



**ROSWELL  
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COMPREHENSIVE CANCER CENTER

# The Pathology of Neoplasia



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# Outline and Objectives



What is Pathology?

What is a Pathology Department?

The pathologist's "tools"

Pathology Definitions and Concepts

How do we approach a pathology specimen?

A General Classification of Neoplasia.

The ugly histologic face of cancer (recognizing malignancy).

Grading and Staging Malignancy.

The Changing World of Pathology

Pathology and Research

# Clinical goals of cancer pathology



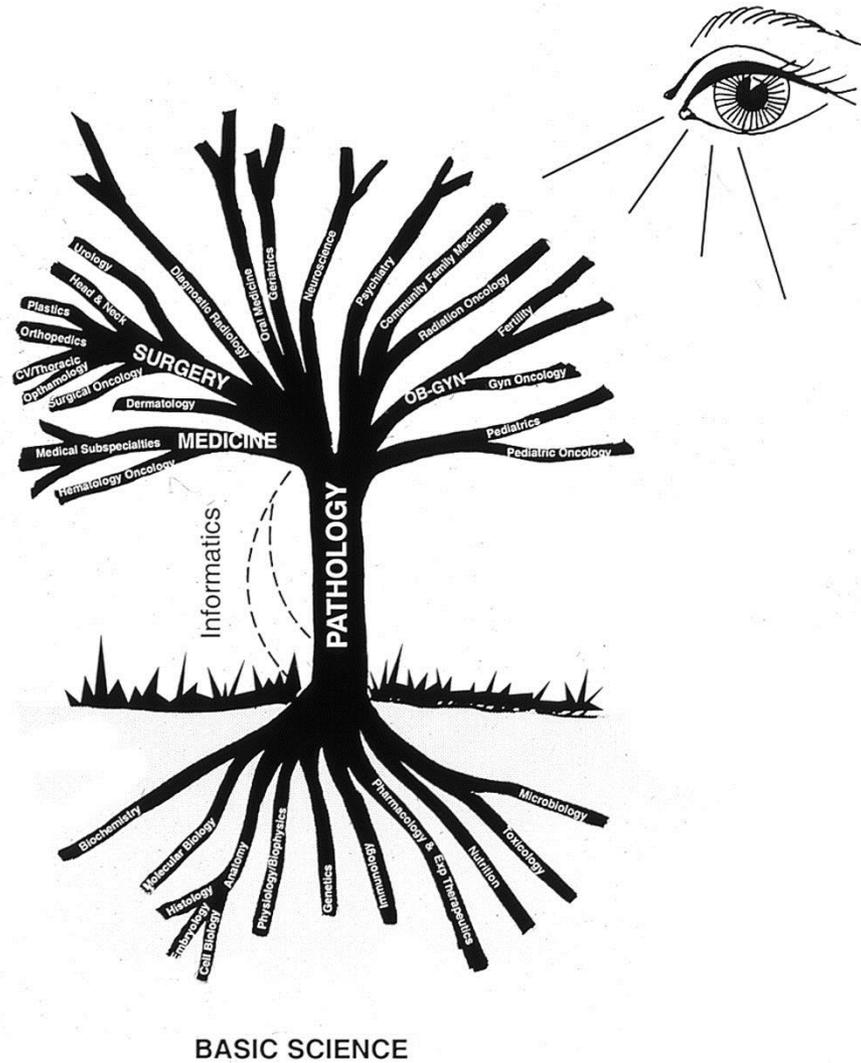
1. Identify presence of cancer
2. Classify cancer
3. Predict biology of cancer and prognosis
4. Identify optimal therapy
5. Evaluate success of treatment

# Pathology



- “...branch of medicine which treats (studies) of the essential nature of disease, especially of the structural and functional changes in tissues and organs of the body which cause or are caused by disease.”
  - Dorland’s Medical Dictionary 24<sup>th</sup> Ed.
- “...something abnormal- the anatomic and physiologic deviations from the normal that constitute disease or characterize a particular disease.”
  - Webster’s Seventh New Collegiate Dictionary

# Biomedical Science Tree



# A Department of Pathology



## **Patient Care**

ANATOMIC PATHOLOGY

CLINICAL PATHOLOGY

## **Experimental (Research)**

TISSUE PROCUREMENT

TRANSLATIONAL

BENCH

# Anatomic Pathology



- **Surgical Pathology**
  - Frozen Section (Intra-operative consultations)
  - Biopsy and Resection specimens
- **Cytopathology**
  - Pap smears (Gynecologic specimens)
  - Fine needle aspirates, washes, brushes
- **Autopsy**

# Clinical Pathology

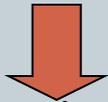


- Hematology
- Chemistry
- Microbiology
- Blood Bank (Transfusion Medicine)
- Tissue Typing (Transplant Pathology)
- Molecular Diagnostics
- Flow Cytometry
  
- Cytogenetics

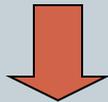
# Anatomic Pathology in Cancer



Patient has signs or symptoms of cancer



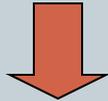
Clinician/Radiologist performs biopsy



Pathologist diagnoses cancer on biopsy



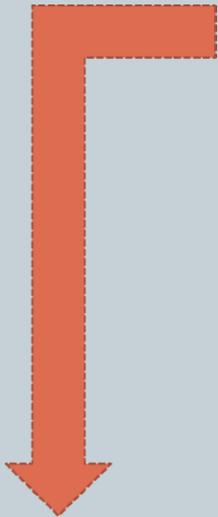
Clinician performs resection/excision



Pathologist stages and evaluates cancer



Molecular Characteristics of Tumor Evaluated for use in  
“Personalized Medicine”



# The Pathologist's Tools

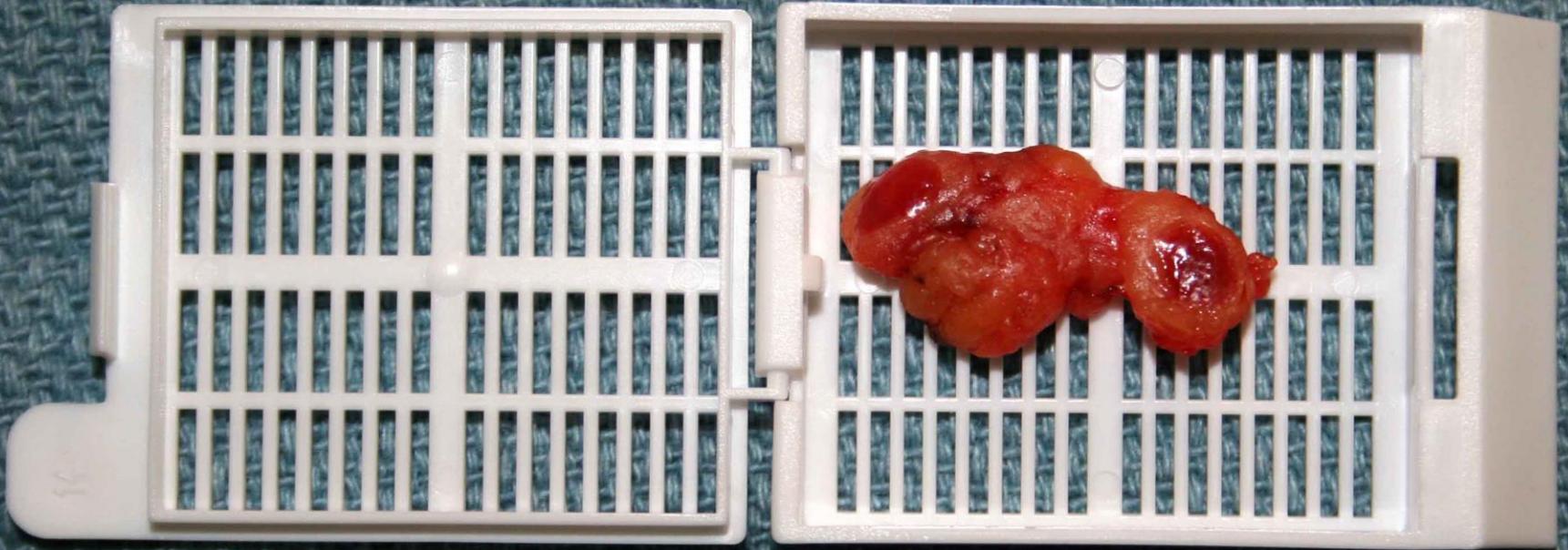


- The “Grossing Station”
- Fixation (usually with Formalin- 37% formaldehyde)
  - Preserve tissue, enhance detail for microscopy
- Tissue Processing (usually overnight)
  - Remove tissue water gradually, replace with paraffin wax
- Paraffin Embed and cut tissue sections
- Hematoxylin and Eosin Stain
- The Light Microscope

# Gross Examination



# Cassettes and Tissue Sections

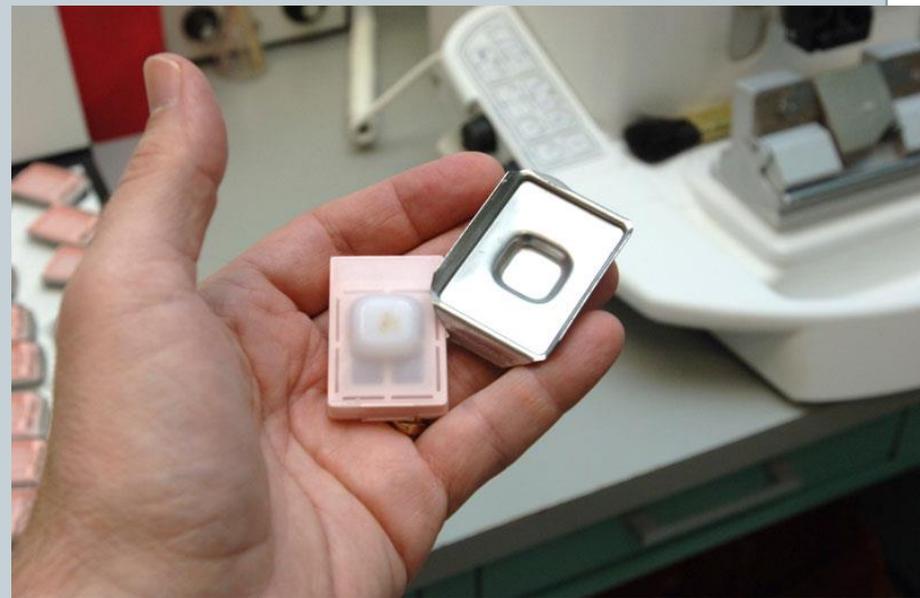


# Tissue Processor



1. Dehydrate Tissue
  - Progressive series of alcohols removes water
2. Clear Ethanol with xylene
3. Replace with paraffin

# Tissue Embedded in Liquid Paraffin



Pictures courtesy of [www.protocolsonline.com](http://www.protocolsonline.com)

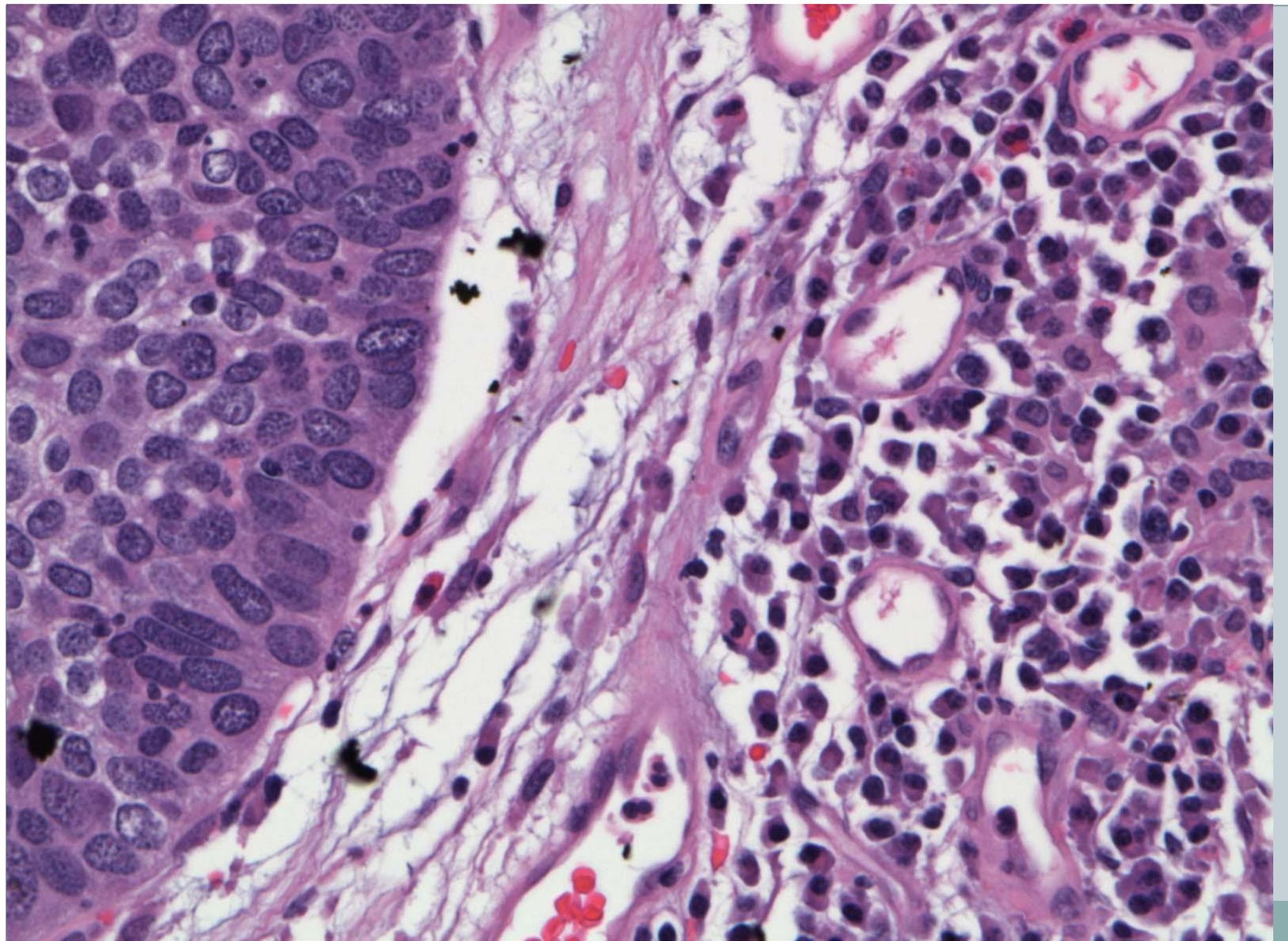
# Sections Cut ( $\sim 5 \mu\text{m}$ ) by microtome



# Hematoxylin and Eosin (the H&E)



- The pink and purple foundation of pathology
- Hematoxylin
  - Purple/blue stain (BASOPHILIC)
  - Stains acidic materials
  - Stains nuclear contents
- Eosin
  - Pink stain (EOSINOPHILIC)
  - Stains most cytoplasmic contents

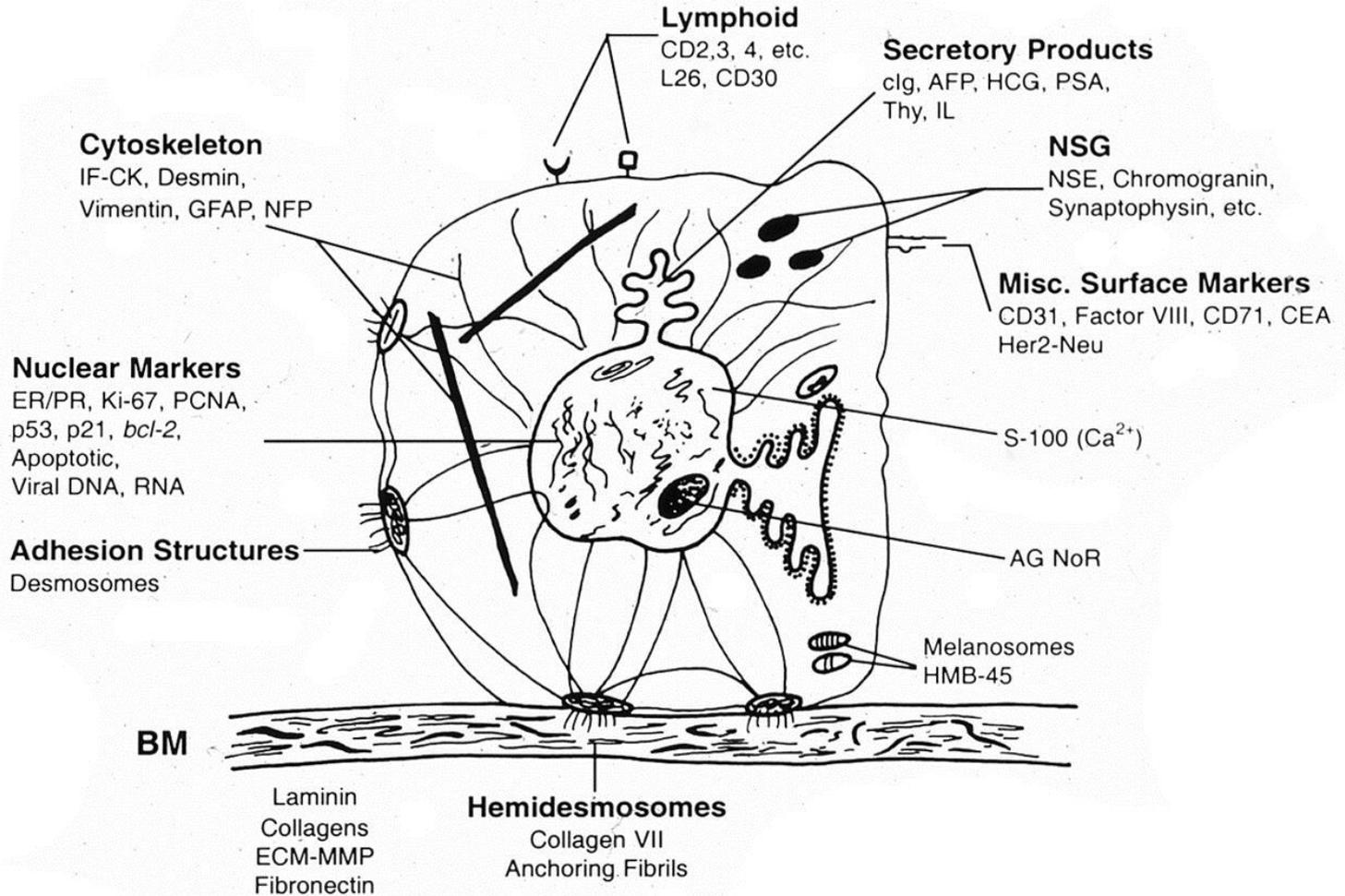


# Ancillary Studies

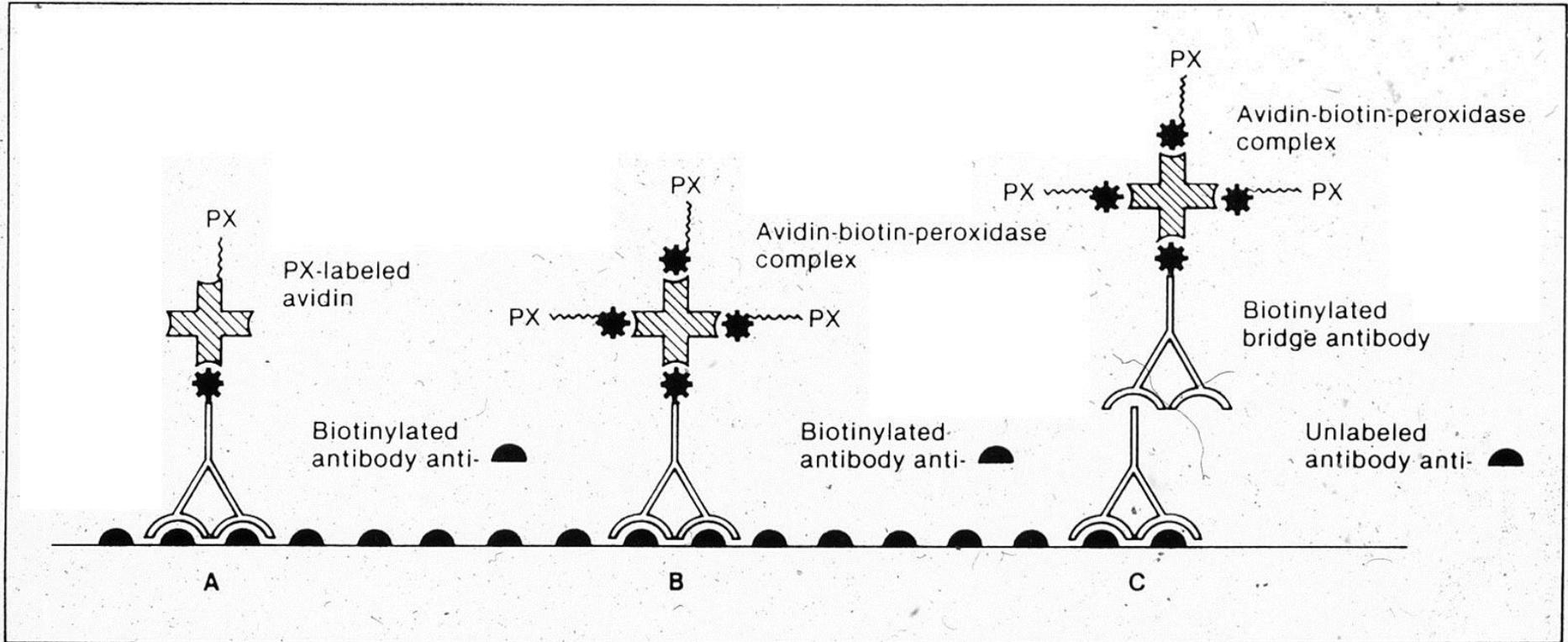


- Flow cytometry
- Immunohistochemical stains
- Cytochemical stains
- Cytogenetics
- Electron microscopy

# Generic IHC Cell



# Immunohistochemistry (IHC)

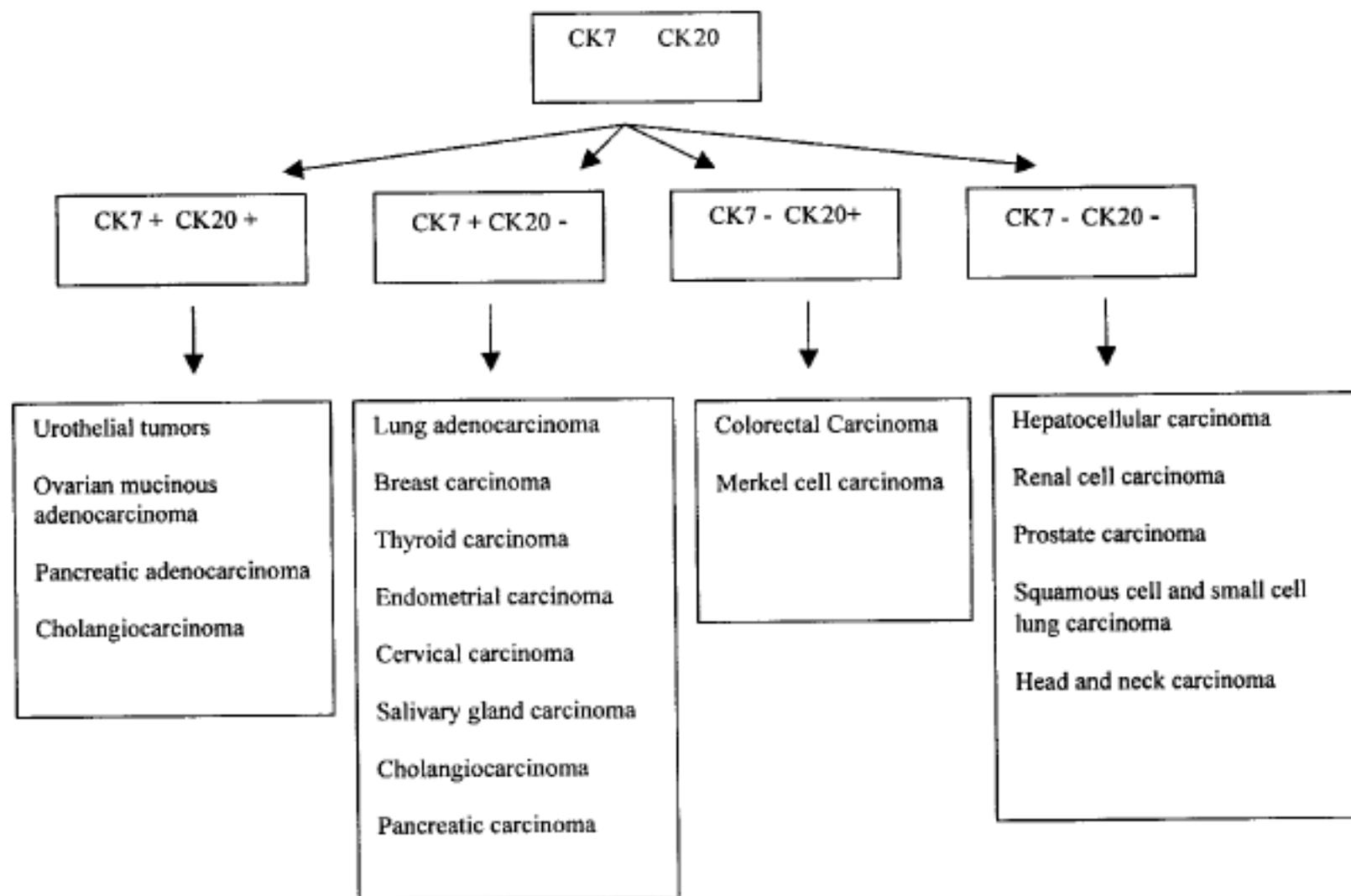


**Fig. 3-2** Biotin-avidin immunoenzymatic techniques. Solid semicircle indicates antigen; PX, peroxidase; \*, biotin; and shaded open cross, avidin. A, biotinylated primary antibody method; B, biotinylated peroxidase method; C, avidin-biotin-peroxidase complex method. (From Falini B, Taylor CR: New developments in immunoperoxidase techniques and their application. *Arch Pathol Lab Med* **107**:105-117, copyright 1983, American Medical Association.)

# IHC: what is it good for?



- Identify or confirm the source of a tumor
  - CK7, CK20, other markers “specific” to tumor type
- Increase the sensitivity of tumor detection
  - eg find individual metastatic melanoma cells in a lymph node using Melan-A
- Predict tumor behavior/prognosis
  - proliferative index (Ki-67)
- Identify potential therapeutic targets
  - Estrogen receptor – Tamoxifen (breast cancer)



**FIGURE 1.** Approach to immunohistochemical markers used in unknown primary cancer.

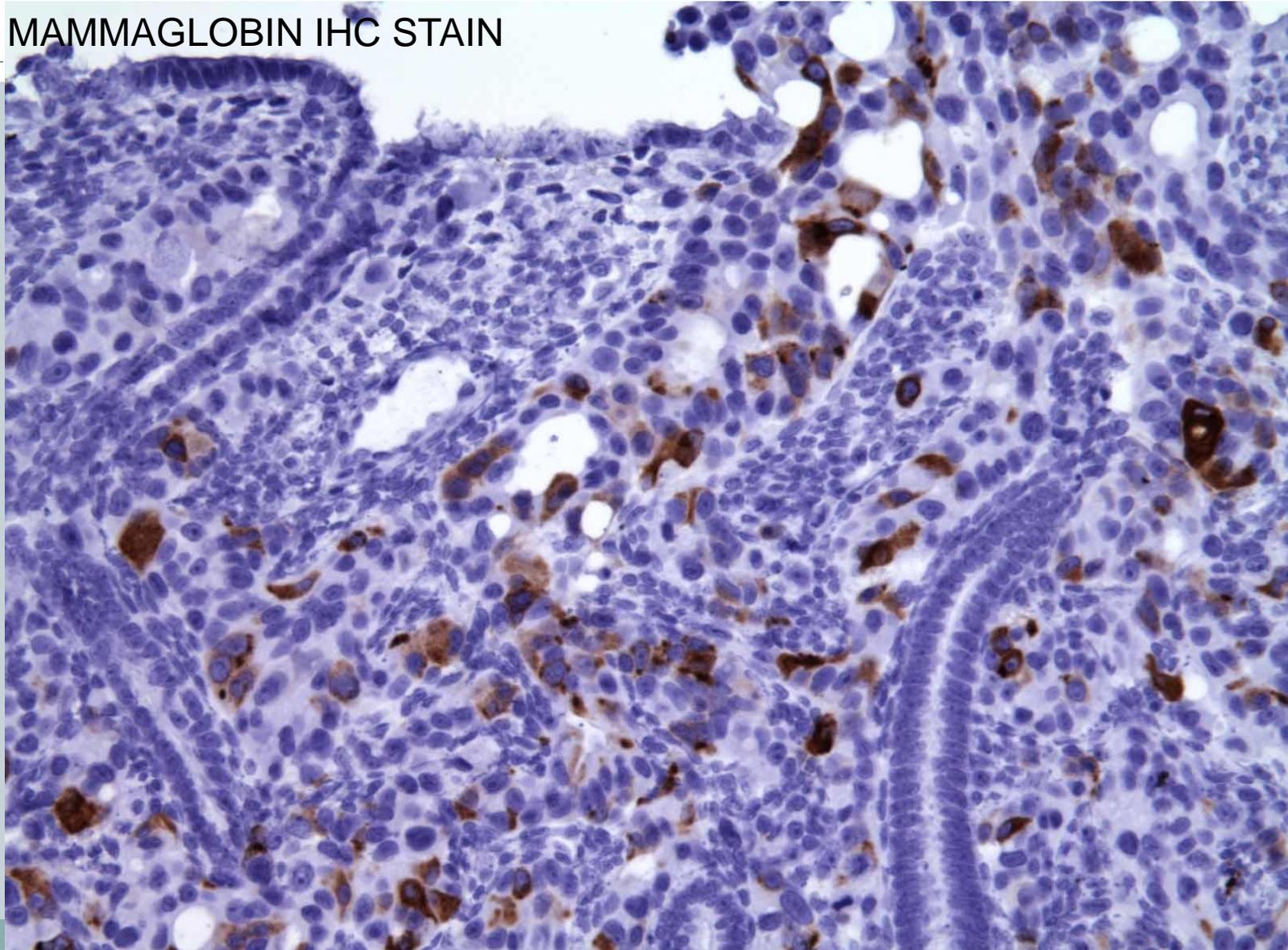
from Varadhachary, GR. *et al.*, *Cancer* **100(9):1776** (2004).

**Additional Markers Used as Suggested by Clinical Data (after a Preliminary Workup with CK7 and CK20)**

<b>Tumor</b>	<b>Marker</b>
Urothelial carcinoma	UROIII, THR, HMWCK
Breast carcinoma	GCDFP-15, ER, PR
Lung (mainly adenocarcinoma)	TTF-1, surfactant A and B
Medullary thyroid carcinoma	TTF-1, Calcitonin
Merkel cell carcinoma	CD117
Hepatocellular carcinoma	Hep par-1
Prostate carcinoma	PSA, PAP
Cholangiocarcinoma	CK19
Mesothelioma	Calretinin

# Breast Cancer Metastatic to Uterus

MAMMAGLOBIN IHC STAIN



# Immunohistochemistry



- **DISADVANTAGES**

- FALSE Negative

- ✦ Antigen- not present in tissue, degraded
- ✦ Antibody- too dilute, expired, wrong antibody

- FALSE Positive

- ✦ Cross reactive or non-specific antibody binding
- ✦ Endogenous peroxidase or avidin/biotin binding
- ✦ Entrapped normal cells
- ✦ Tumor uptake of normal cell antigens

# Definitions and Concepts



# Definitions



- TUMOR

Swelling.

- CANCER

“crab”, tumor with fatal course and association with formation of secondary tumors (metastasis)

# Definitions

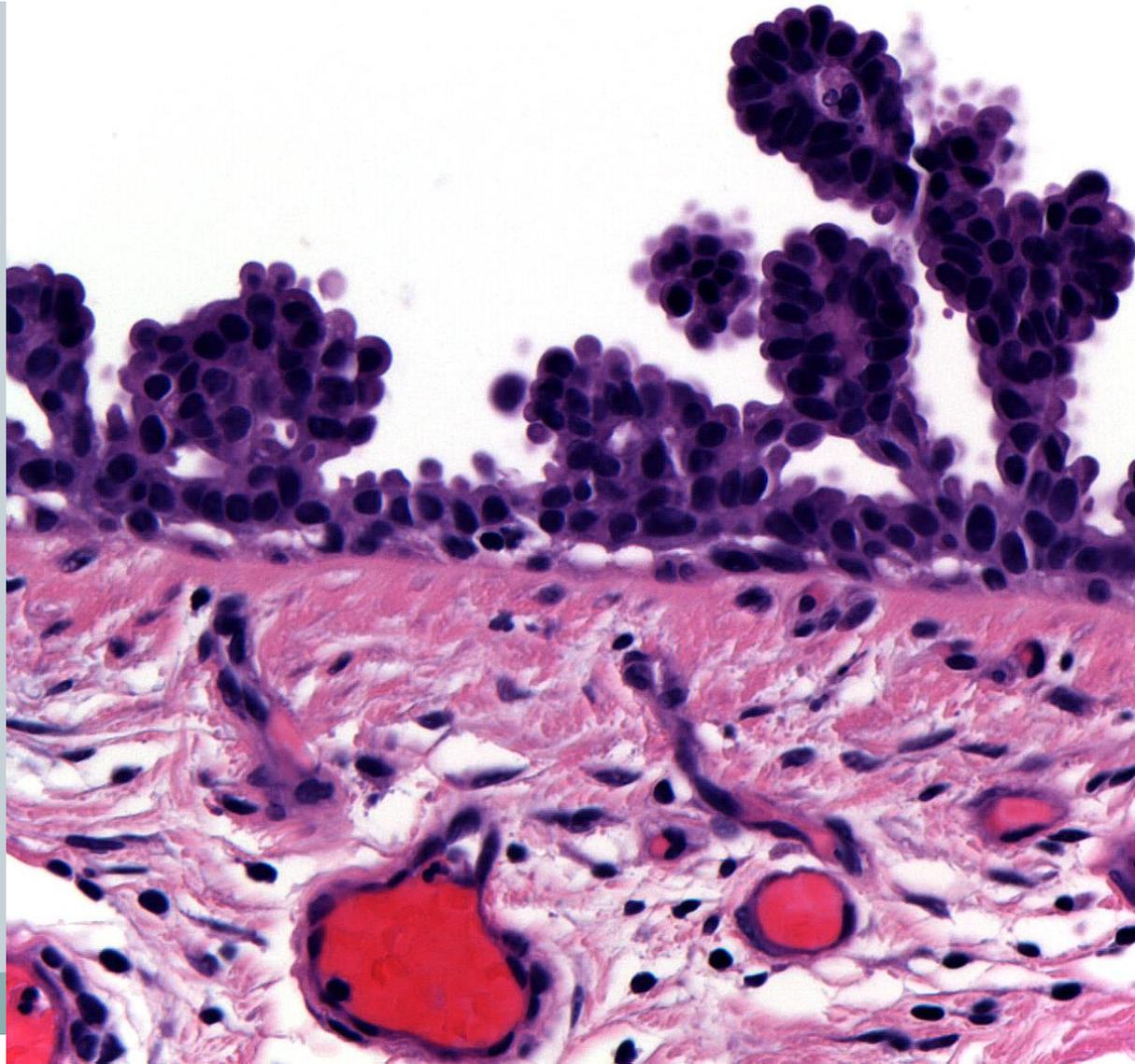


- EPITHELIUM (epithelial) → when malignant it is called CARCINOMA

Derived from ectoderm or endoderm: the protective, absorptive and secretory lining of the body both externally (e.g. skin), and internally (e.g. lining of colon, pancreatic glands)

Common types of epithelium are: squamous and columnar/glandular

# Epithelium and Basement Membrane



# Definitions



- **MESENCHYME (mesenchymal) → when malignant it is called SARCOMA**

Largely derived from mesoderm: structural and functional elements of the body- “connective tissue” (cartilage, bone, collagen, nerve, blood vessels, etc...)

# Definitions



- **NEOPLASIA**

Any new or abnormal growth (typically implies a clonal population of cells).

- **NEOPLASM**

Mass of new tissue which persists and grows independently of its surrounding structures and which has no physiologic use

# Definitions



- **METAPLASIA**

A change in tissue cells to a form not normal for that tissue, usually reversible and protective

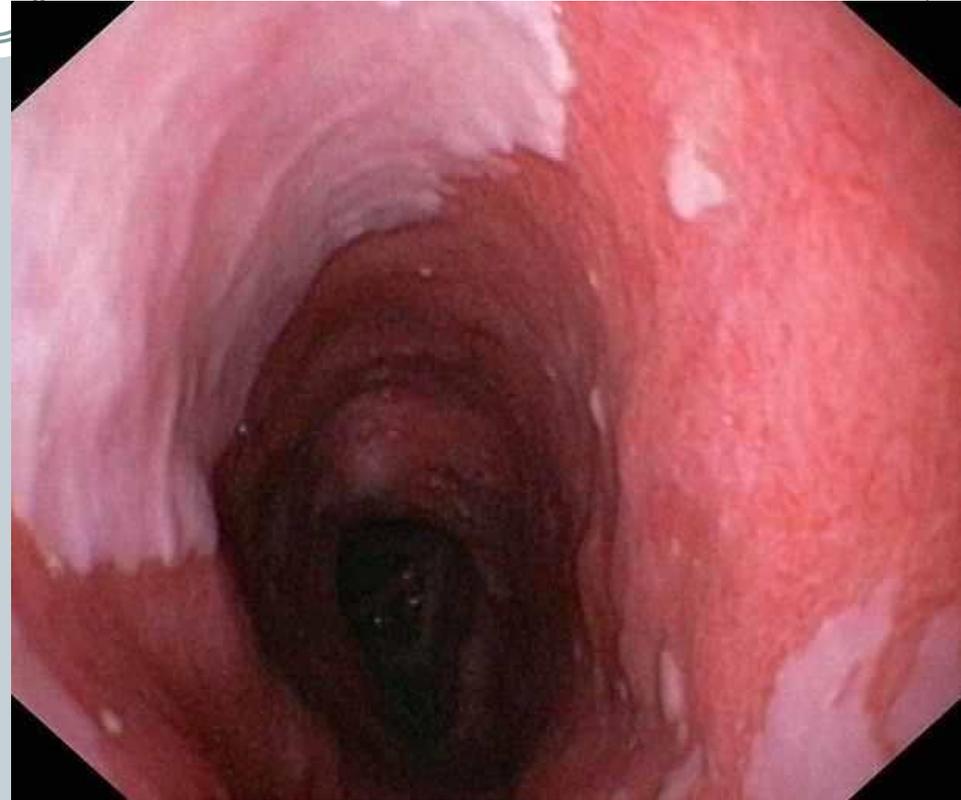
- **HYPERPLASIA**

An increase in the NUMBER of cells, while maintaining normal tissue architecture

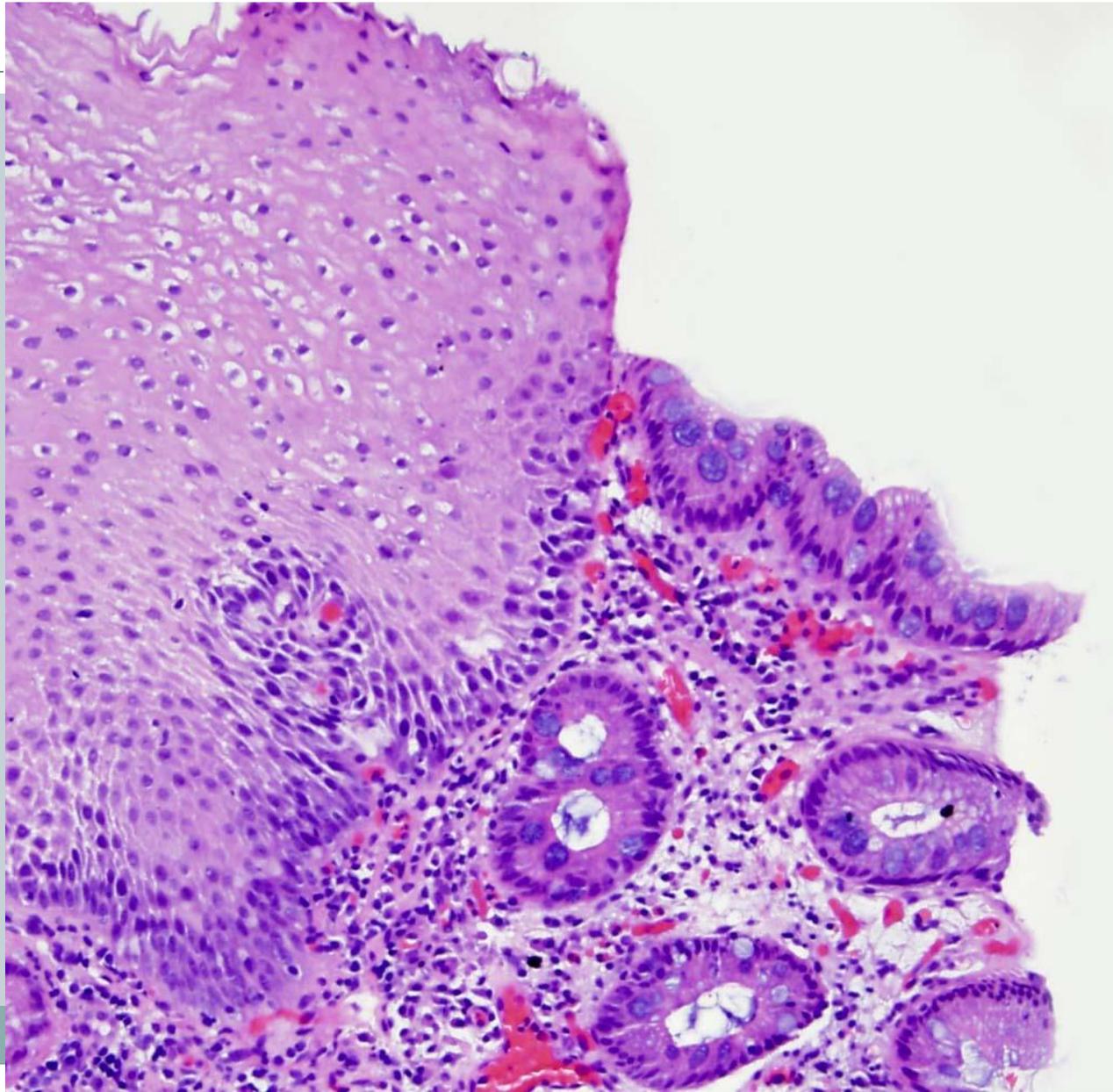
Normal esophagus



Barrett's metaplasia



# Metaplasia (Barrett's Esophagus)



# Definitions

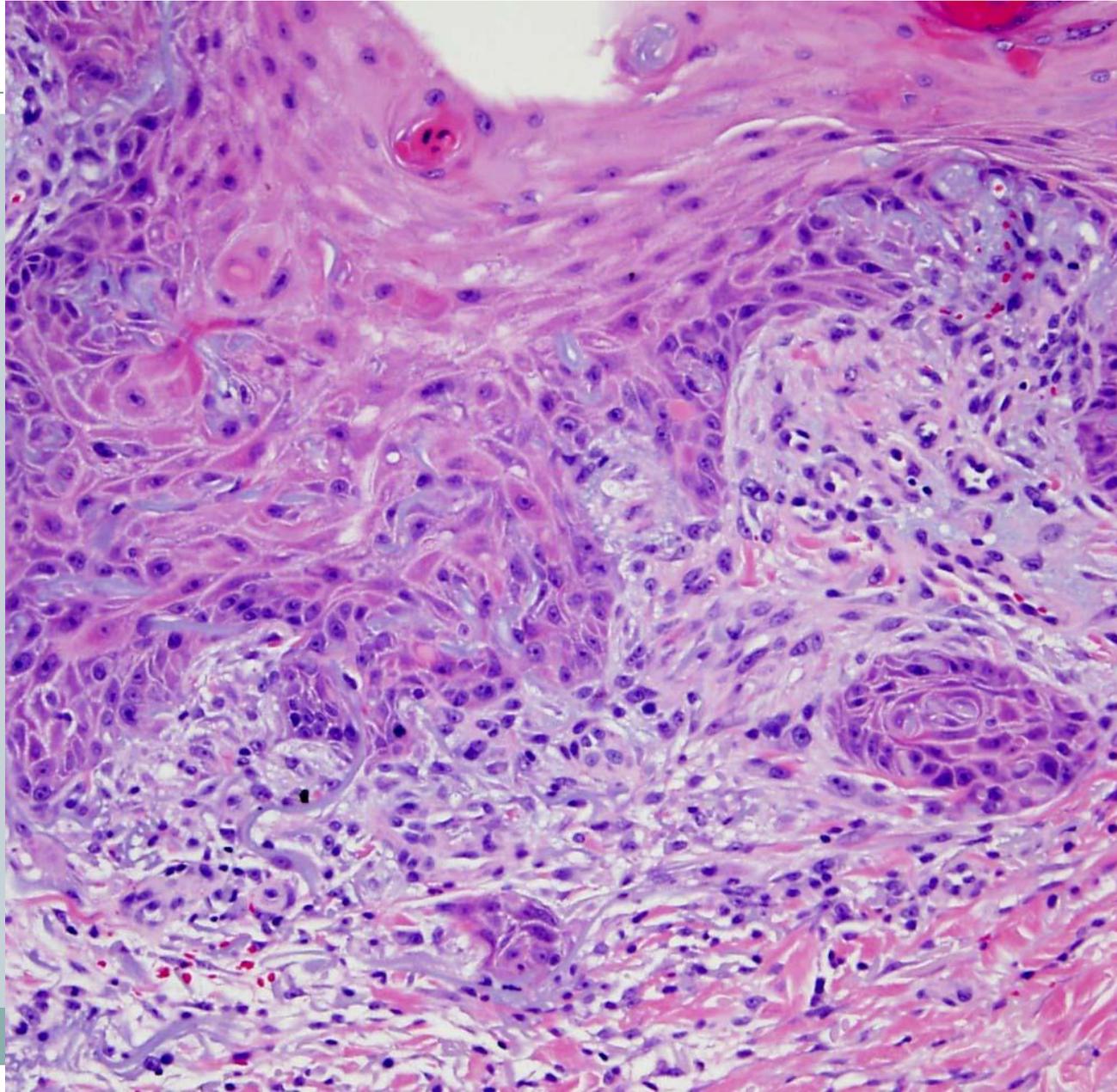


- **INVASION**

The penetration of neoplastic epithelial cells through the basement membrane.

Also used less specifically to refer to cells (epithelial or mesenchymal) penetrating any adjacent existing structure.

# Invasion (Squamous Cell Carcinoma)



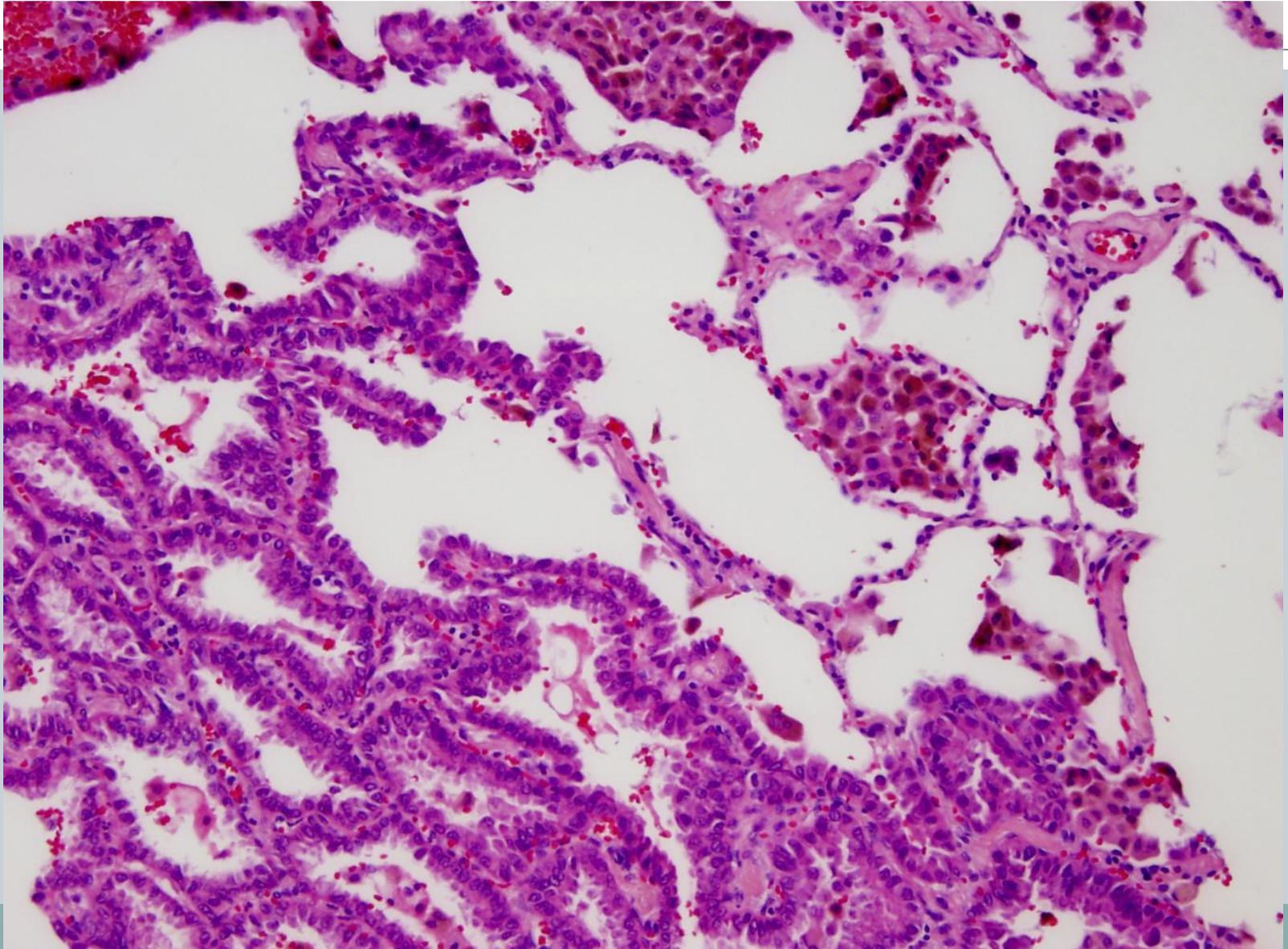
# Definitions



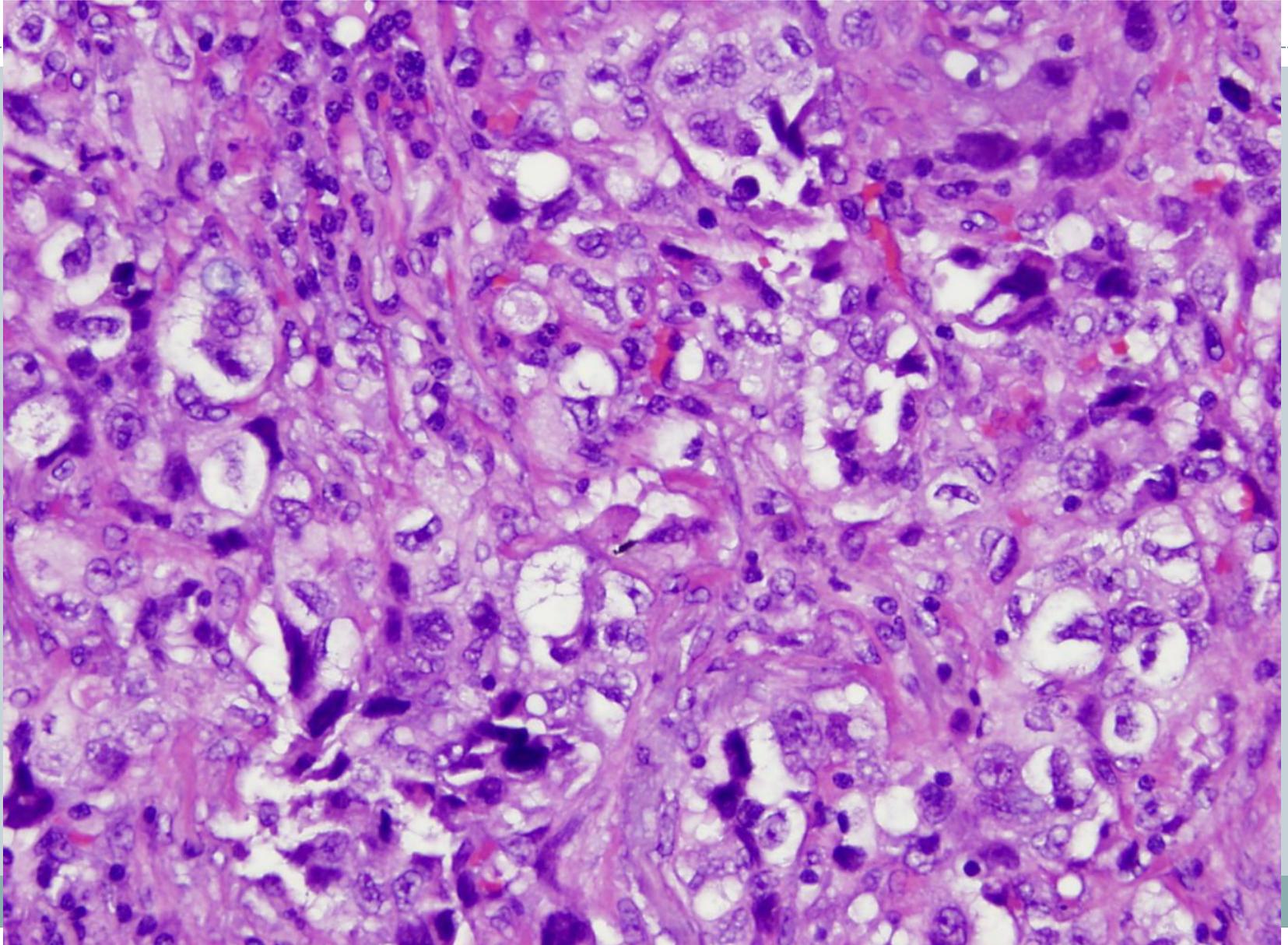
- **DIFFERENTIATION**

Degree to which a neoplasm recapitulates normal tissue in all its characteristics (often assessed as a **GRADE**)

# Well Differentiated Lung Adenocarcinoma (Bronchioloalveolar Carcinoma 200x)



# Poorly differentiated lung adenocarcinoma (200x)



# Definitions



- **ATYPIA**

The condition of being irregular, refers generally to abnormalities of histologic appearance- not always neoplastic in nature (can be “reactive”, as in setting of radiation therapy or inflammation)

- **ANAPLASIA**

A loss of normal differentiation and form.

# Definitions



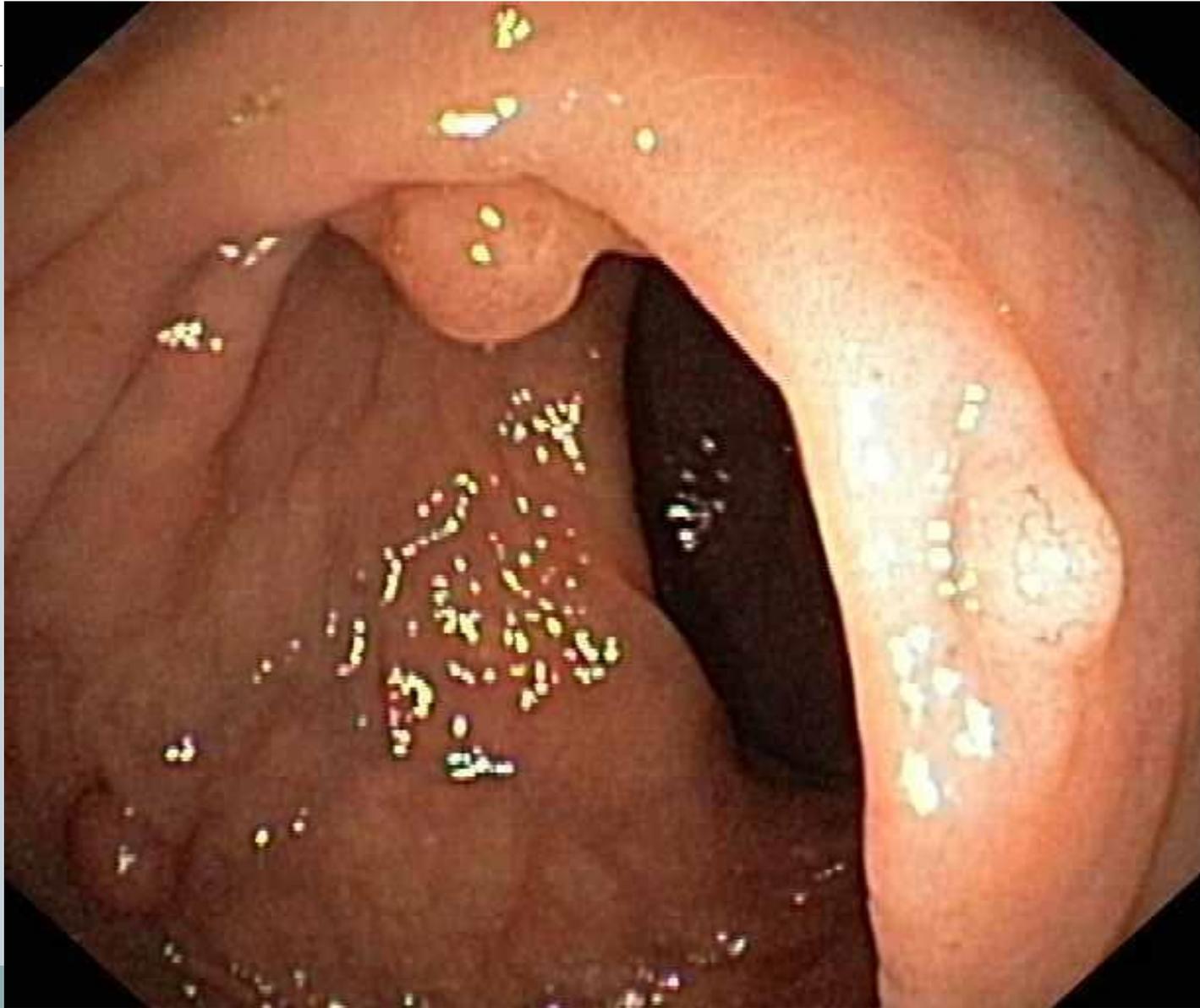
- **DYSPLASIA**

Abnormality of maturation and development, manifesting as architectural, organizational and cytologic atypia

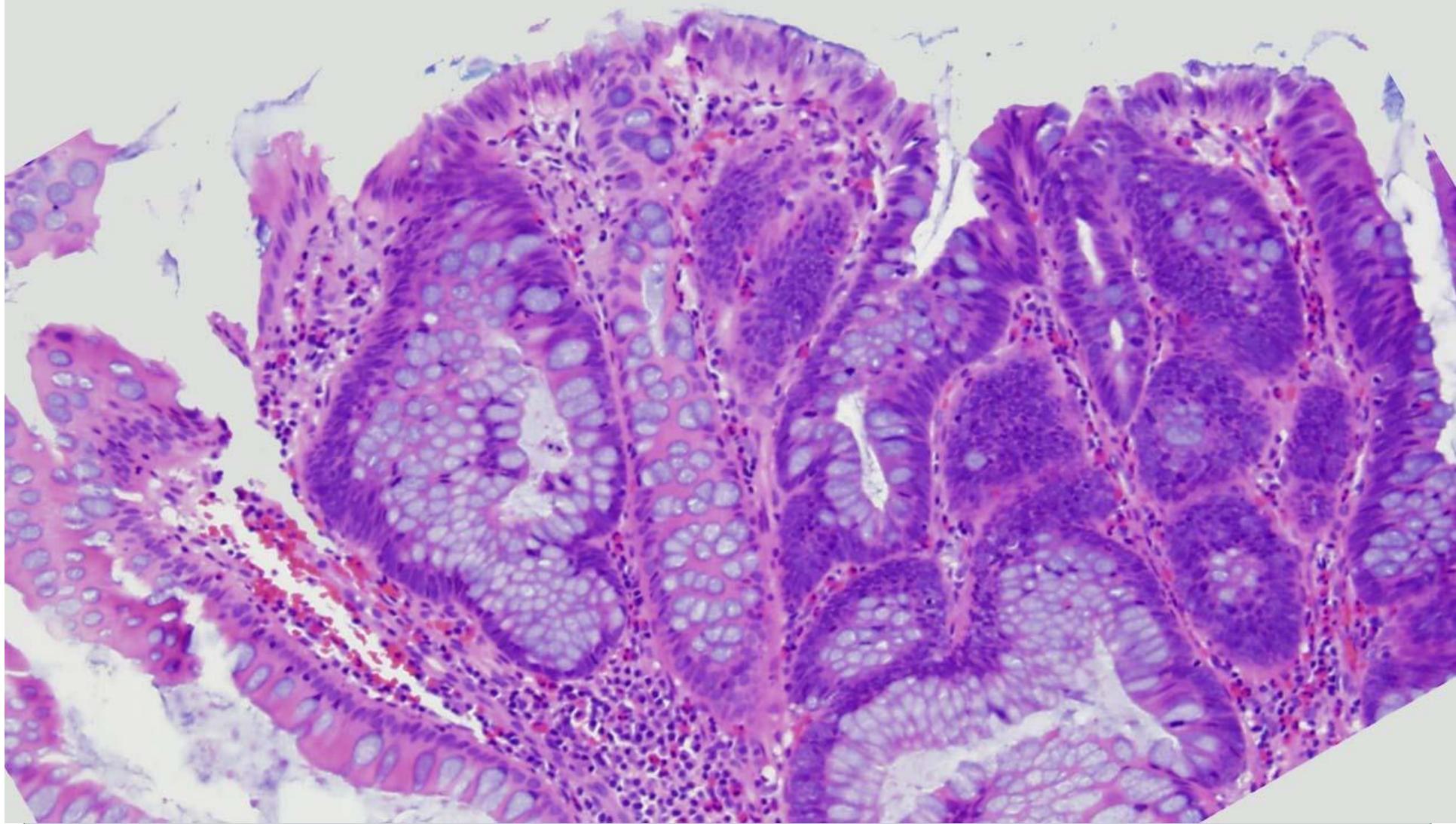
MILD → MODERATE → SEVERE  
(SEVERE usually is **Carcinoma in-situ**)

**DYSPLASIA IS ALWAYS ATYPICAL, ATYPIA IS NOT ALWAYS DYSPLASTIC!**

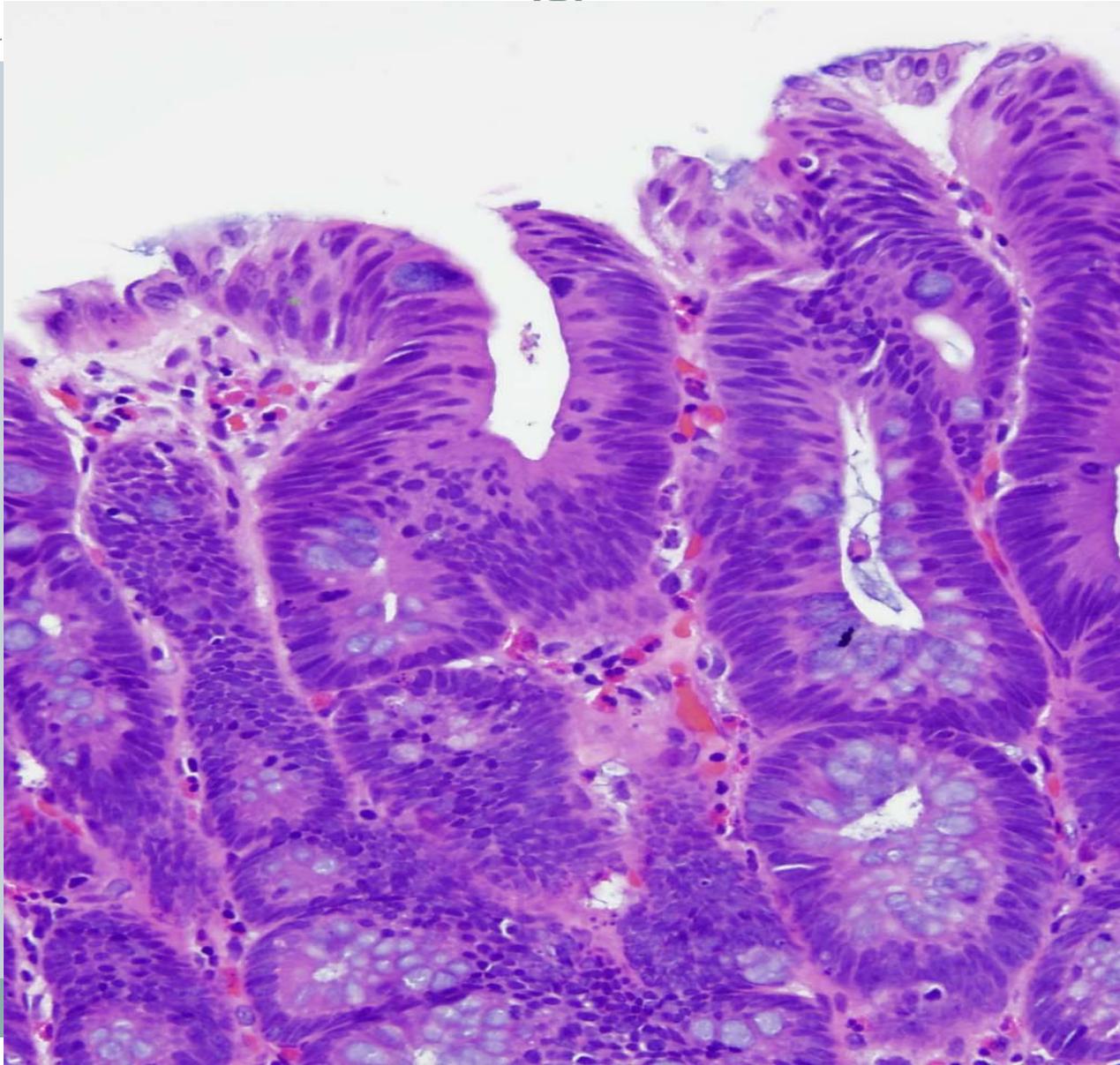
# Colonoscopy



# Colonic Adenoma (Dysplasia 100x)



# Colonic Adenoma (Dysplasia 200x)



# Definitions



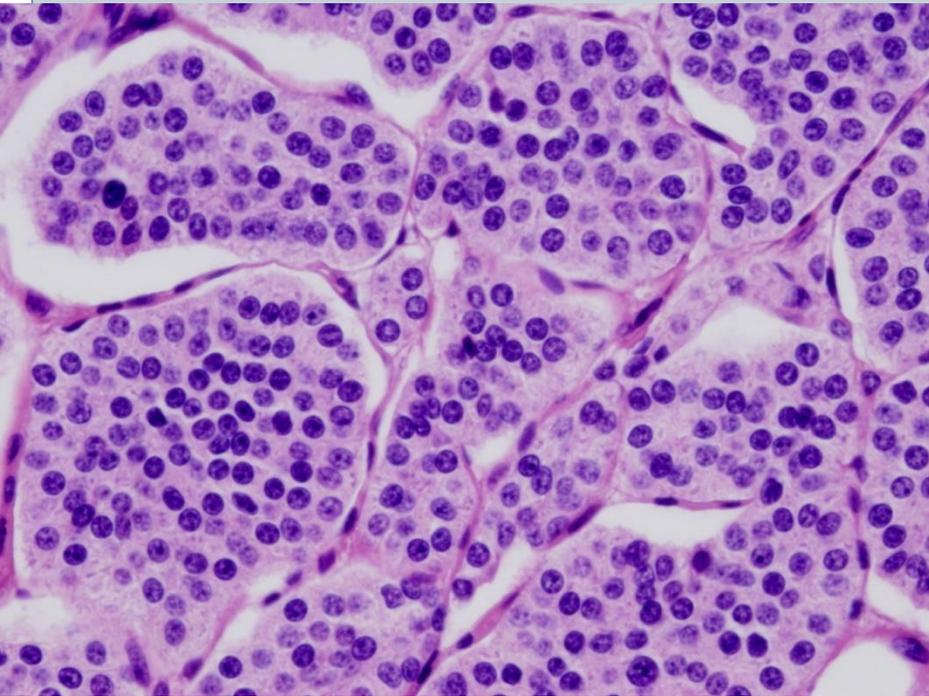
- **PLEOMORPHISM**

Variation in cellular size and shape

- **MALIGNANT**

A neoplasm with invasive and metastatic capacity.

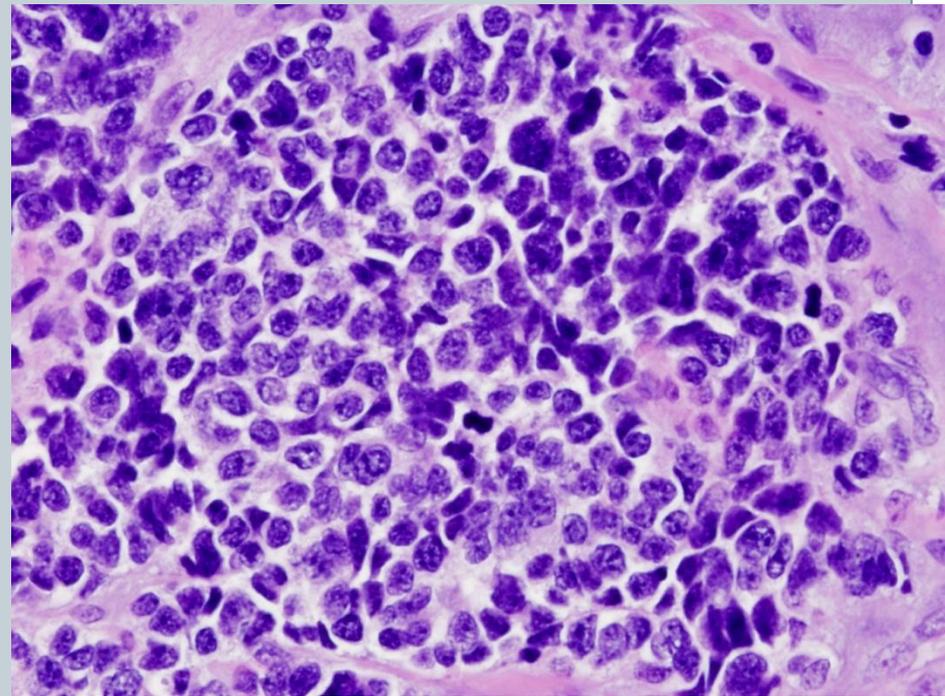
# Pulmonary Neuroendocrine Carcinoma



Carcinoid (400x)

LOW GRADE, MINIMAL TO NO ATYPIA

MONOMORPHIC

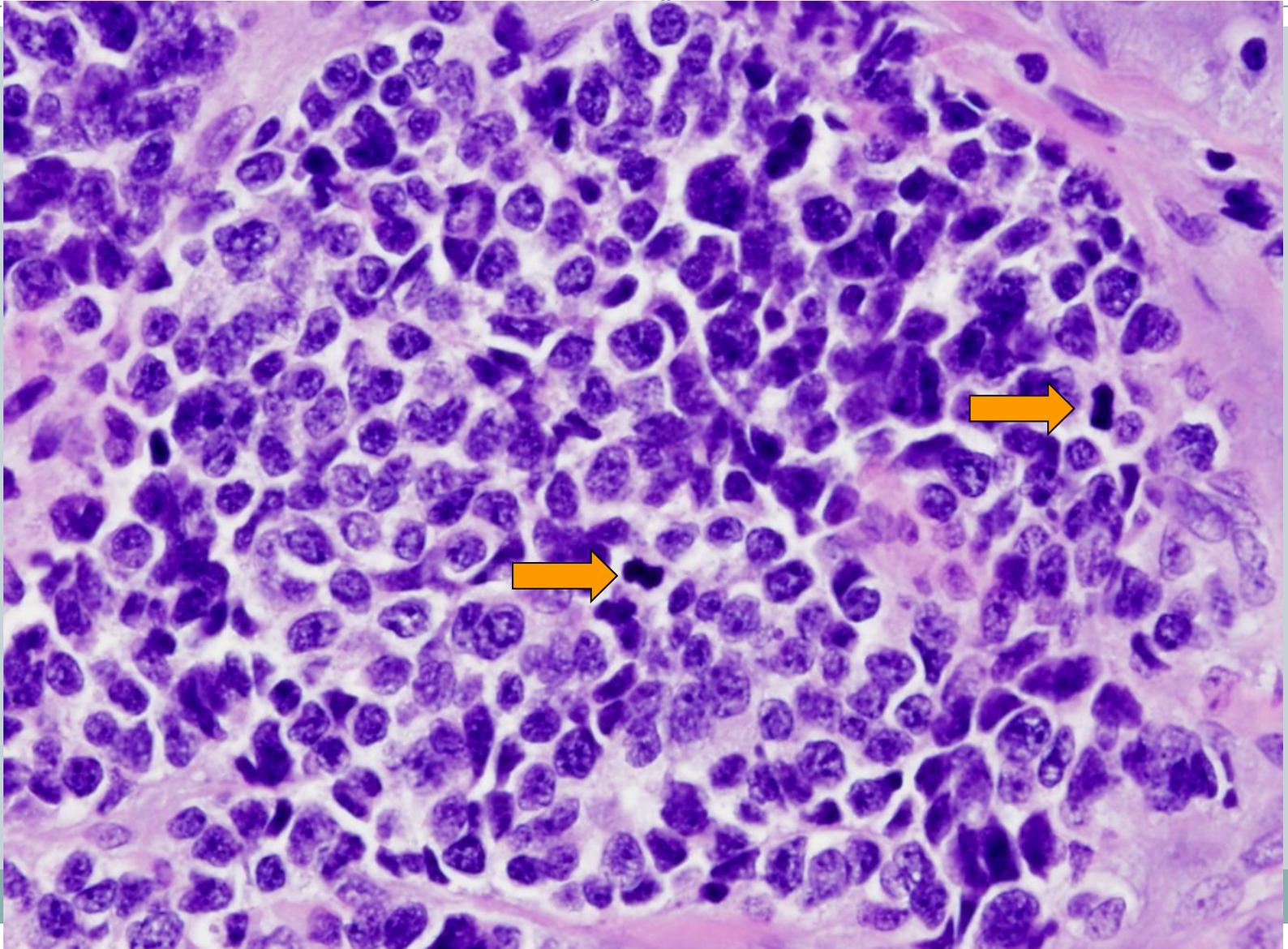


Small Cell Carcinoma (400x)

HIGH GRADE, SEVERE ATYPIA

PLEOMORPHIC

## NEC: Small Cell Carcinoma (400x)



# Beware: gross photos ahead



**APPROACHING A PATHOLOGIC SPECIMEN.**

# Approaching a pathologic specimen



- **GROSS APPEARANCE**

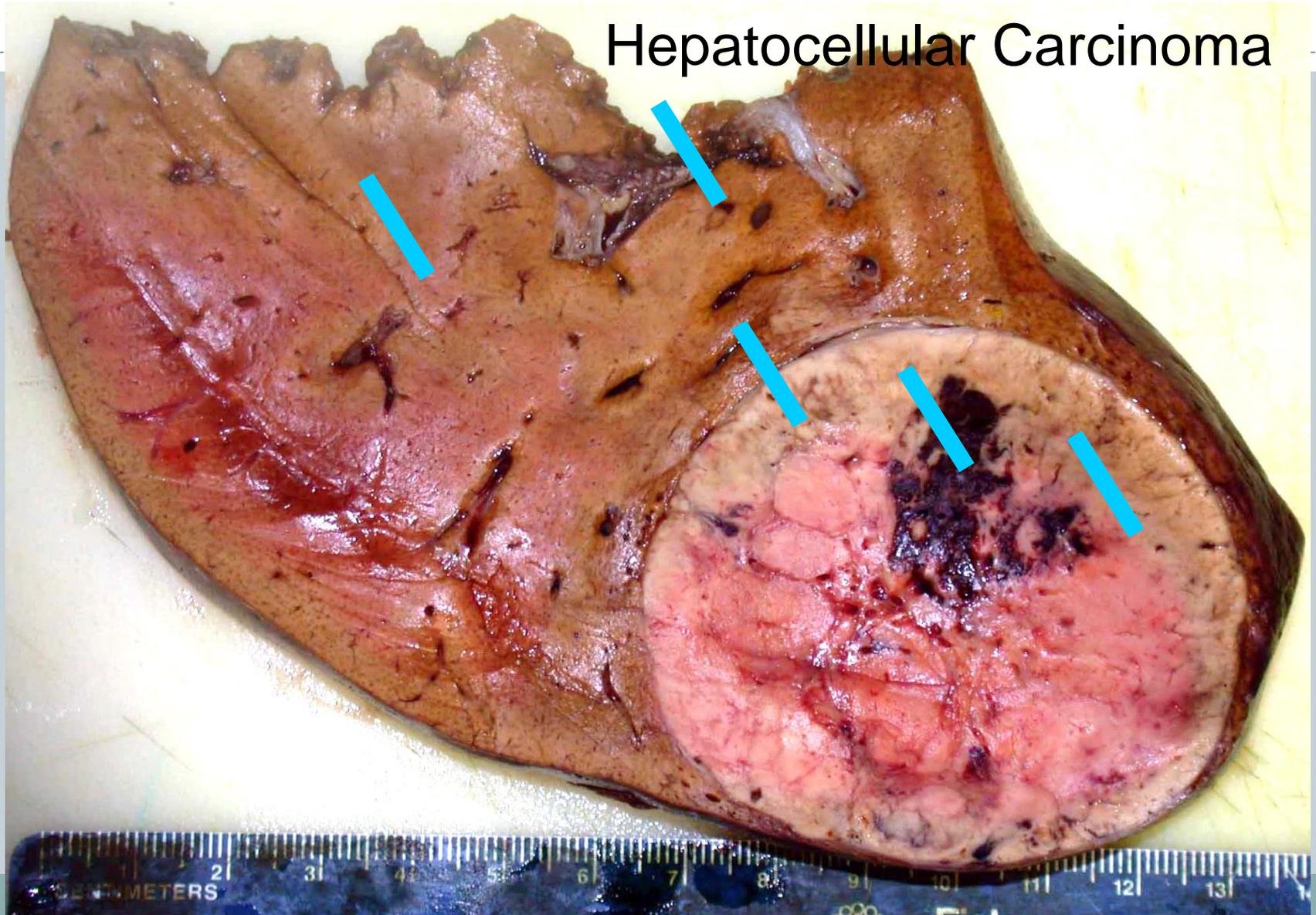
- “dissect” and describe the specimen
- Take carefully selected portions of tissue for subsequent examination under the microscope

- **MICROSCOPIC APPEARANCE**

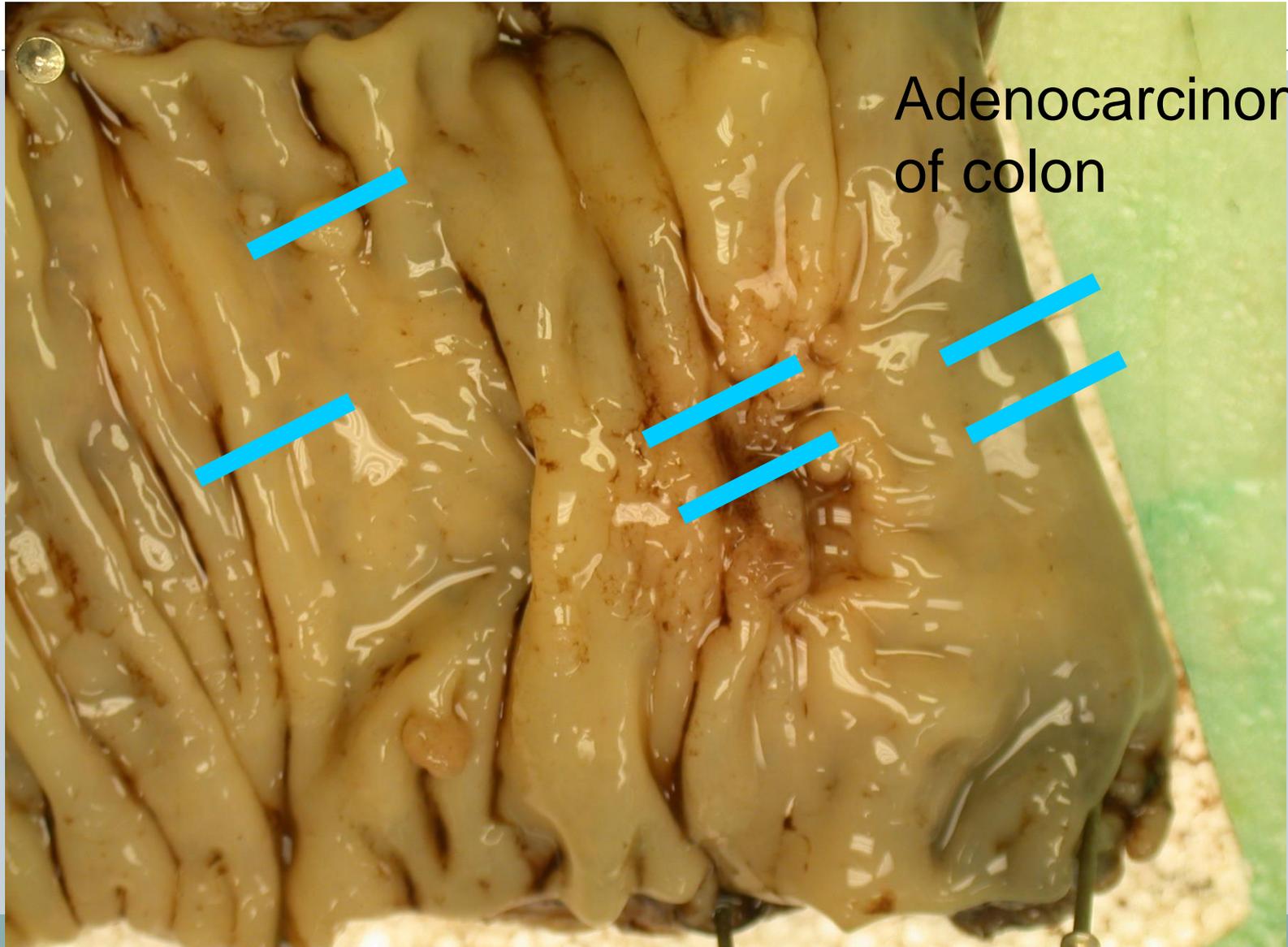
- Routine Hematoxylin and Eosin stained slides
- Special histologic techniques (stains, immunohistochemistry)

# Gross Specimen...

## Hepatocellular Carcinoma



# Another Gross Specimen



Adenocarcinoma  
of colon

# Approaching a pathologic specimen



- Is there pathology present?
- What is the general nature of the pathology?
  - Infectious, neoplastic, inflammatory/autoimmune
- If it IS neoplastic, what parameters must be collected?
  - Benign or malignant?
  - Tumor type, grade, stage, resection margin status

# General Types of Neoplasia



- **EPITHELIAL** (eg. Carcinoma)
  - Generally derived from ectoderm or endoderm
- **MESENCHYMAL** (eg. Sarcoma)
  - Generally derived from mesoderm (neural tissue is an exception → it's ectodermal)
- **HEMATOPOEITIC** (eg. Lymphoma)
  - Generally derived from mesoderm
- **MIXED** (eg. Carcinosarcoma)
- **OTHER** (eg. Germ cell tumor)

# Epithelial Tumors



adenoma  
papilloma  
carcinoma  
etc

# Carcinoma

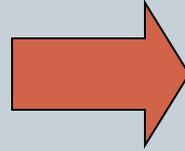
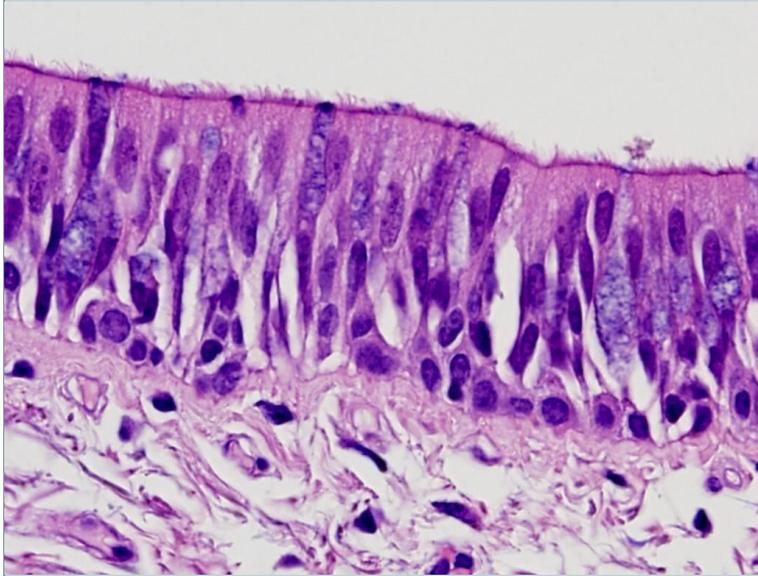


- Malignant tumor of epithelium
- Comes in different types depending on origin:
  - Squamous cell carcinoma
  - Adenocarcinoma (glandular)
  - Neuroendocrine carcinoma
- Sometimes preceded by a pre-invasive lesion: severe dysplasia (carcinoma *in-situ*)

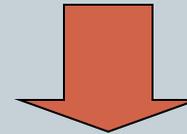
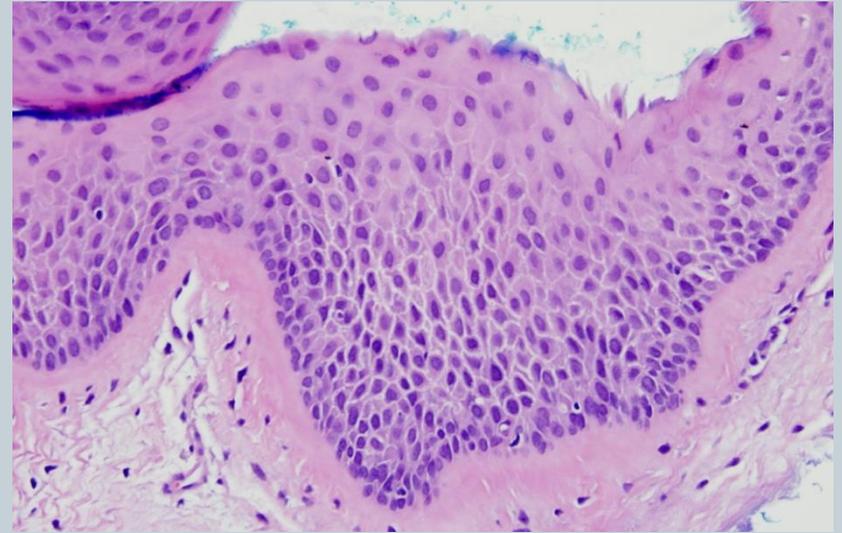
# Adenocarcinoma of Lung



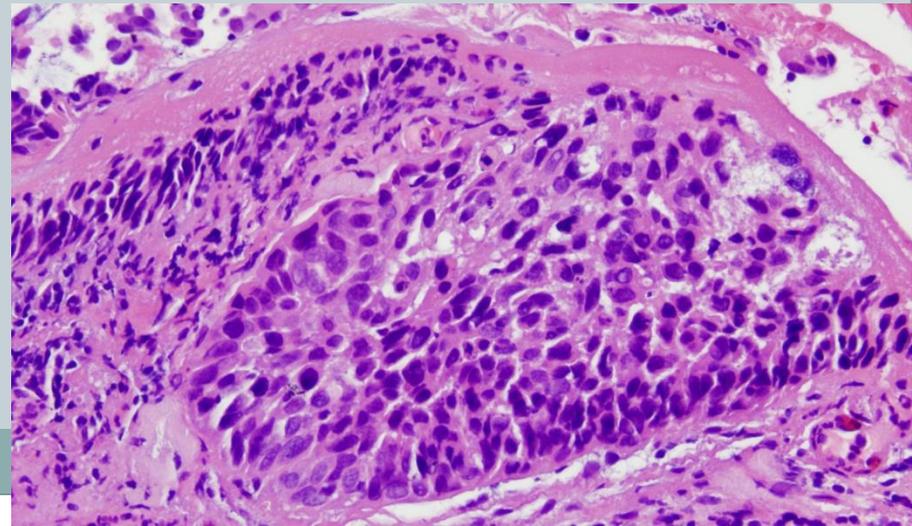
Normal Bronchial Epithelium (400x)



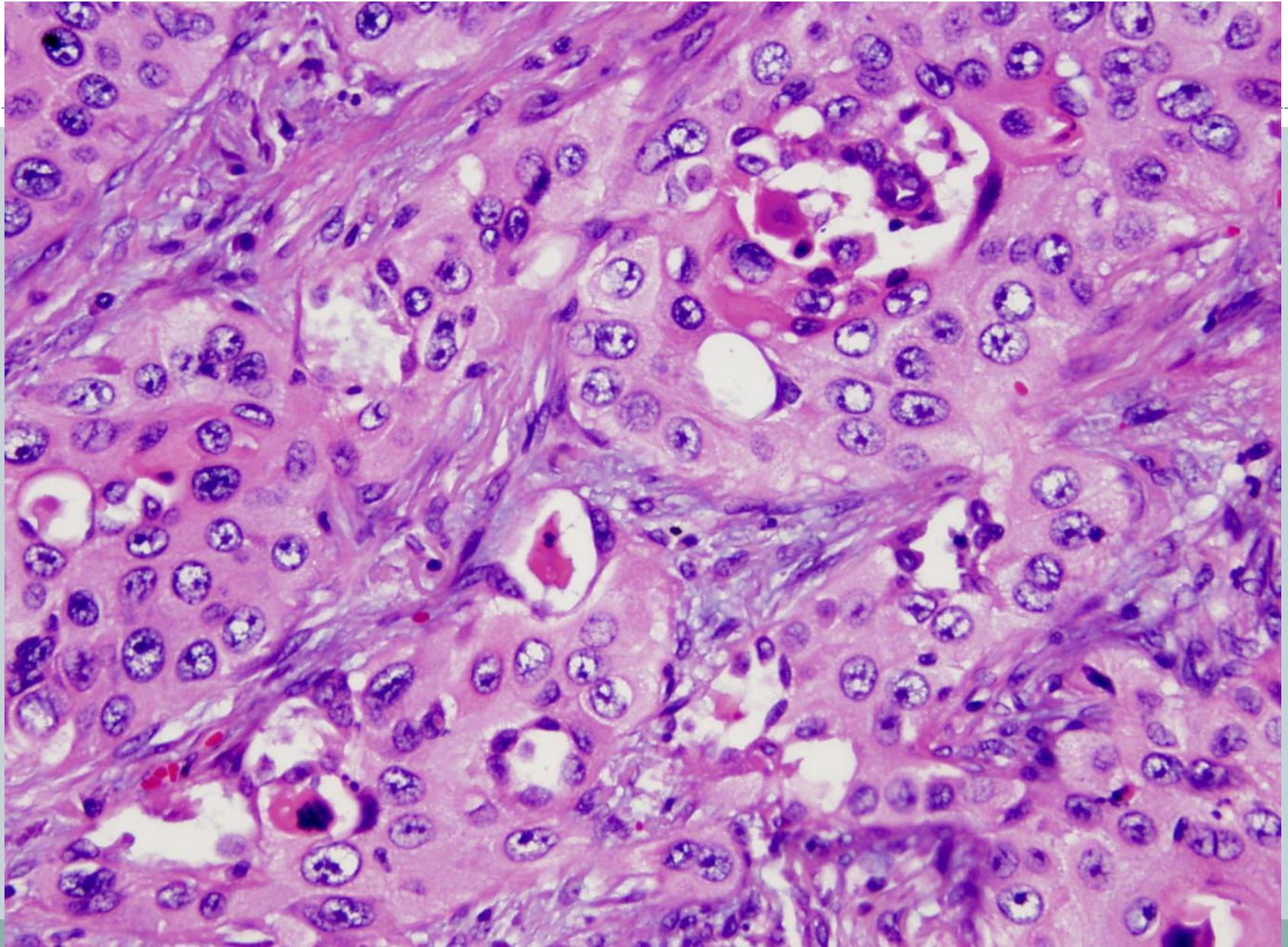
Bronchial Squamous Metaplasia (200x)



Severe Bronchial Squamous Dysplasia/Carcinoma in-situ (200x)



# Invasive Squamous Cell Carcinoma (400x)



# Carcinoma



- One hallmark of an epithelial neoplasm is cellular expression of **cytokeratin** (CK) intermediate filaments
- Cytokeratin expression profile can also help identify the primary site/source of a carcinoma (immunohistochemistry)
  - CK 7, CK 20, CK 5/6

# Mesenchymal tumors



- OMA
- SARCOMA

# Mesenchymal tumors



- Tumors of connective/mesenchymal tissue

Named according to their putative origin and differentiation:

<u>Tissue Type</u>	<u>Malignant</u>	<u>Benign</u>
Smooth muscle	leiomyosarcoma	leiomyoma
Skeletal muscle	rhabdomyosarcoma	rhabdomyoma
Blood vessels	angiosarcoma	angioma
Cartilage	chondrosarcoma	chondroma
Bone	osteosarcoma	osteoma
Adipose (fat)	liposarcoma	lipoma

# Chondrosarcoma (Humerus)



# Mesenchymal Tumors



- *Usually* express the intermediate filament **vimentin**, and NOT cytokeratins
- May also express markers of differentiation:

Smooth Muscle →

smooth muscle actin

Nerve →

S100

Vascular →

Cluster of Differentiation 31  
(CD31)

# Hematopoietic Neoplasia



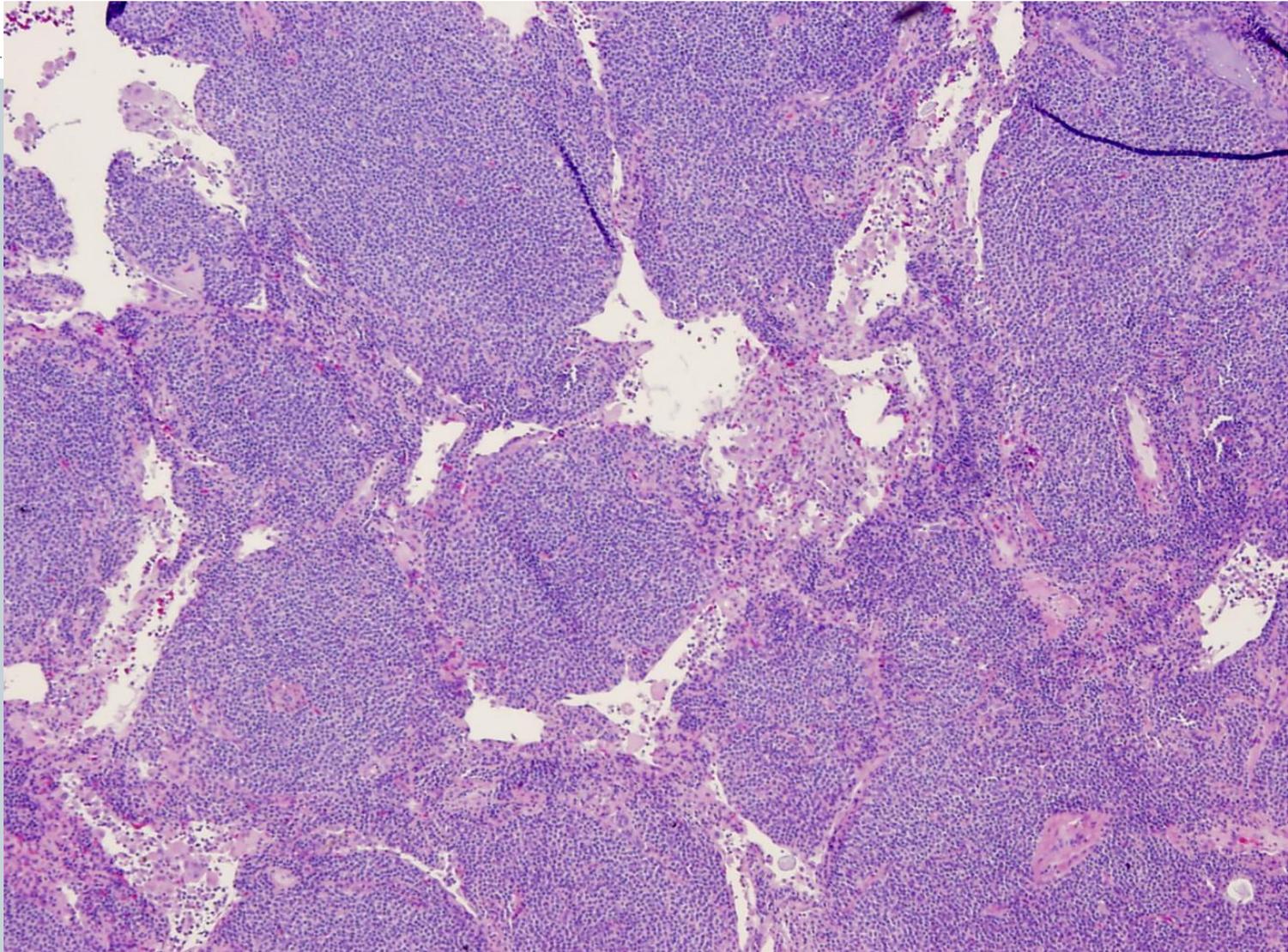
leukemia  
lymphoma

# Hematopoietic Neoplasia

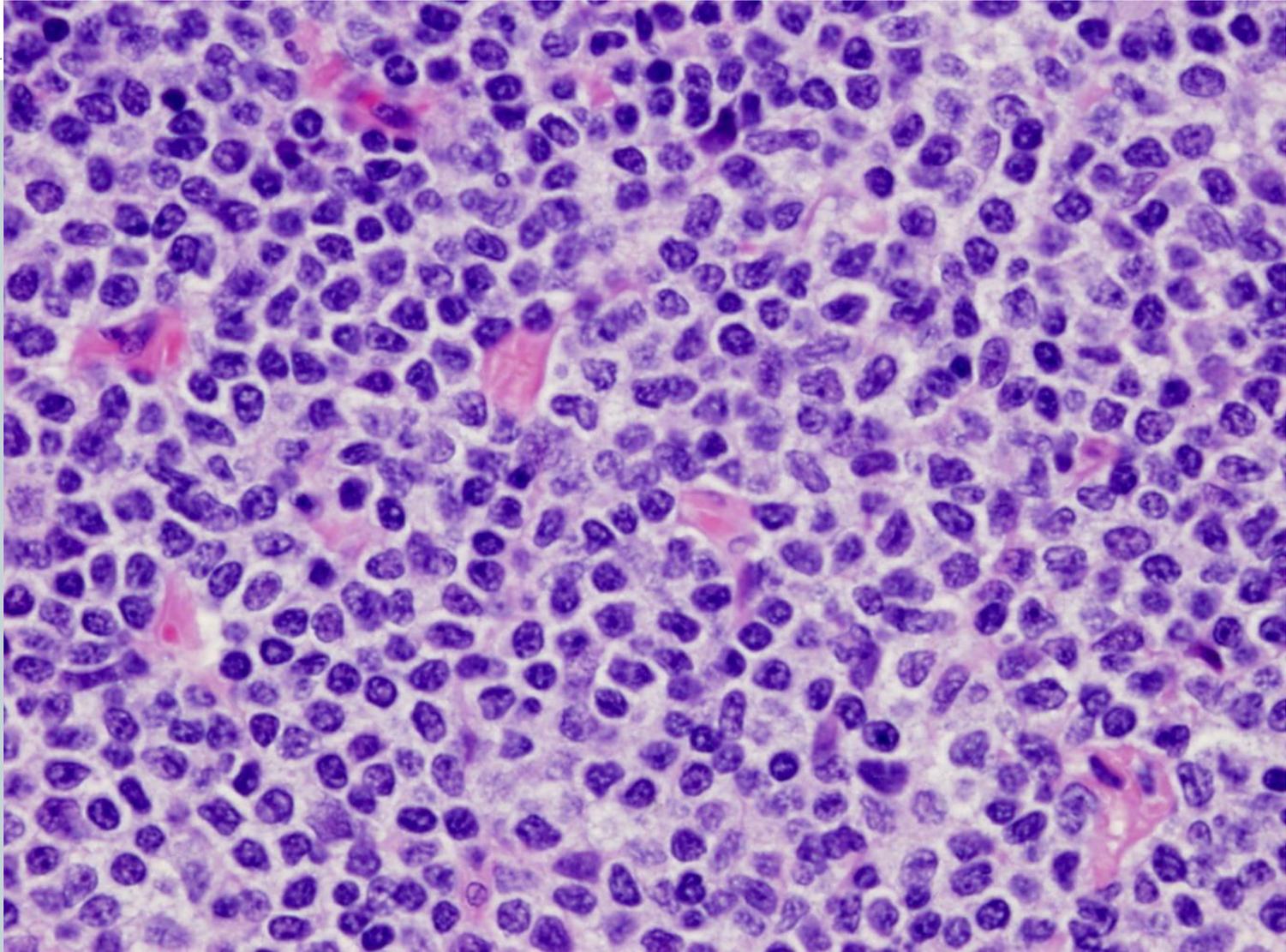


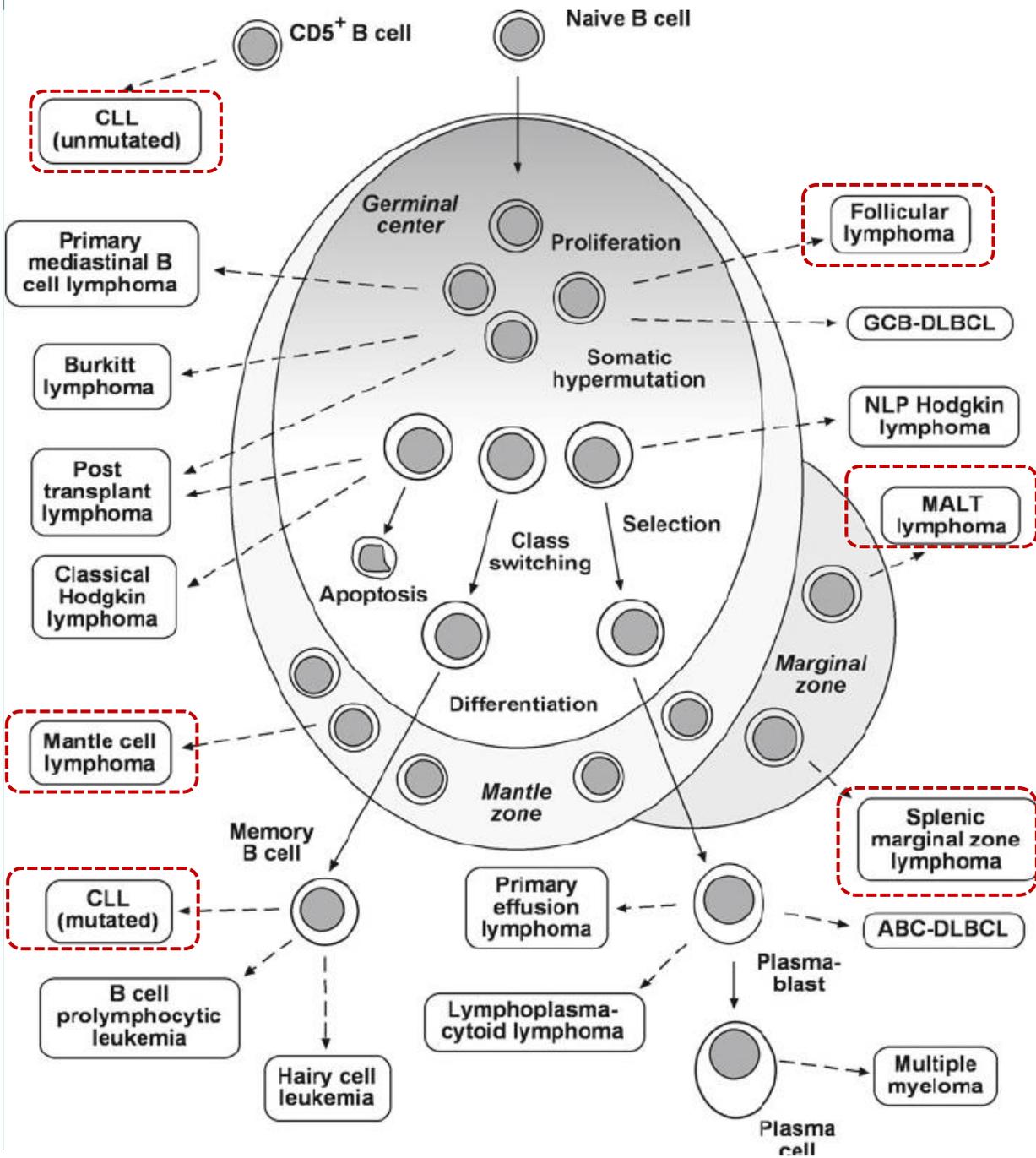
- Derived from bone marrow cells (red, white)
- **Lymphoma** (cells usually involve lymph node or other lymphoid tissue like spleen)
  - ✦ T-cell (CD3+, CD20-)
  - ✦ B-cell (CD20+, CD3-)
  - ✦ NK cell (CD56+)
- **Leukemia** (cells circulate in blood)
  - ✦ Myeloid (acute or chronic)
  - ✦ Lymphoid (acute or chronic)

# MALT Lymphoma of Lung (40x)



# MALT Lymphoma (400x)

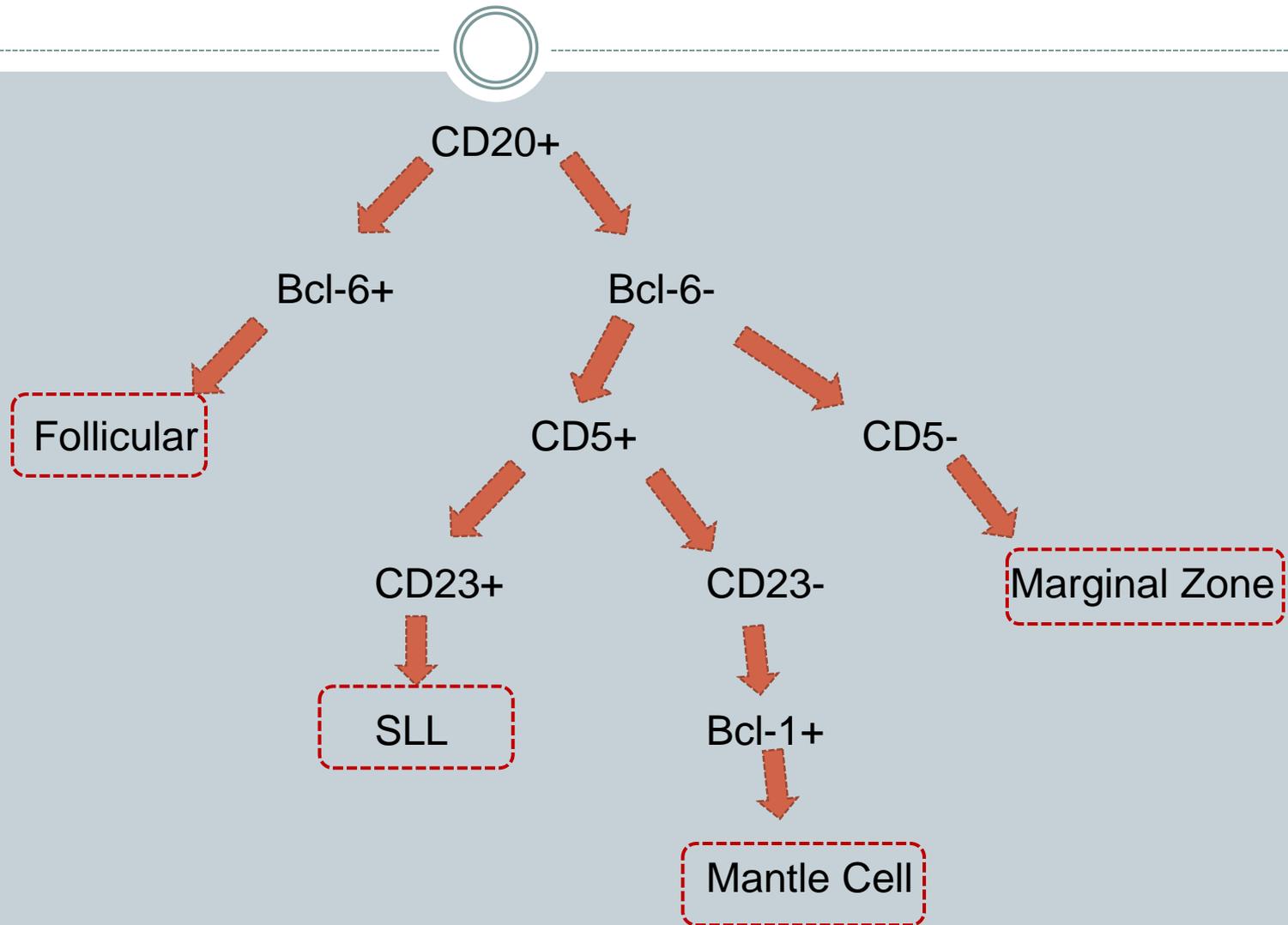




# Origin of B-cell lymphoma

Figure from: Lymphoma: Methods and Protocols, Methods in Molecular Biology, Volume 971. R. Kuppers (ed.), Springer 2013

# Simplified IHC small B-cell lymphoma





So how do we know if a bunch of cells is  
benign or malignant?

# Recognizing Malignancy



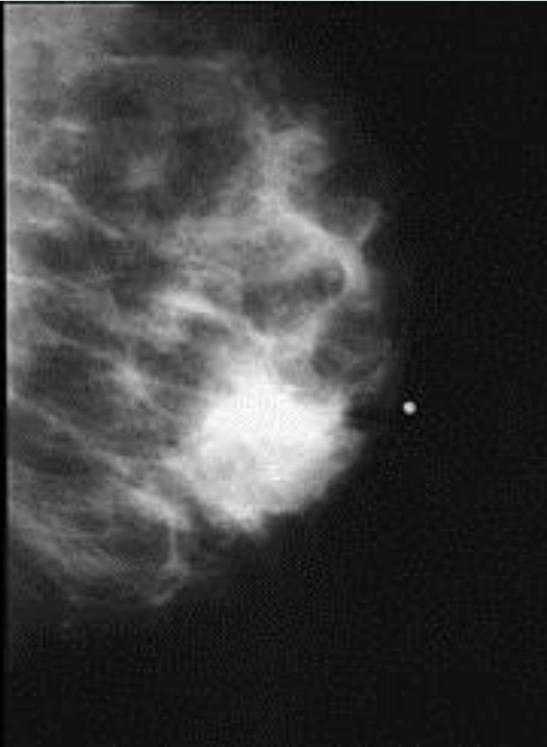
1. Architecture and Behavior
2. Proliferation (mitotic rate, antigenic markers)
3. Necrosis
4. Cytology (nuclear and cytoplasmic)

# Recognizing Malignancy



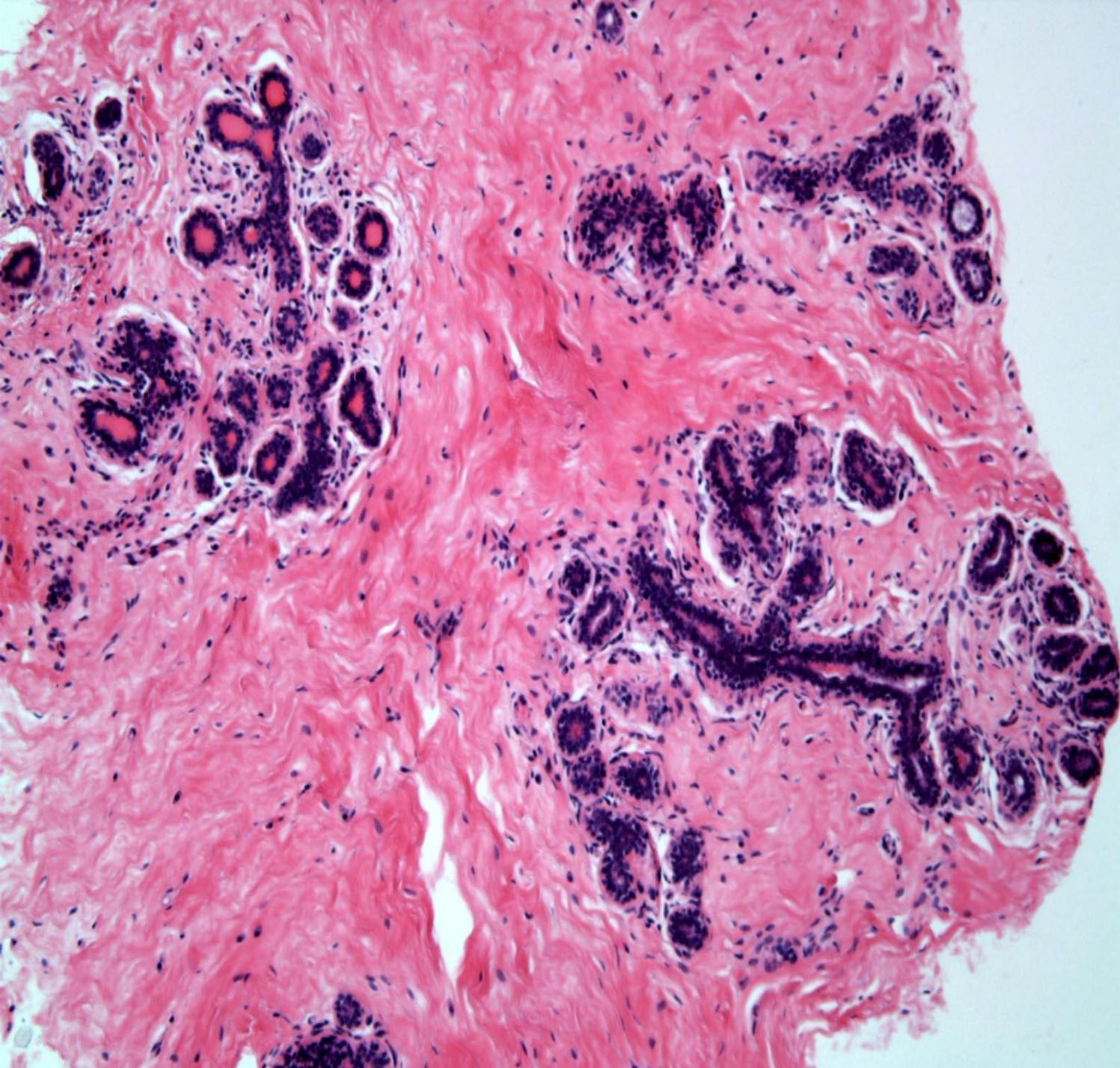
- **Architecture and behavior**
  - How closely does tumor resemble normal tissue?
  - What is the contour of the tumor?
  - Is there invasion of adjacent tissue?
  - Is there invasion of blood vessels or nerves?
  - Does it have a capsule?

# Mammogram of Ductal Carcinoma



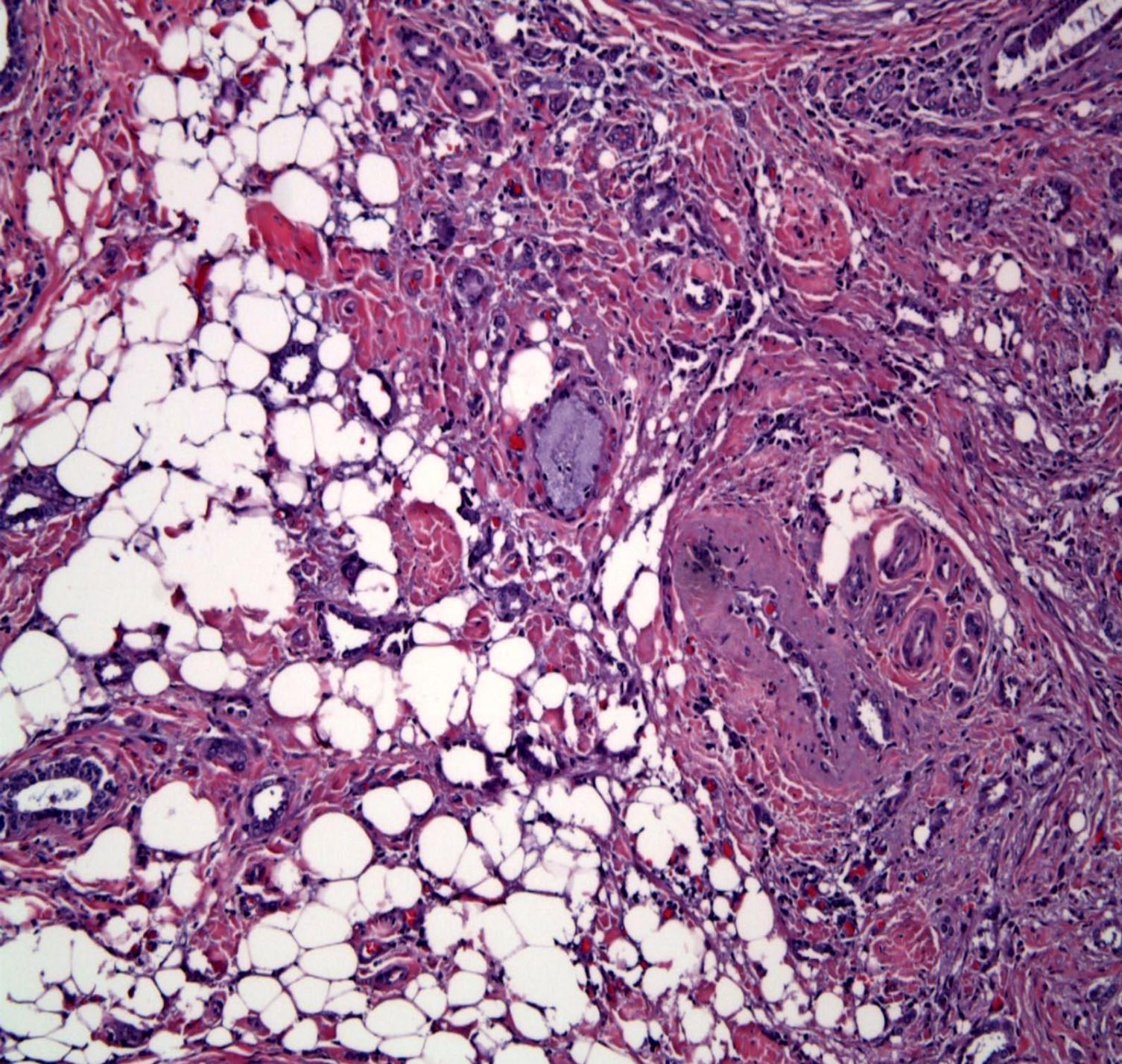
Copyright © 1999 by W. B. Saunders  
Company  
All rights reserved.  
Produced in the United States of  
America  
ISBN: 0-7216-8462-9

Image from: [medic.med.uth.tmc.edu](http://medic.med.uth.tmc.edu)



## BENIGN

- Organized
- Well circumscribed
- No infiltration of adjacent tissue.
- Normal stroma



## MALIGNANT

- Disorganized.
- Poorly circumscribed.
- Infiltrates adjacent fat.
- Desmoplastic stroma.

# Recognizing Malignancy



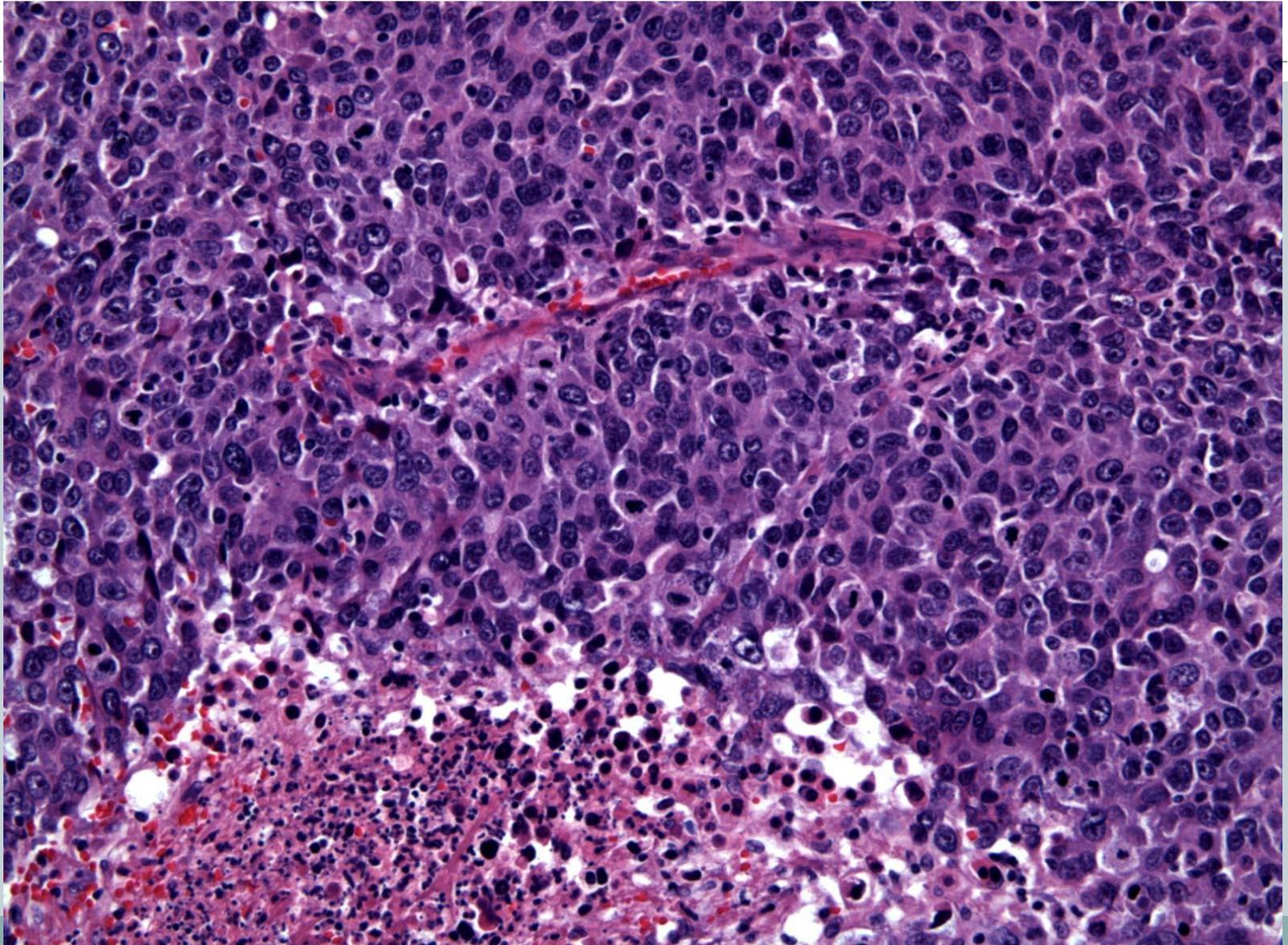
- **Proliferative Rate**

- What is the mitotic count? (number of mitoses per 10 high-power 400x microscopic fields)
- Are mitoses normal in form?
- What is the percentage of cells expressing markers of proliferation? (Ki-67/Mib-1)

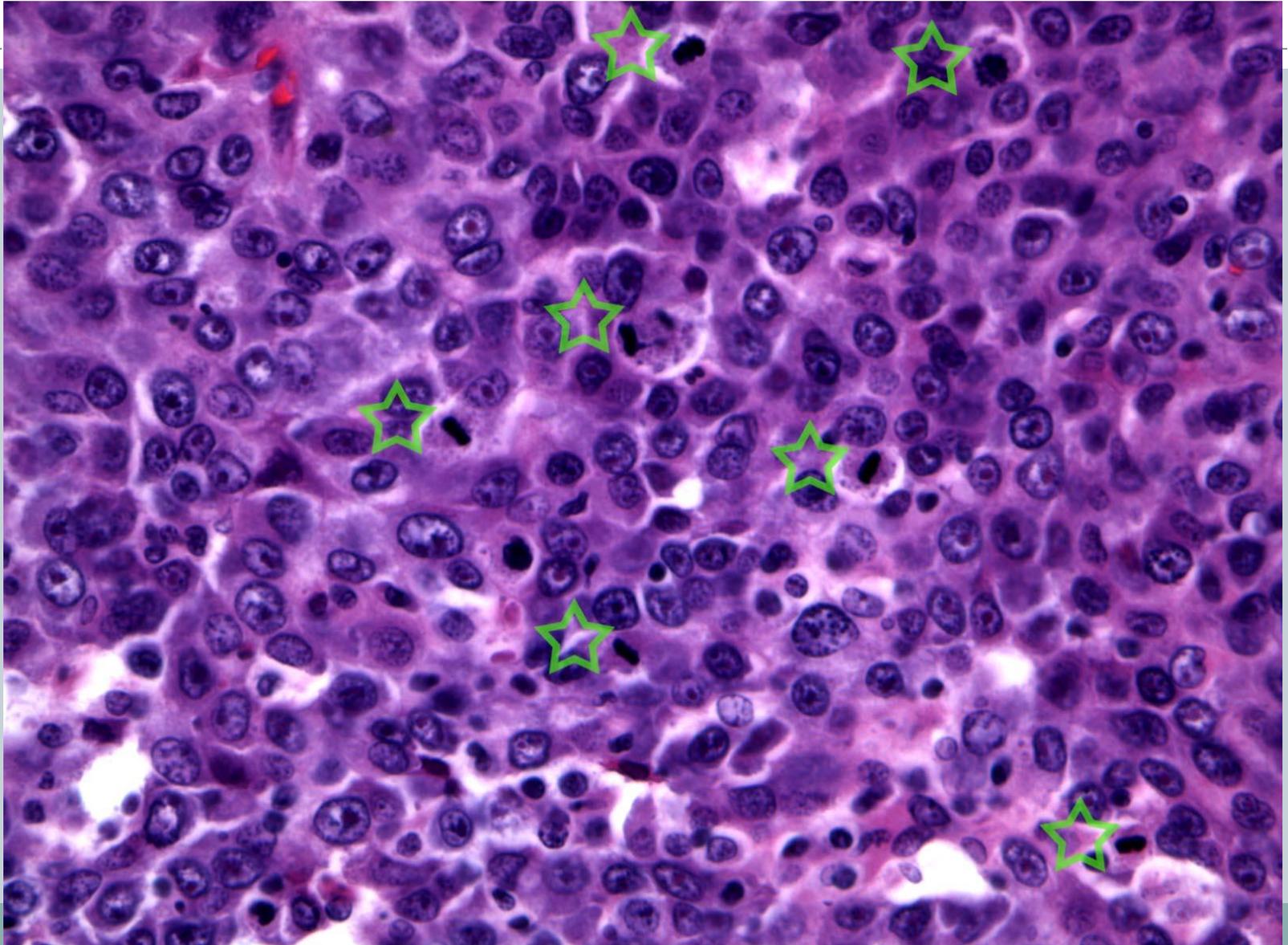
- **Necrosis**

- Is there tumor necrosis? (function of rapid uncontrolled proliferation, loss of cell cycle control)

# Hepatocellular Carcinoma with Necrosis



# Hepatocellular Carcinoma with Mitosis

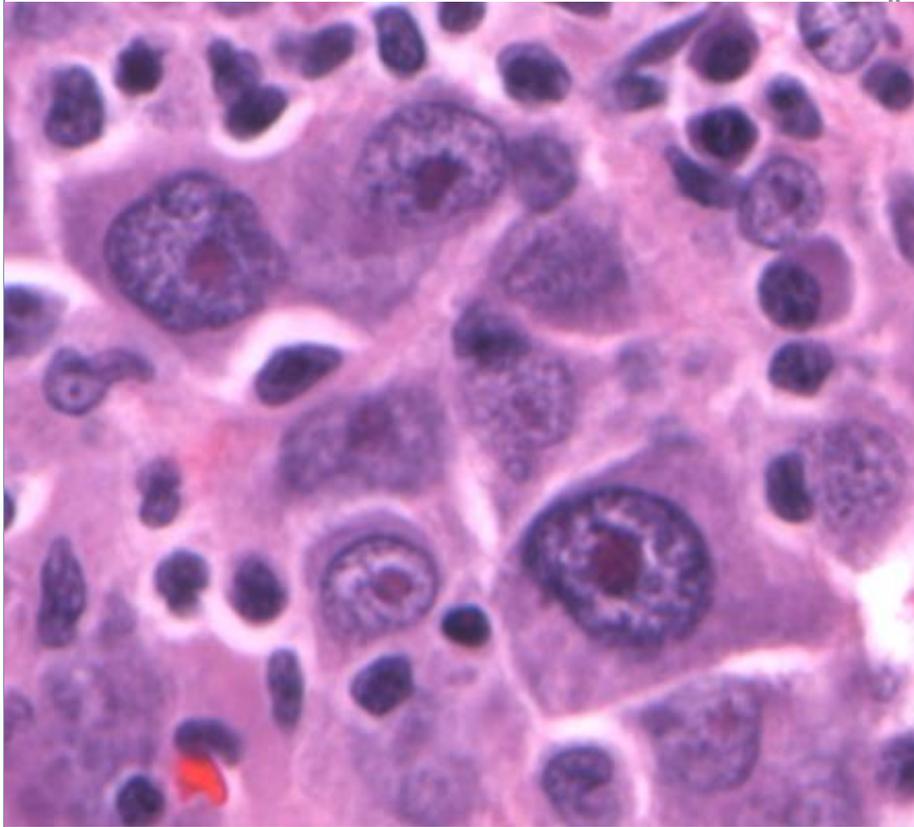


# Recognizing Malignancy



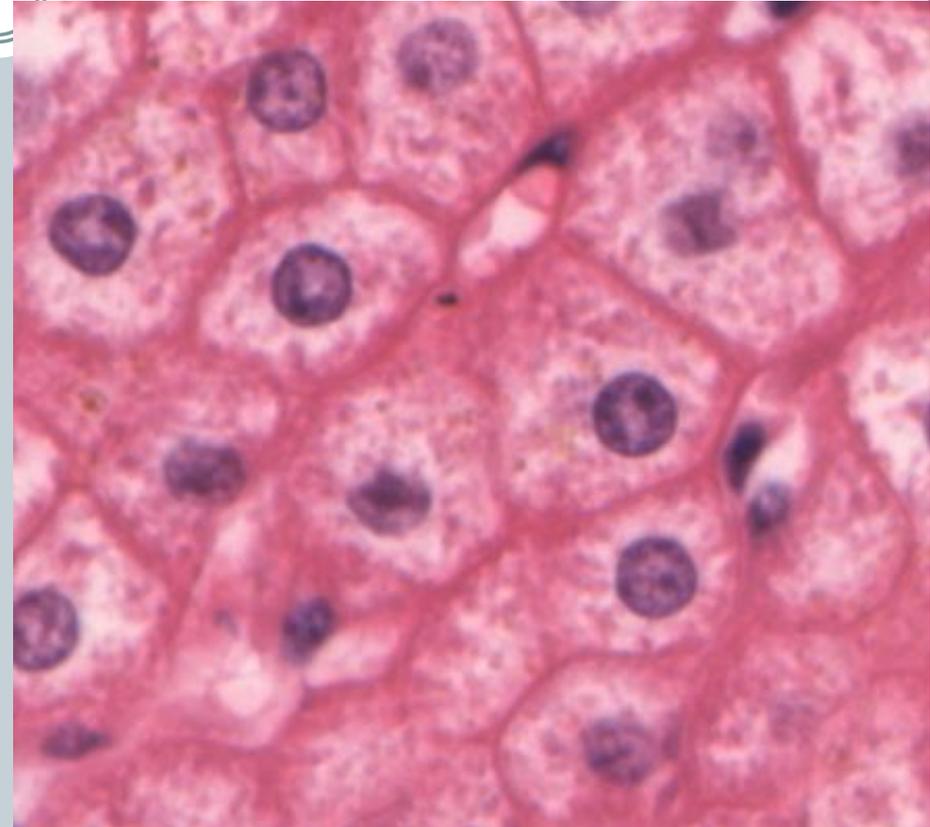
- Cytology (a function of rapid proliferative rate and abnormal, active cellular “machinery”)
  - What is the character of the nuclear chromatin?
  - Are there abnormal nucleoli present?
  - What is the contour of the nuclear membrane?
  - What is the nucleus:cytoplasmic ratio? (N:C ratio)
  - Is the cytoplasm mature?

# Benign or malignant nuclei (400x)?



#1

**MALIGNANT**



#2

**BENIGN**

END OF LECTURE ONE

