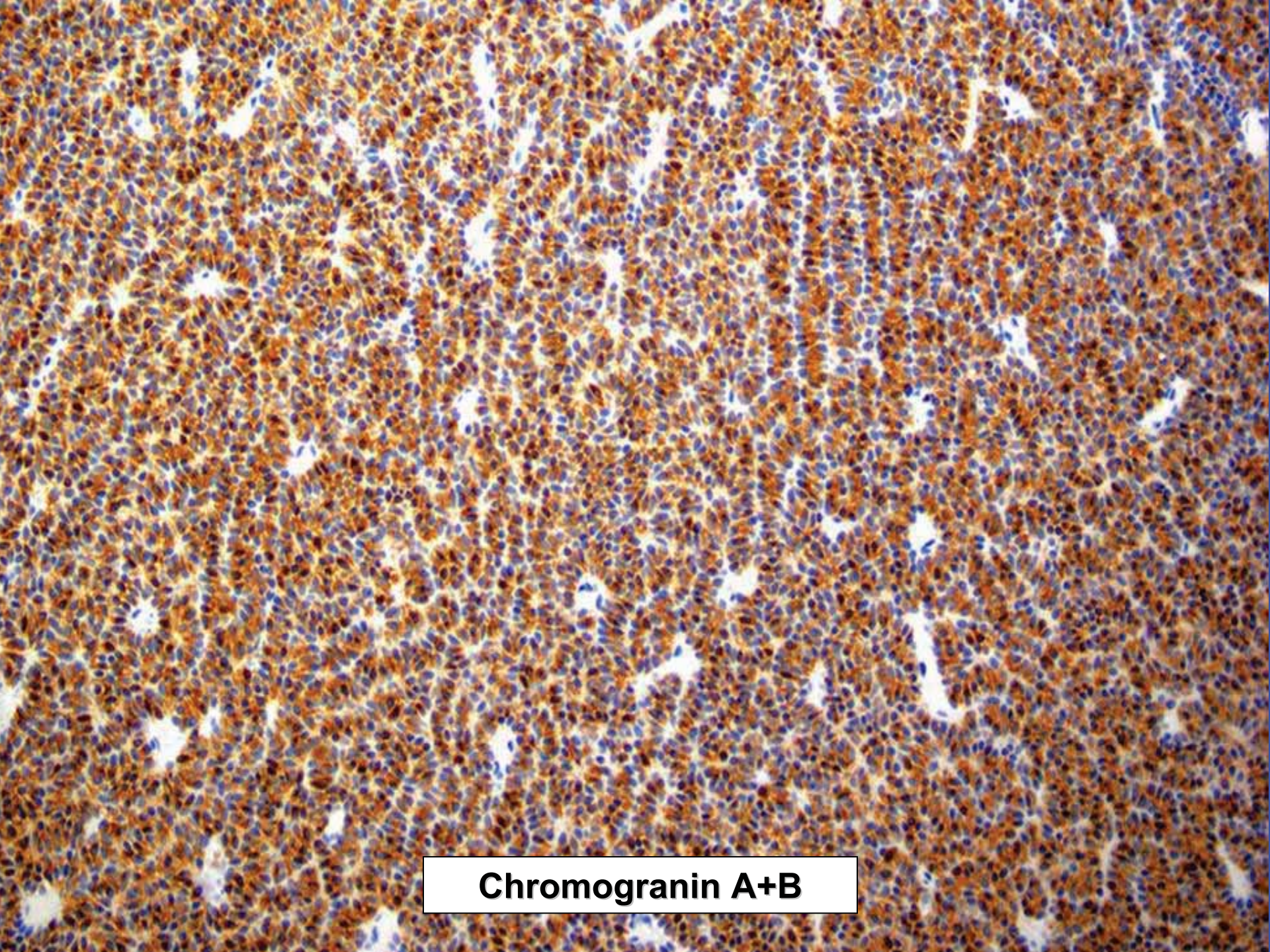
Mass in the Neck



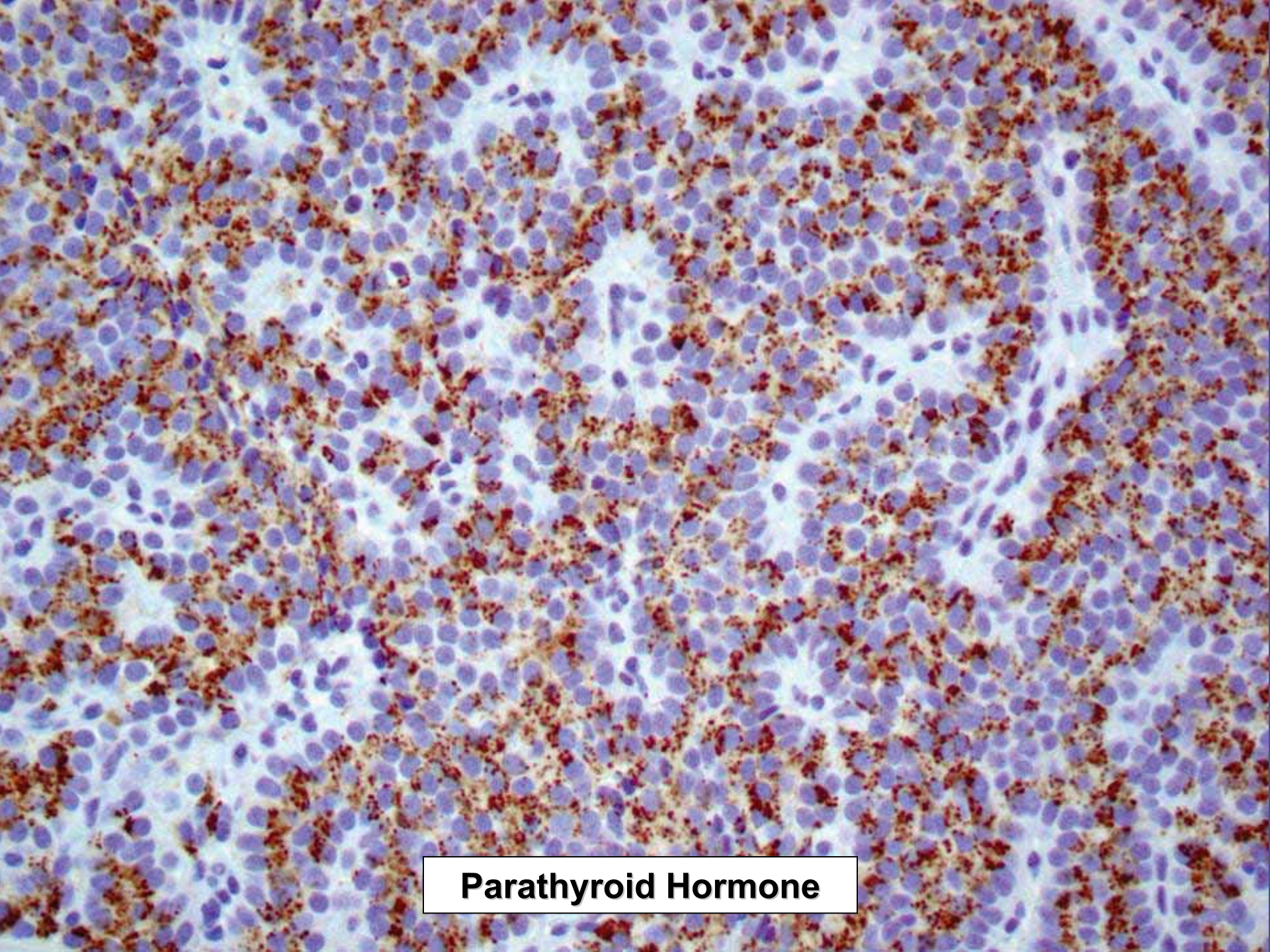




PGP9.5



Chromogranin A+B

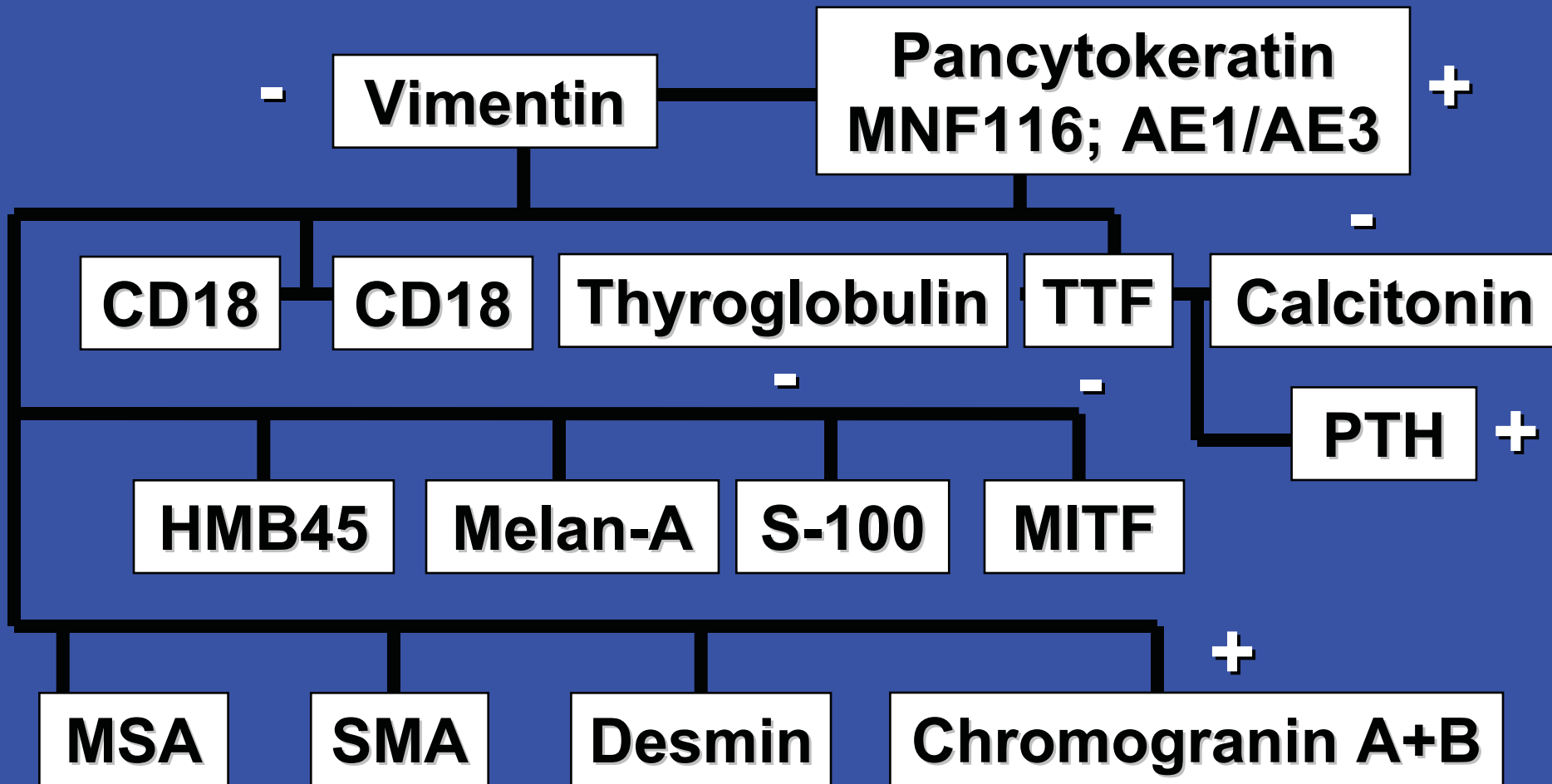


Parathyroid Hormone



**What's
your Diagnosis**

Parathyroid Carcinoma

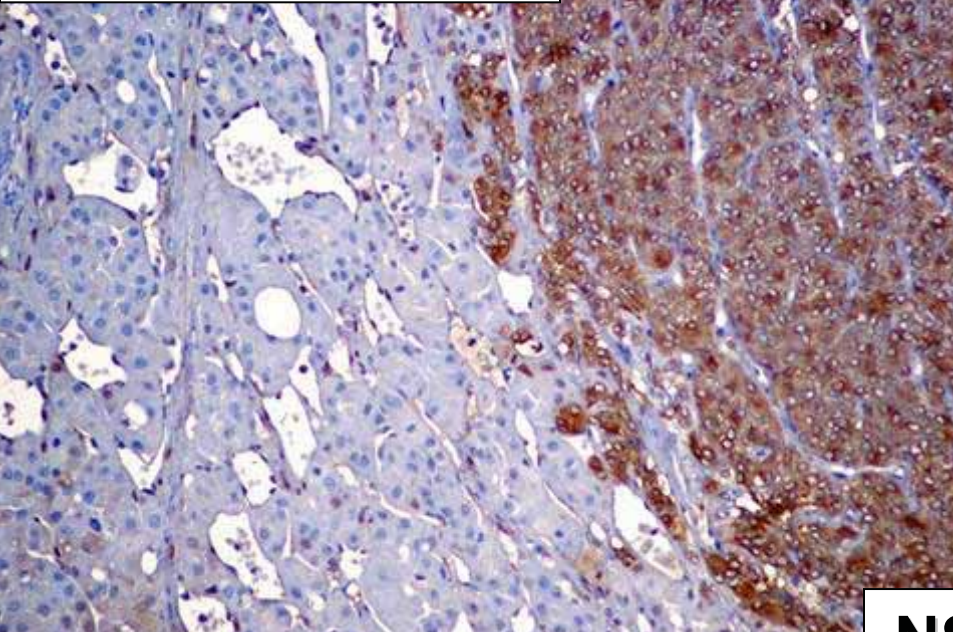


Neuron Specific Enolase (NSE)

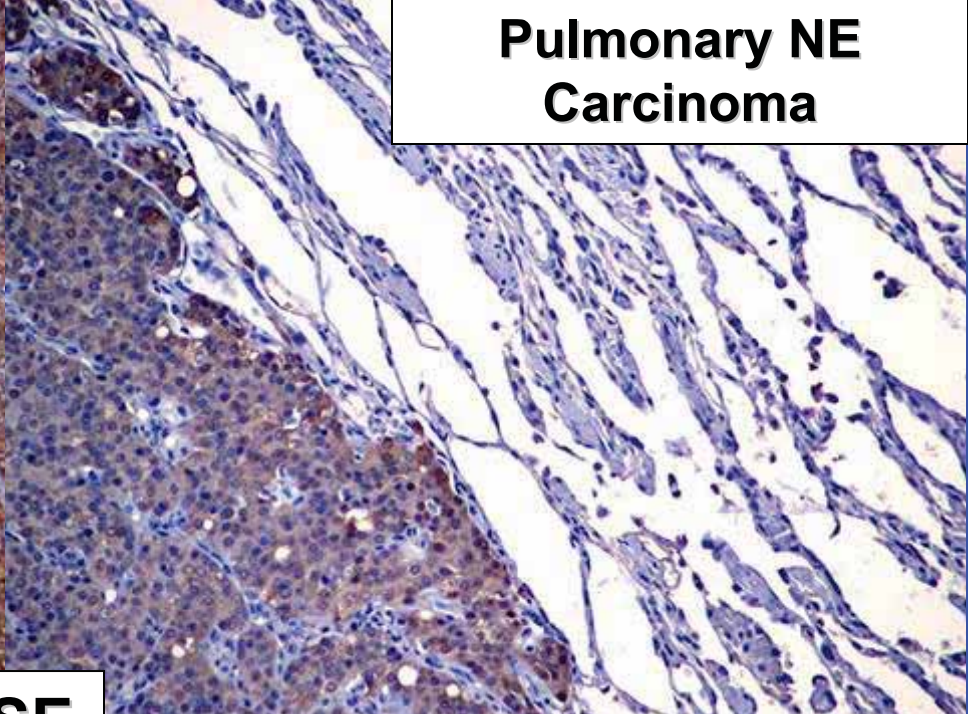


- Enolases are products of the three genetic loci:
 - non-neuronal (alpha-alpha): expressed in wide variety of tissues, including fetal and glial cells
 - muscle enolase (beta-beta): expressed in muscle
 - neuronal (gamma-gamma): neurons
 - hybrid enolases: megakaryocytes
- **Normal tissue:**
 - neurons, nerve fibers (monoclonals)
 - variety of neuroendocrine cells
 - polyclonal antibodies: less specific, similar to PGP 9.5, often not concurrent
- **Neoplasms:**
 - most neuroendocrine tumors including neuroendocrine carcinomas
 - schwannomas, melanomas, astrocytomas, gangliomas, glioblastomas, meningiomas

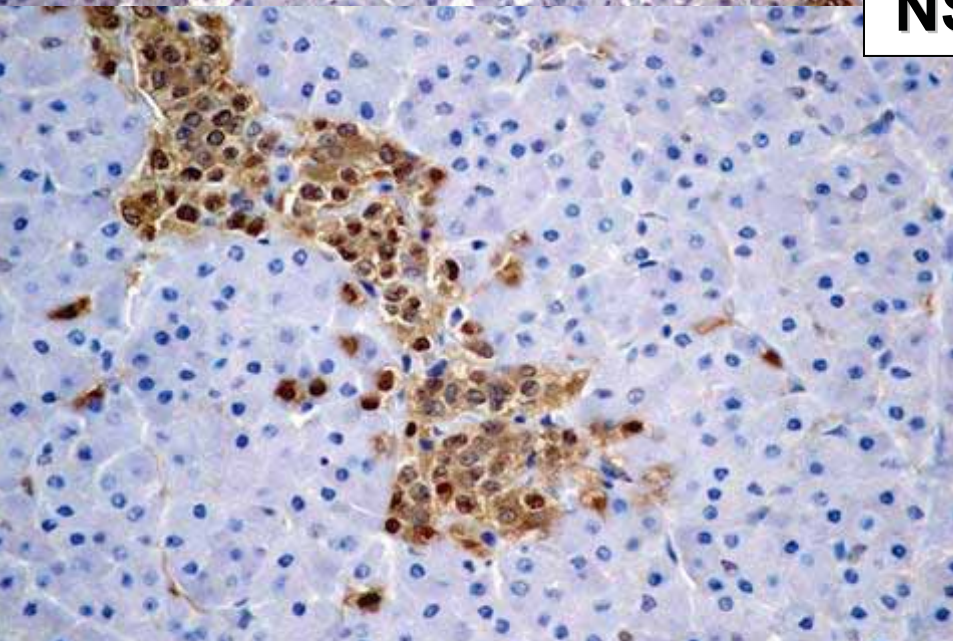
Pheochromocytoma



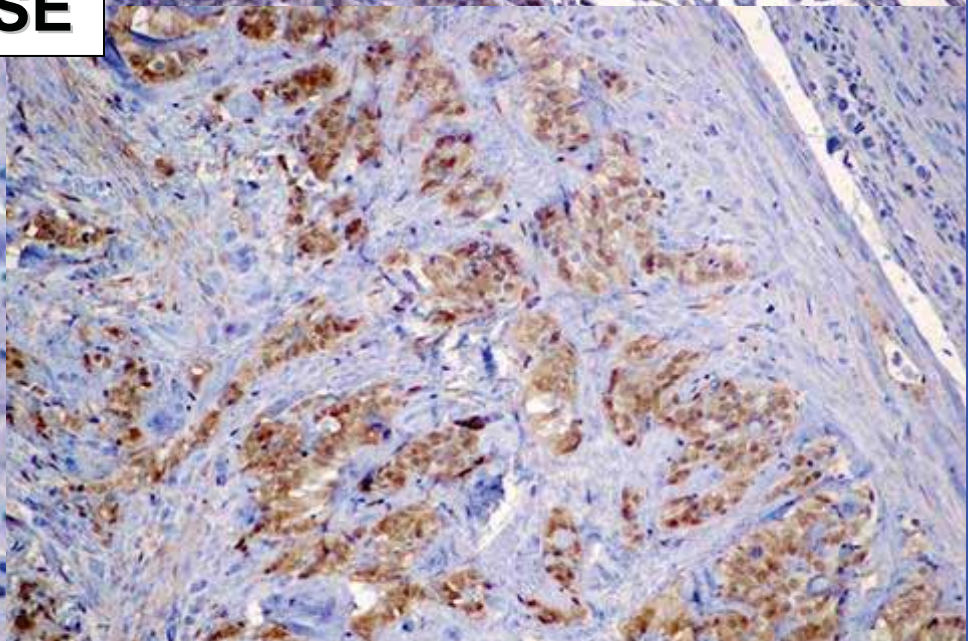
Pulmonary NE Carcinoma



NSE



Pancreatic Islet



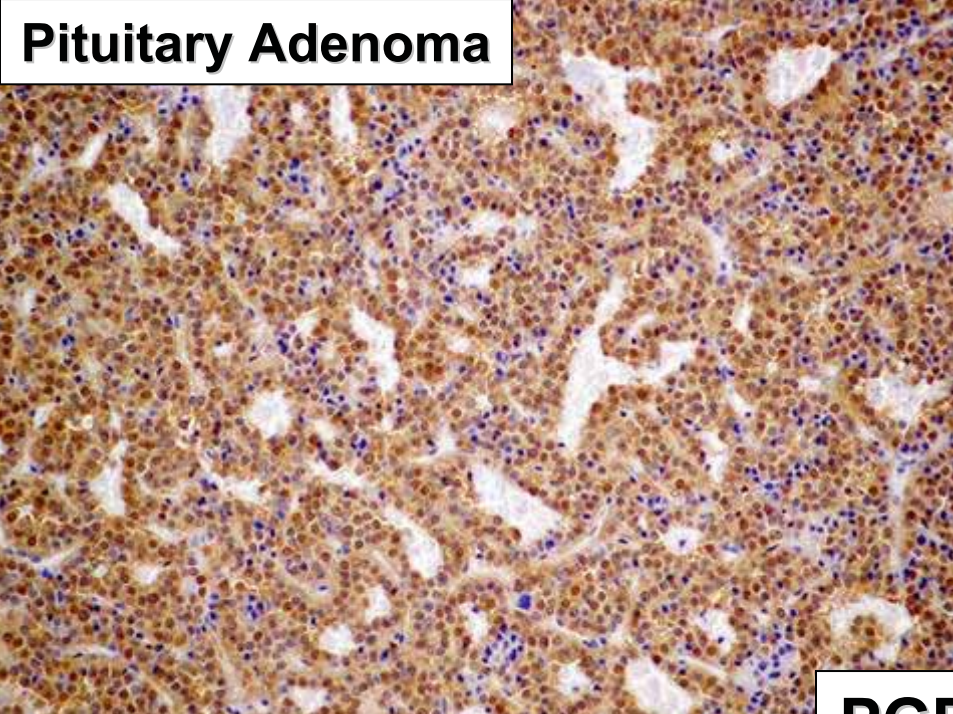
C-cell Carcinoma

Protein Gene Product 9.5 (PGP 9.5)

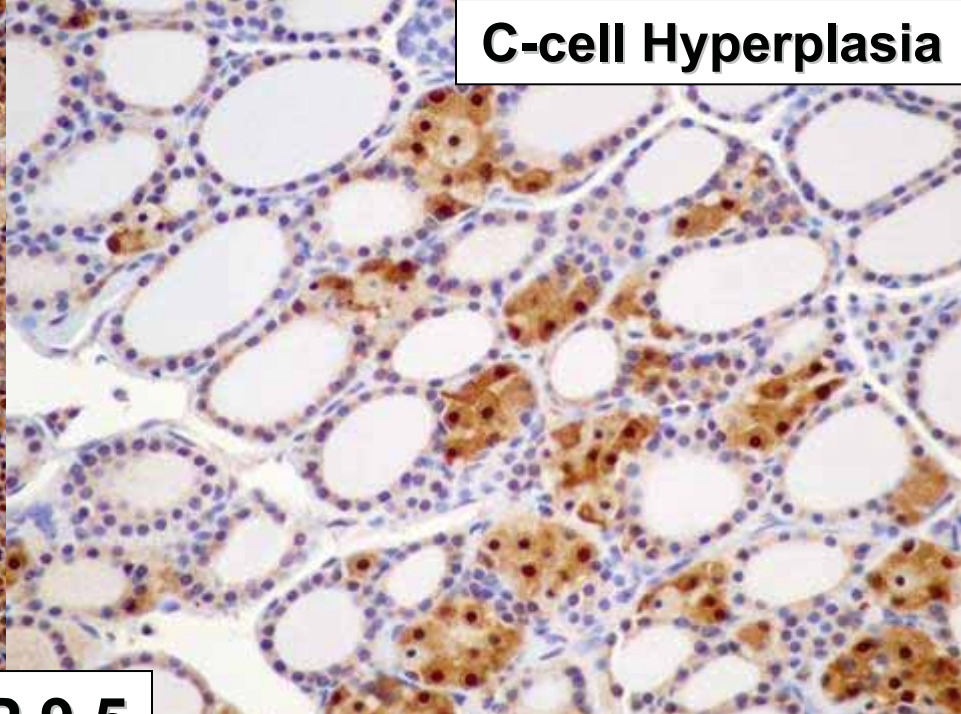


- Ubiquitin carboxyterminal hydrolase that degrades abnormal denatured proteins
- Similar staining but different distribution as NSE
- **Normal tissue:** - neurons, nerve fibers
 - variety of neuroendocrine cells
 - does not stain neuroendocrine cells in gastrointestinal tract
- **Neoplasms:** - most neuroendocrine tumors including neuroendocrine carcinomas

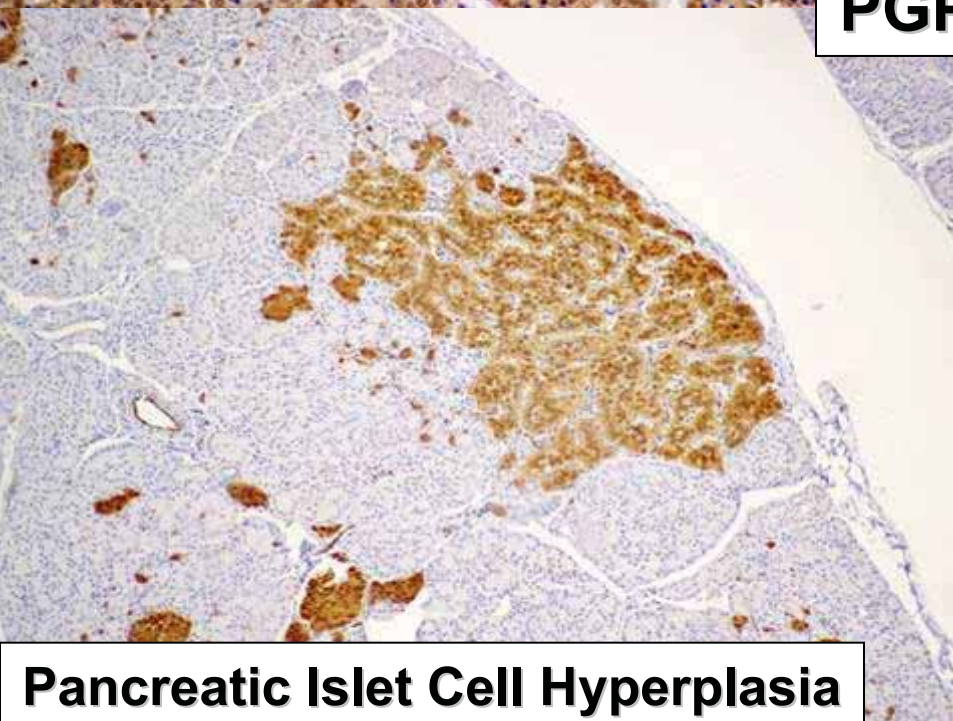
Pituitary Adenoma



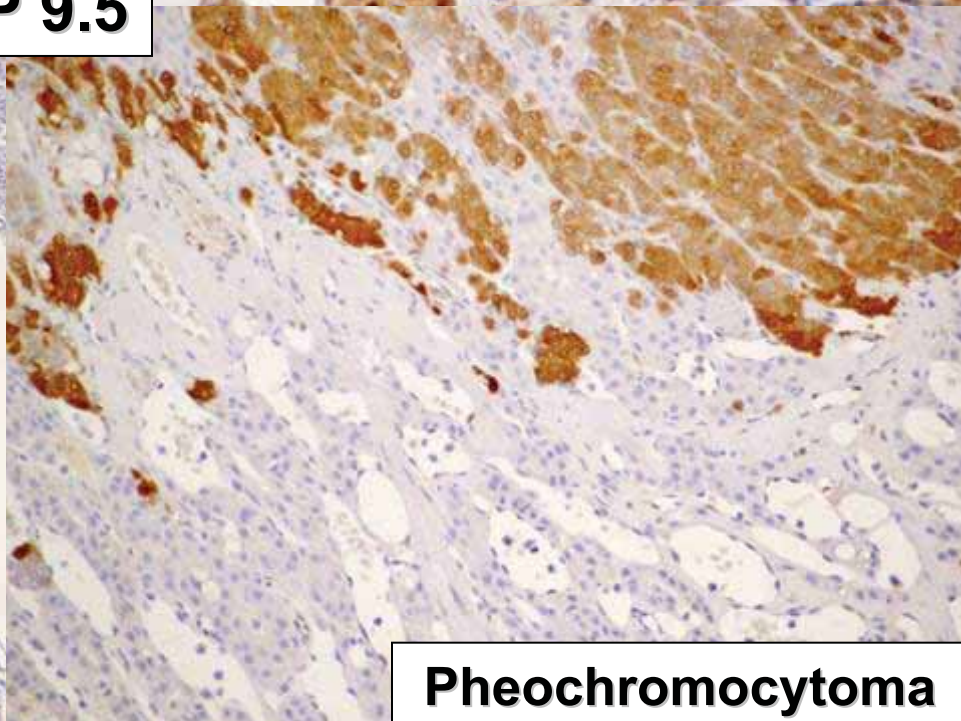
C-cell Hyperplasia



PGP 9.5



Pancreatic Islet Cell Hyperplasia

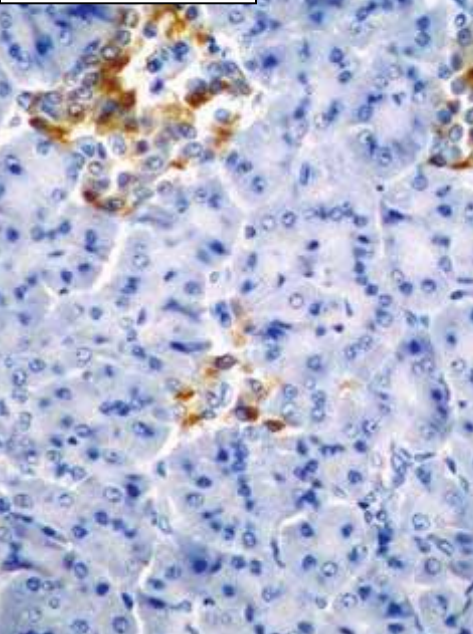


Pheochromocytoma

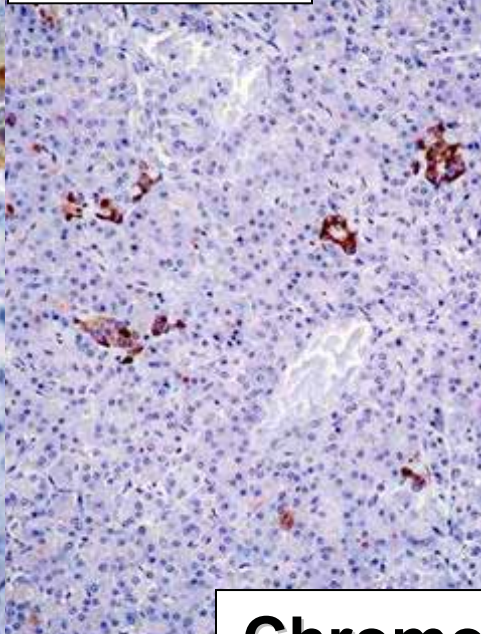
Chromo- and Secretogranins

- Matrical proteins associated with neurosecretory granules, widely distributed in neuroendocrine cells and neurons
- Two groups: - A (chromogranin (ChGr) A and B)
- B (secretogranin (SGr) I and II)
- Neuroendocrine cells have distinctive patterns:
 - many neuroendocrine cells contain all granins
 - pancreatic beta cells: ChGr A
 - gastric, small intestinal carcinoids: ChGr A
 - pituitary lactotrophs and somatotrophs: ChGr B
 - rectal neuroendocrine carcinoma: ChGr B, SGr II
- Most antibodies only directed against ChGr A, some antibodies recognize ChGr A fragments: chromostatin, parastatin, vasostatin

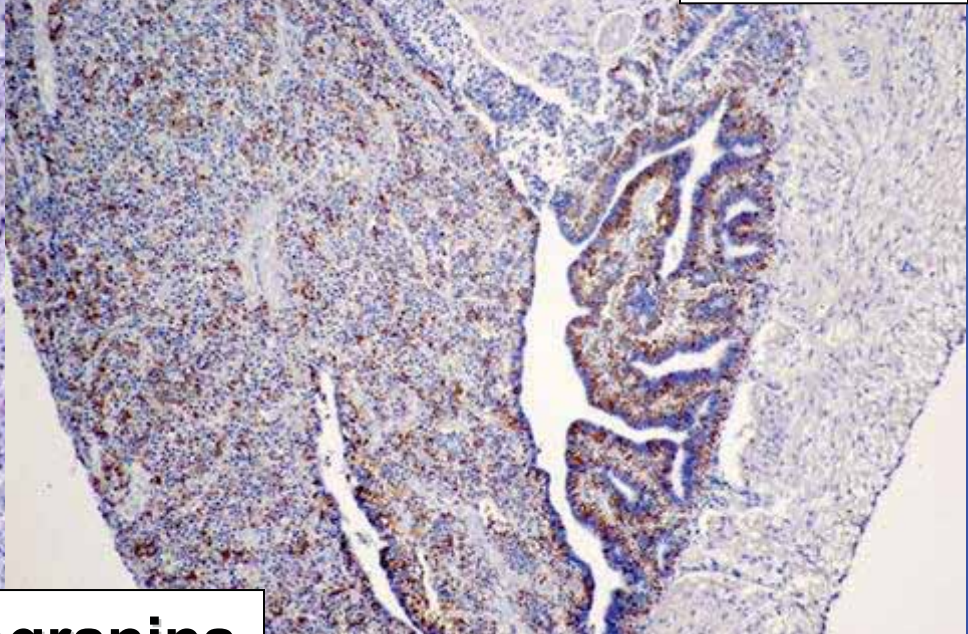
ChGr A



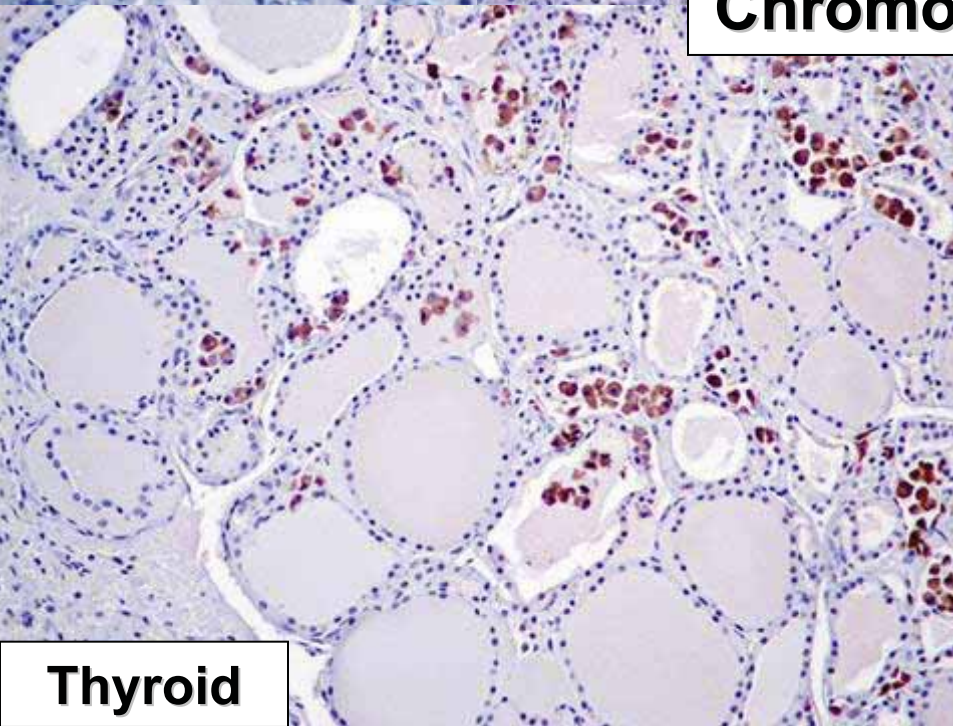
ChGr A+B



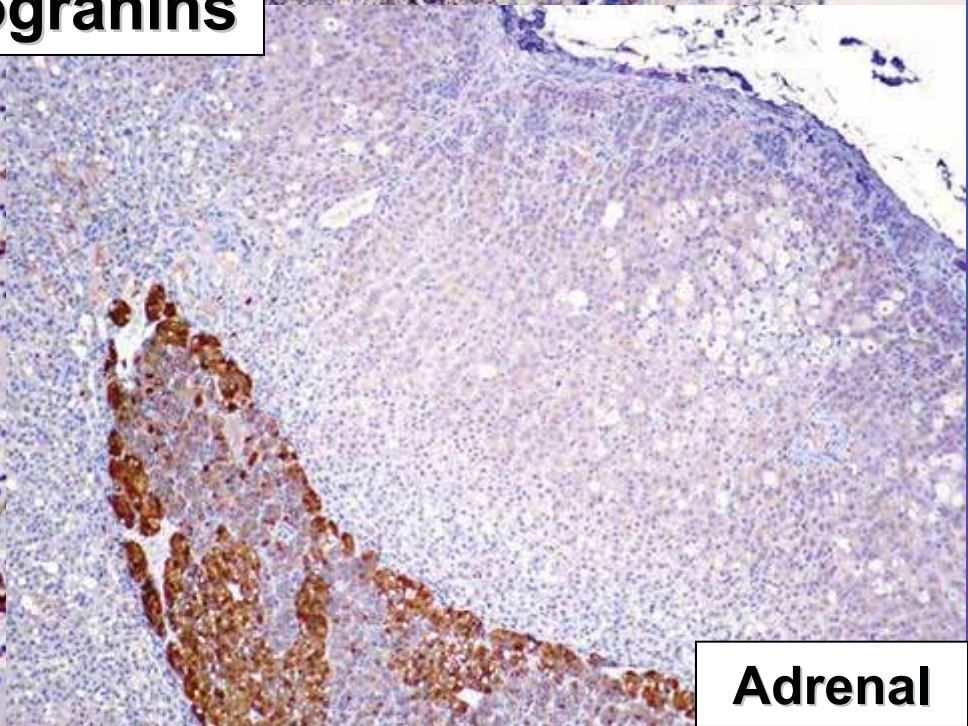
Pituitary



Chromogranins

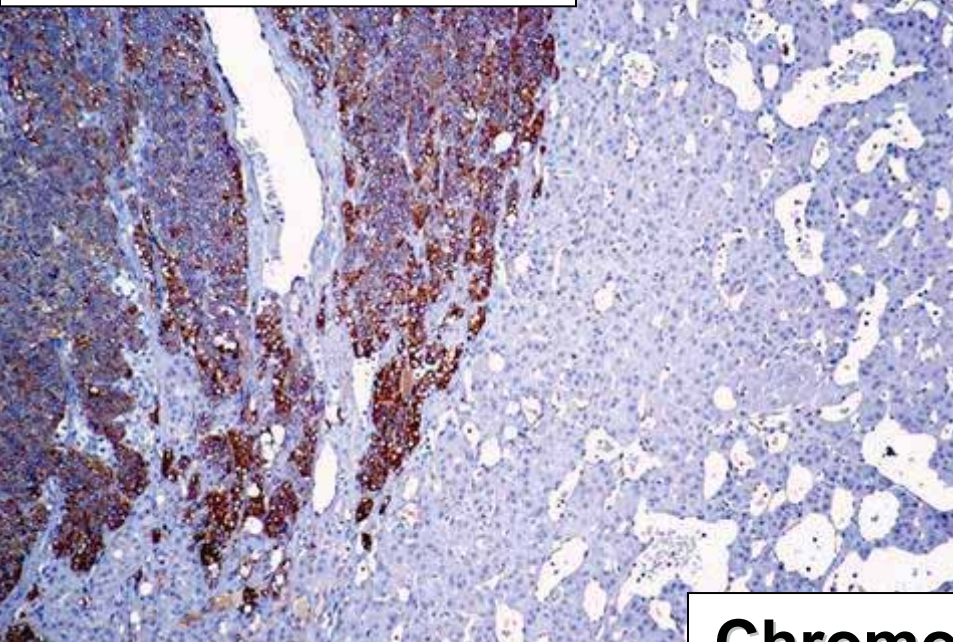


Thyroid

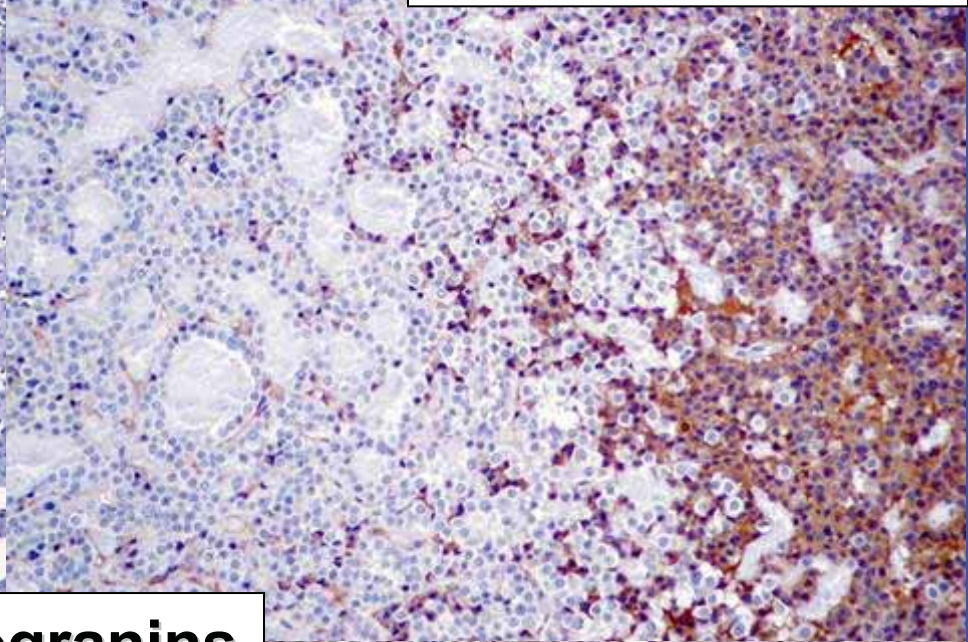


Adrenal

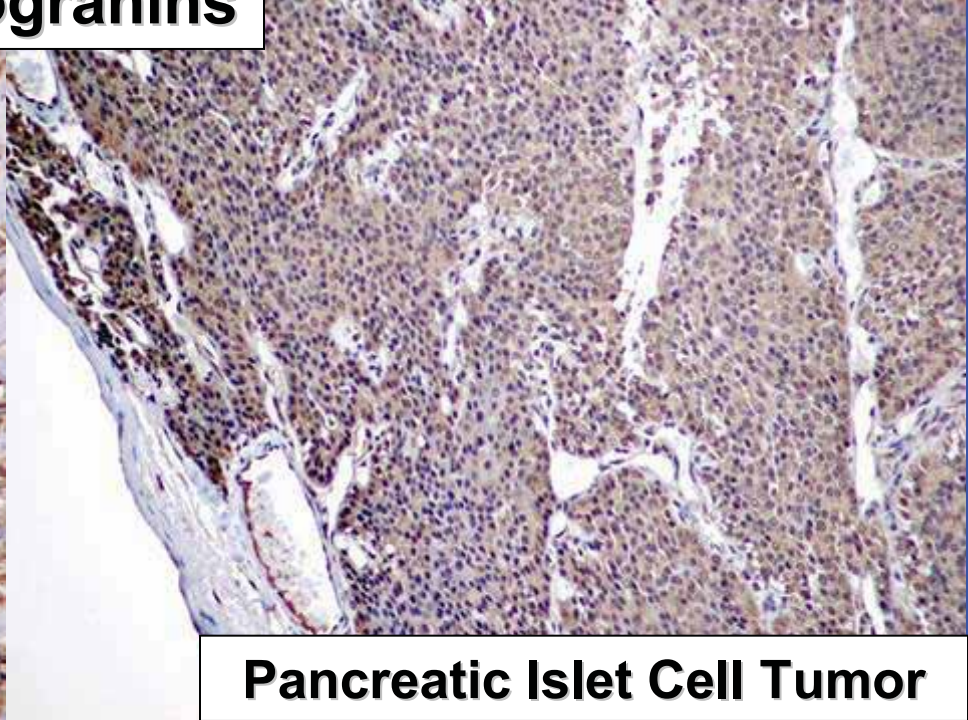
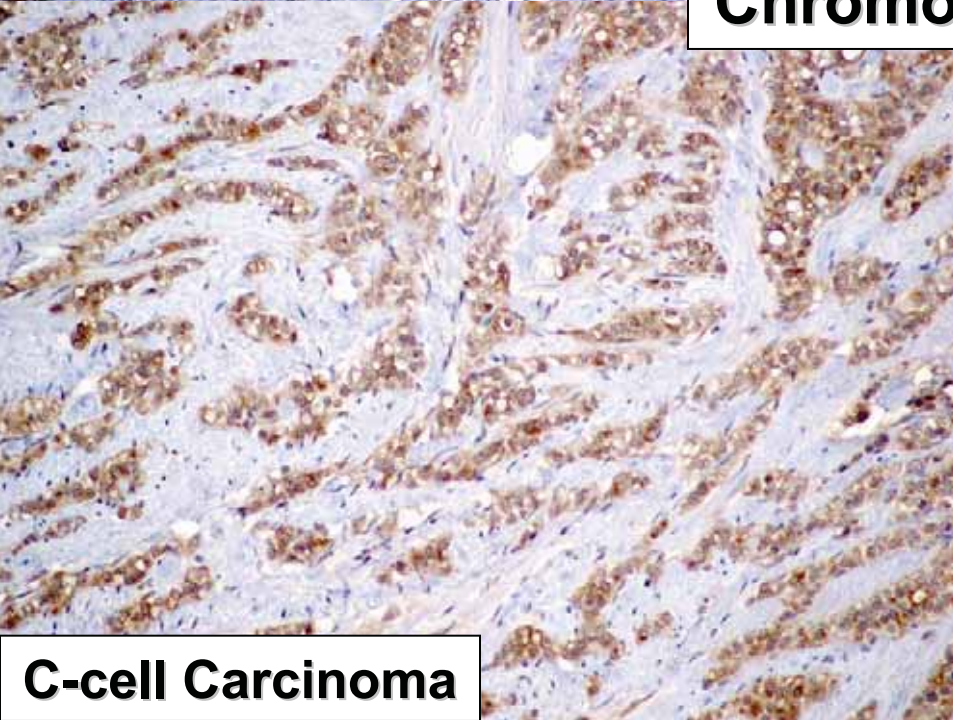
Pheochromocytoma



Pituitary Carcinoma



Chromogranins



C-cell Carcinoma

Pancreatic Islet Cell Tumor