How Do Pathologists Make a Diagnosis

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A pathologist provides care to which of the following patients?

A. 52-year-old female with an abnormal mammogram who has a biopsy performed
B. 21-year-old male requiring many units of blood after a motor vehicle accident
C. 72-year-old male with a fungal infection in his lung
D. A neonate who is being tested for Down's Syndrome
E. 14-year-old female with low blood count following the beginning of menarche

Objectives

- Describe the scope of practice for pathology and laboratory medicine
- Discuss the *value* of pathology in providing best patient care
- Describe the process and quality systems used to ensure accurate results
- Understand the pathologic features neoplasms
- Describe the “team” of medical professionals

Scope of Practice for Pathology and Laboratory Medicine

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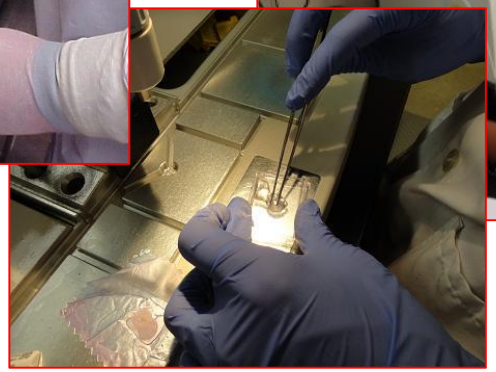
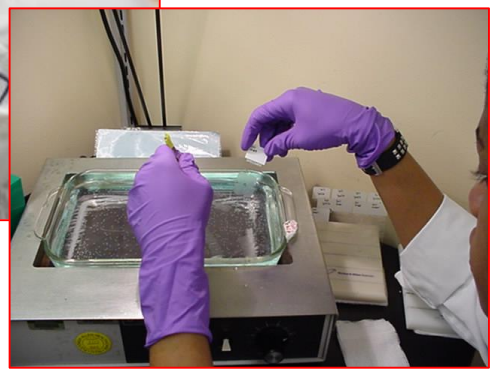
E. 14-year-old female with low blood count following the beginning of menarche

52-year-old female with an abnormal mammogram who has a biopsy performed

- A biopsy of tissue is sent to the laboratory
- Specimen is processed
- Tissue is thinly cut and put on a glass slide



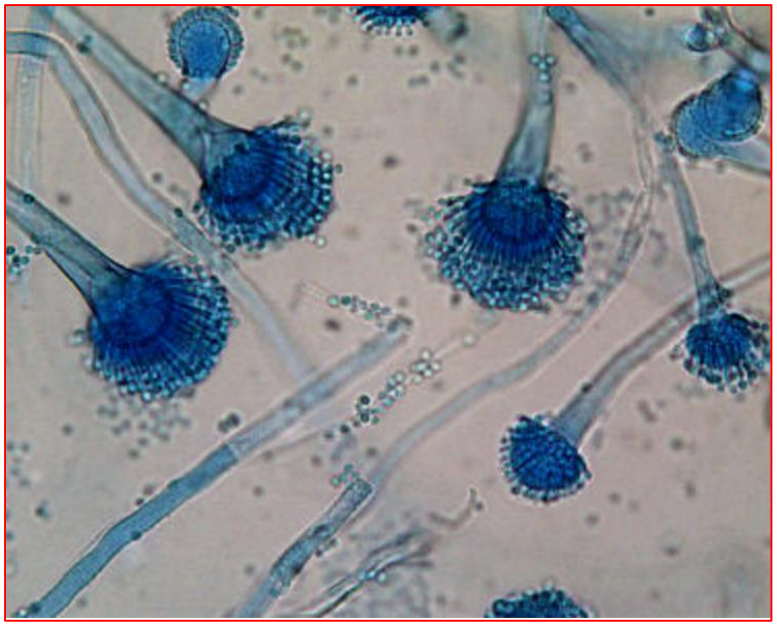


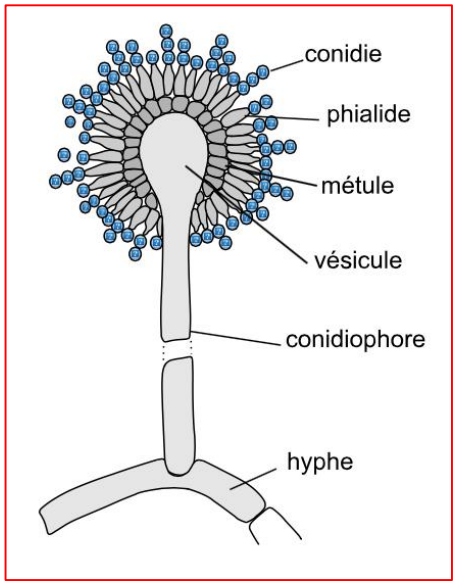
21-year-old male requiring many units of blood after a motor vehicle accident

- Patients requiring large amounts of blood activates the Massive Transfusion Protocol
- Pathologist works with clinicians to ensure appropriate blood products to stabilize patient
- Review relevant laboratory studies to guide therapy

72-year-old male with a fungal infection in his lung

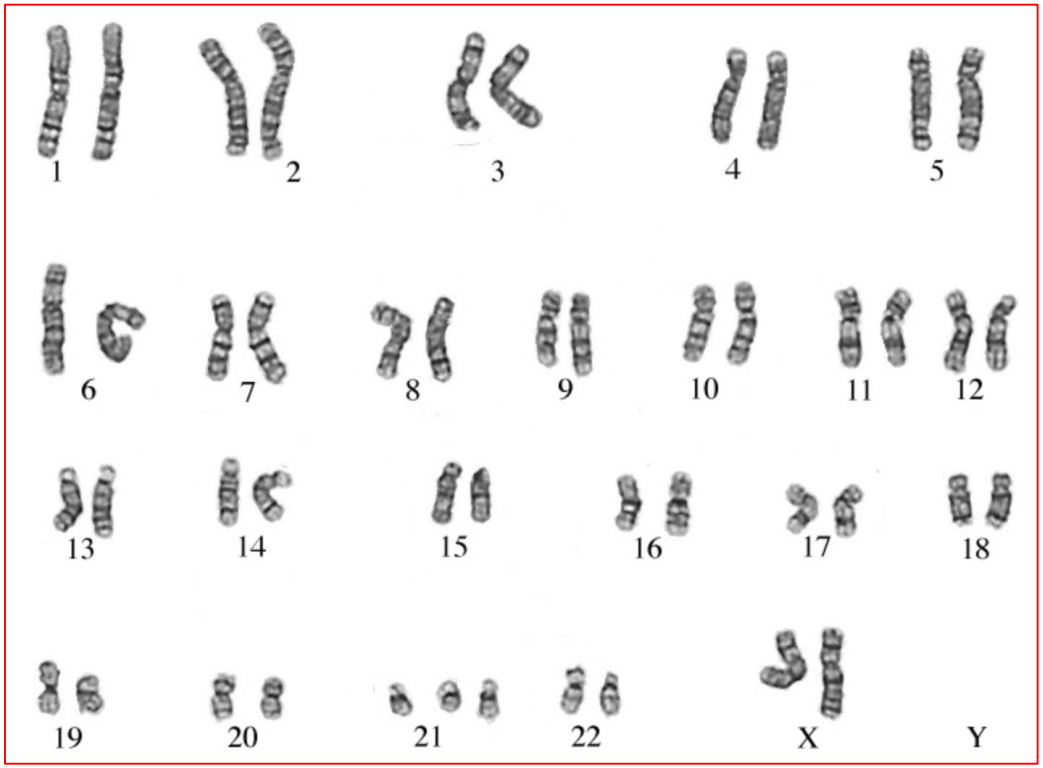
- A sputum sample is sent to the microbiology laboratory
- Specimen cultured on growth medium with proper nutrients
- A slide is prepared when the fungus grows





A neonate who is being testing for Down's Syndrome

- A blood sample is sent to the laboratory and white bloods cells are removed
- The DNA (genetic material) is removed and tested



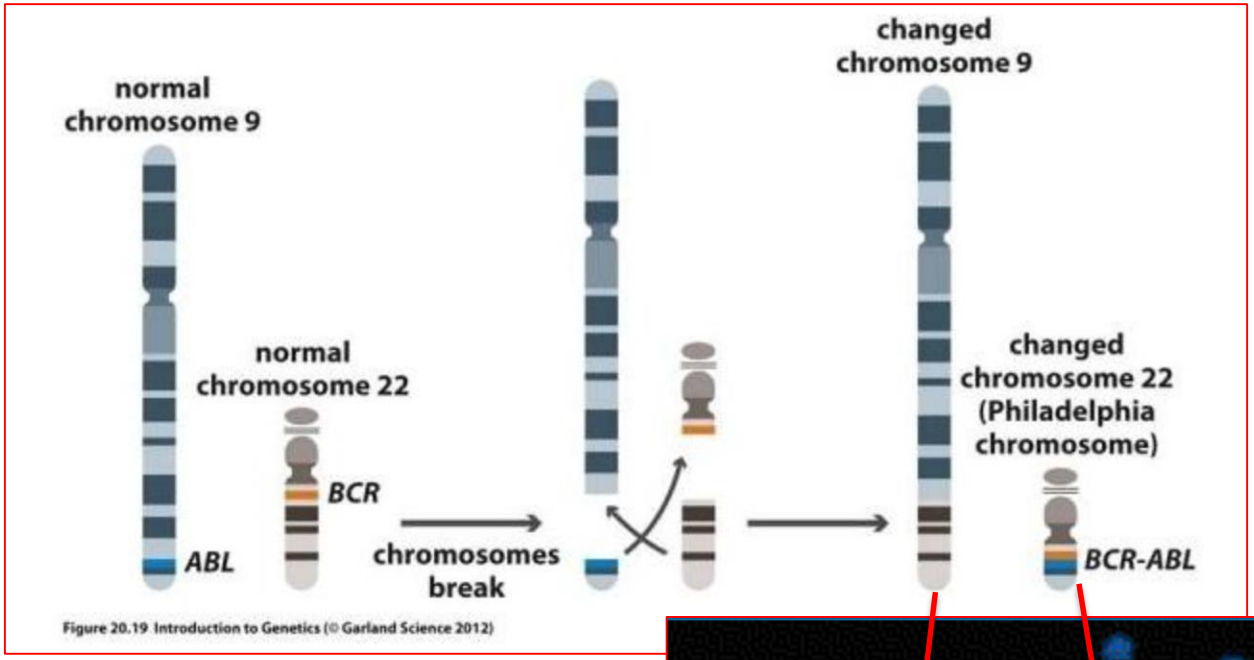
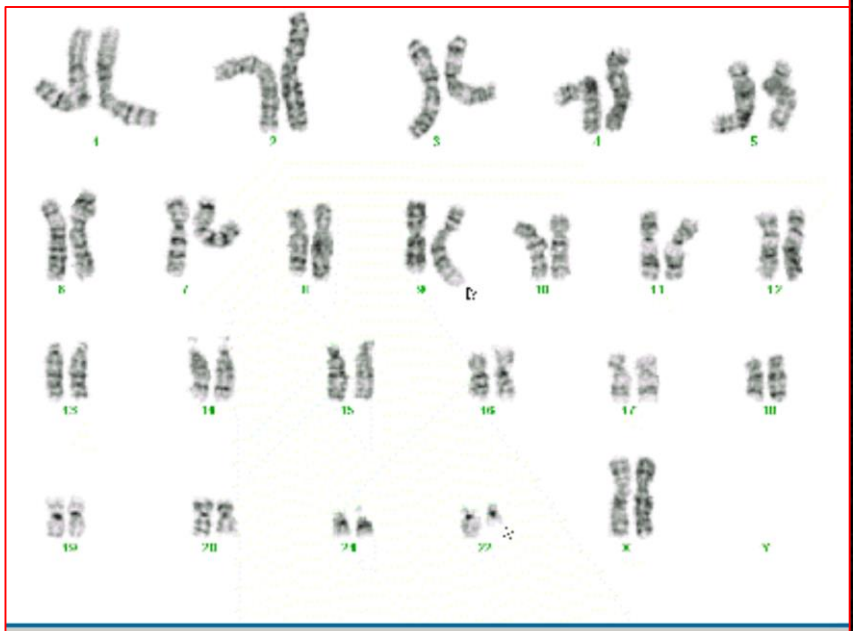
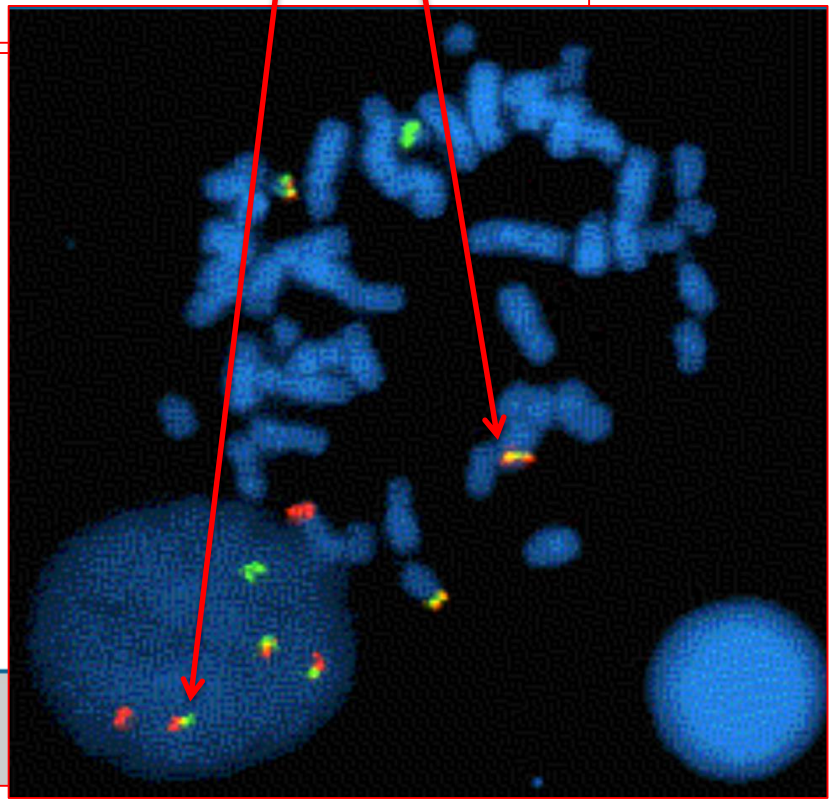


Figure 20.19 Introduction to Genetics (© Garland Science 2012)

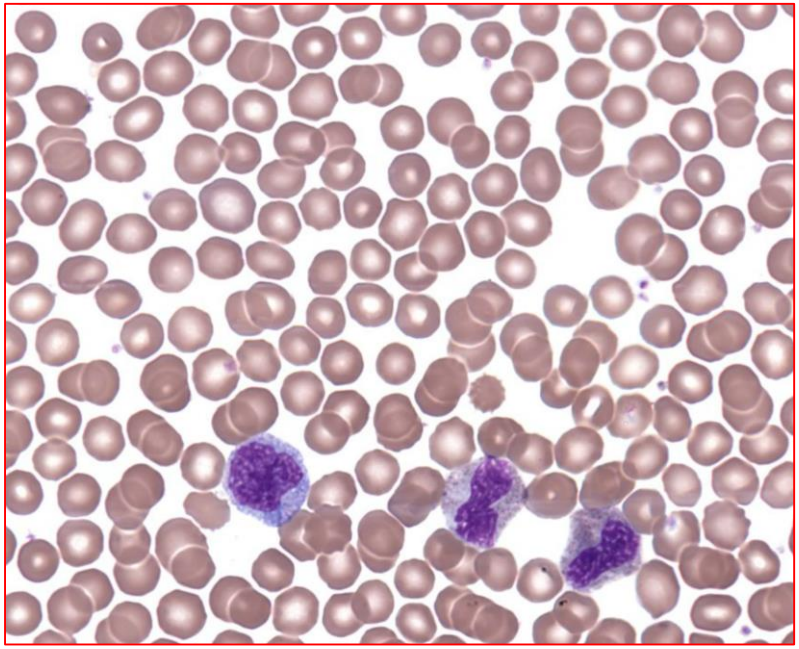


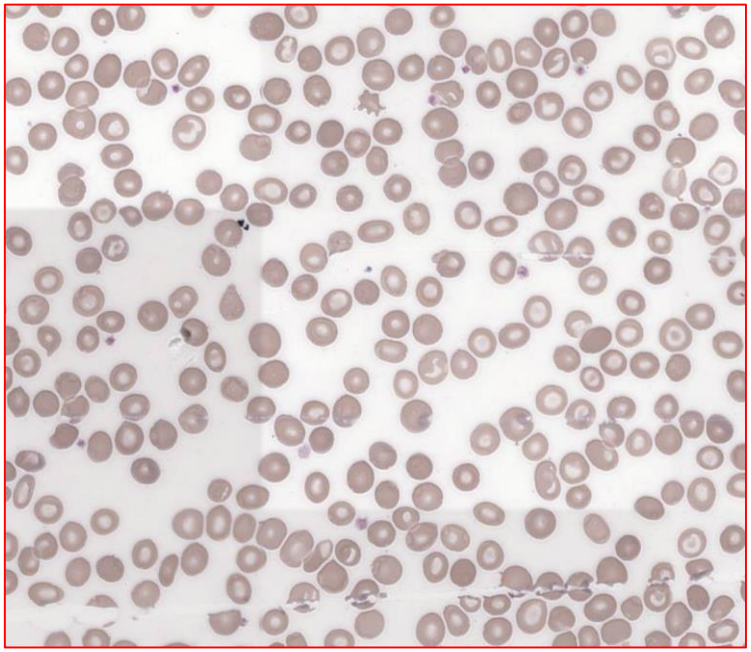
Karyotype showing the Philadelphia chromosome.
46,XX,t(9;22)(q34.1;q11.2



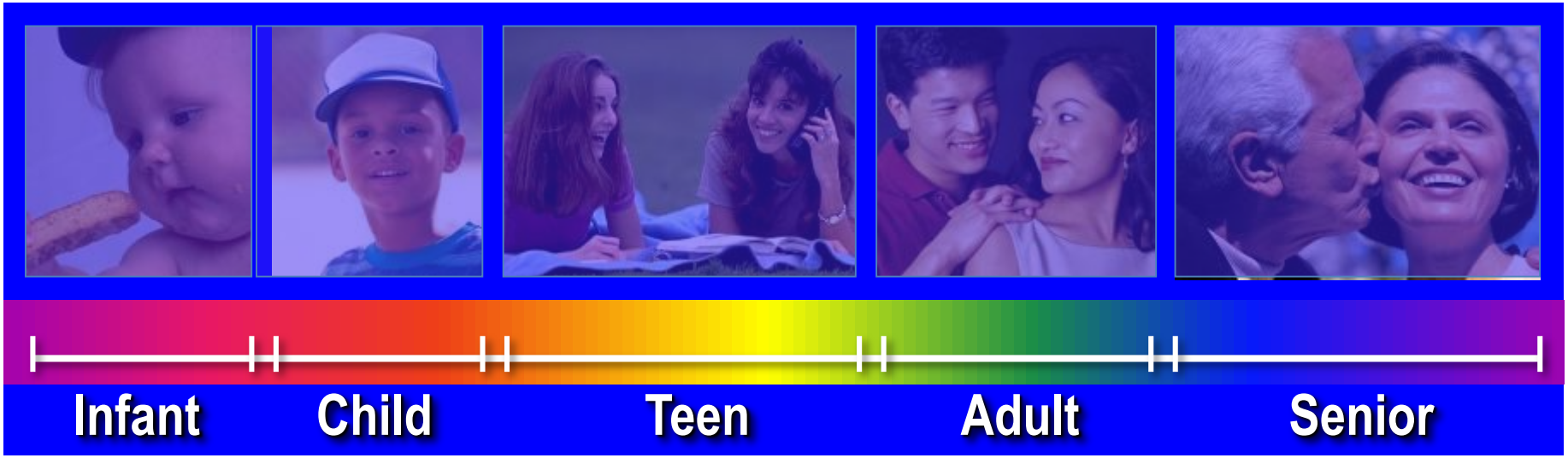
14-year-old female with low blood count following the beginning of menarche

- A tube of blood is sent to the lab for a complete blood count
- Results indicate a microcytic anemia and a peripheral blood smear is made



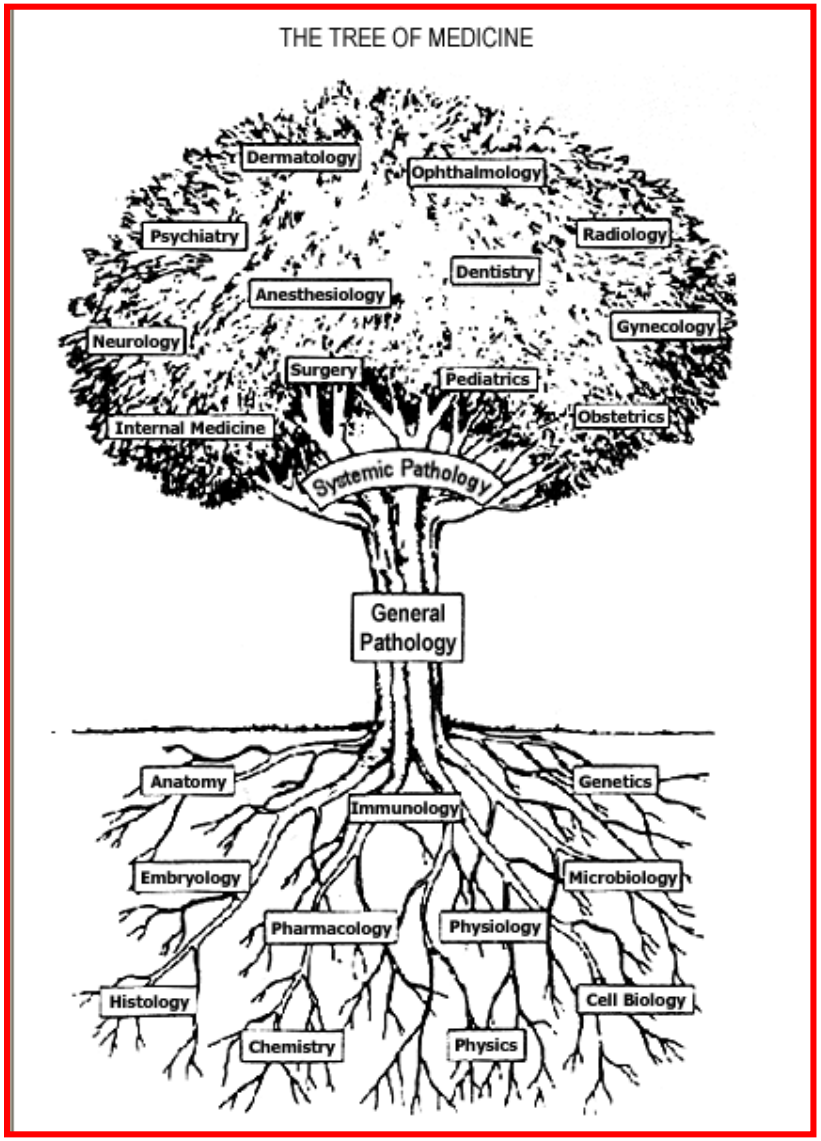


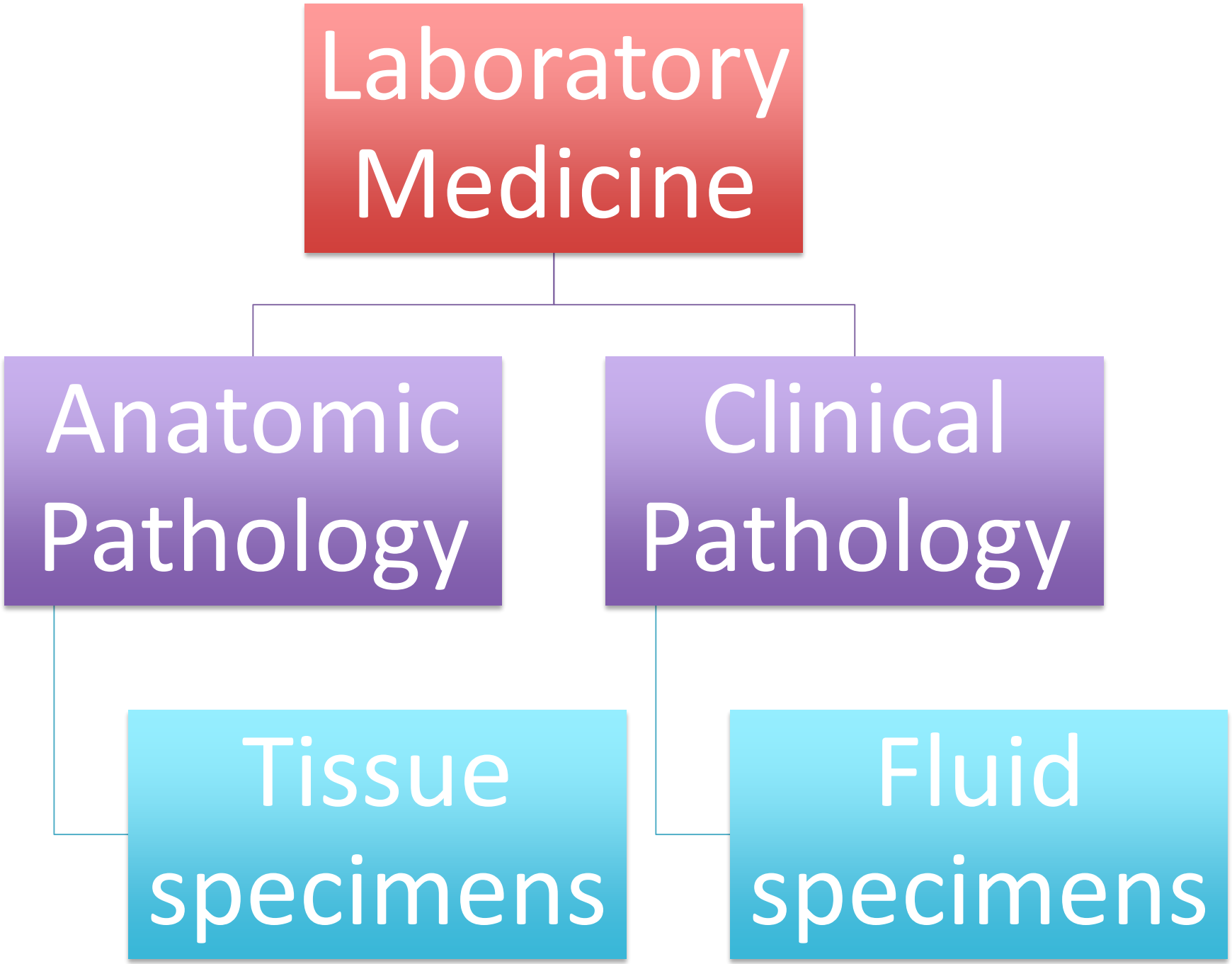
Laboratory Medicine Impacts Nearly Everyone

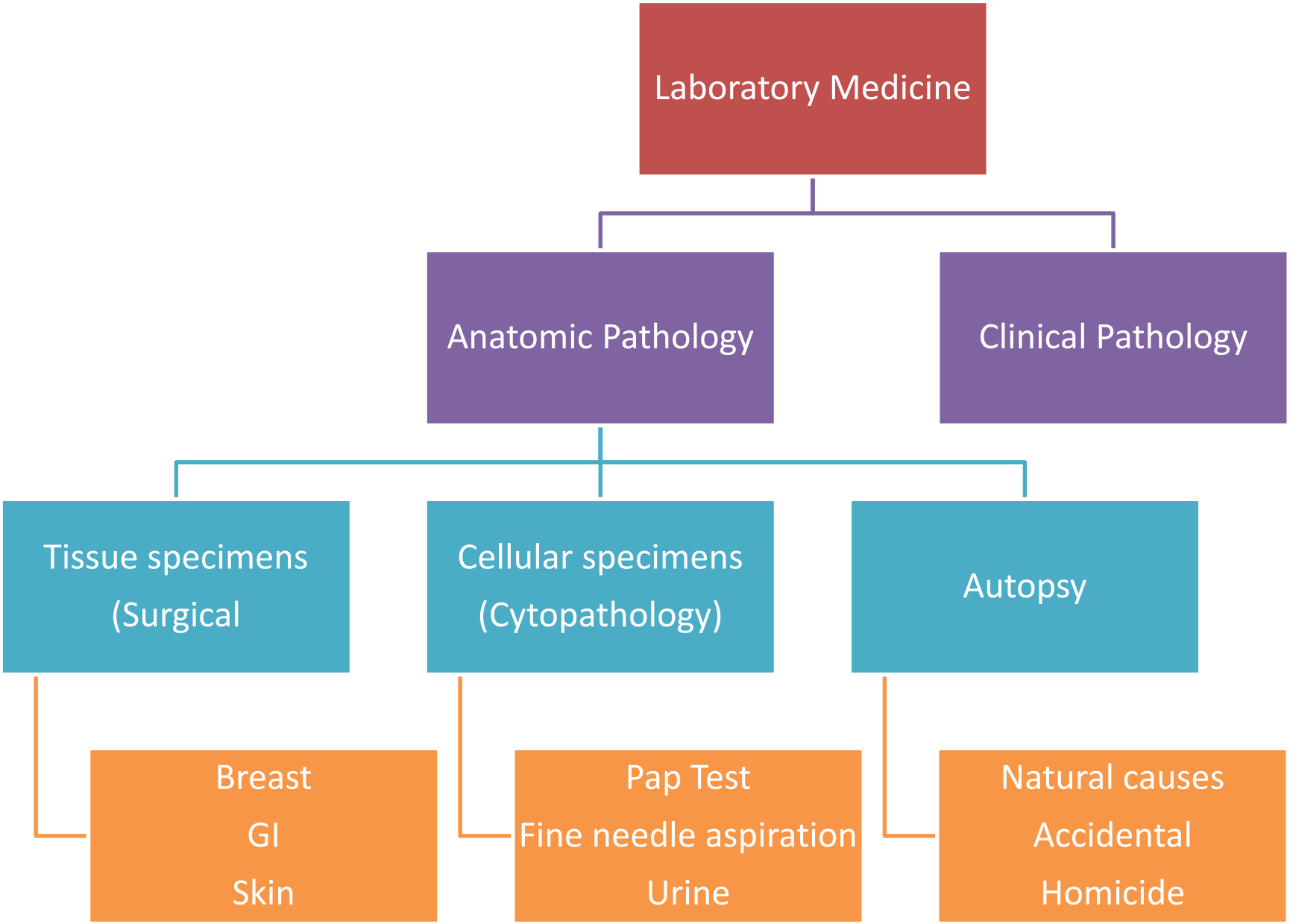


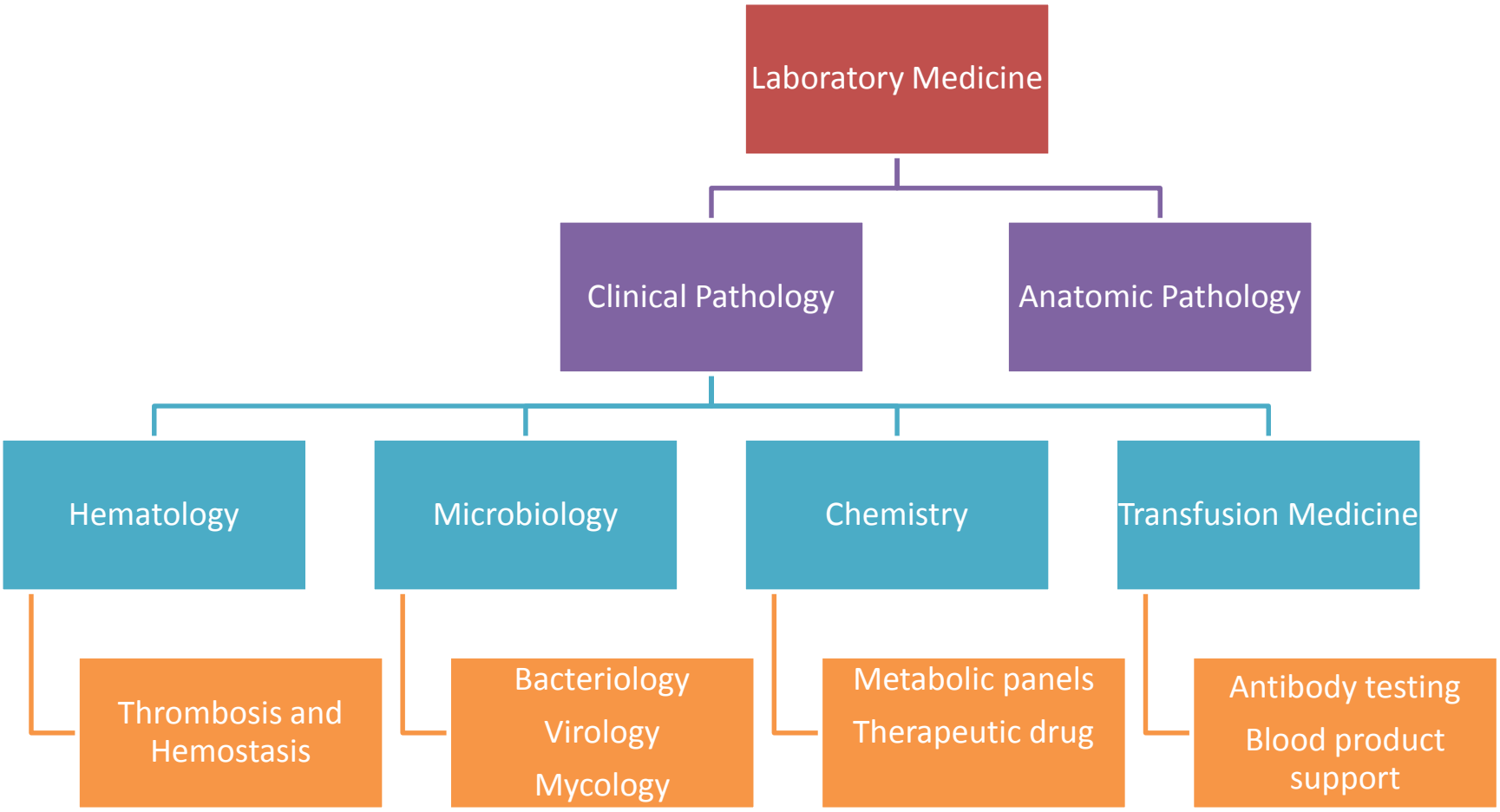
70% to 80% of medical decisions have a laboratory component

Tree of Medicine




Laboratory Medicine
Anatomic Pathology
Clinical Pathology
Tissue specimens
Fluid specimens


Laboratory Medicine
Anatomic Pathology
Clinical Pathology
Tissue specimens (Surgical
Cellular specimens (Cytopathology)
Autopsy
Breast
GI
Skin
Pap Test
Fine needle aspiration
Urine
Natural causes
Accidental
Homicide


Laboratory Medicine
Clinical Pathology
Anatomic Pathology
Hematology
Microbiology
Chemistry
Transfusion Medicine
Thrombosis and Hemostasis
Bacteriology
Virology
Mycology
Metabolic panels
Therapeutic drug
Antibody testing
Blood product support

Value of Pathology to Patient Care

Value in Patient Care

$$\text{Value} = \frac{\text{Benefit}}{\text{Cost}}$$

Value of Laboratory Medicine in Patient Care

- *An accurate result*, from an
- *Appropriate test(s)*, provided at the
- *Right time*, on the
- *Right specimen*, from the
- *Right patient*, with result interpretation based on
- *Correct reference data*, and at the
- *Right and reasonable price*

$$\text{Value} = \frac{\text{Benefit}}{\text{Cost}}$$

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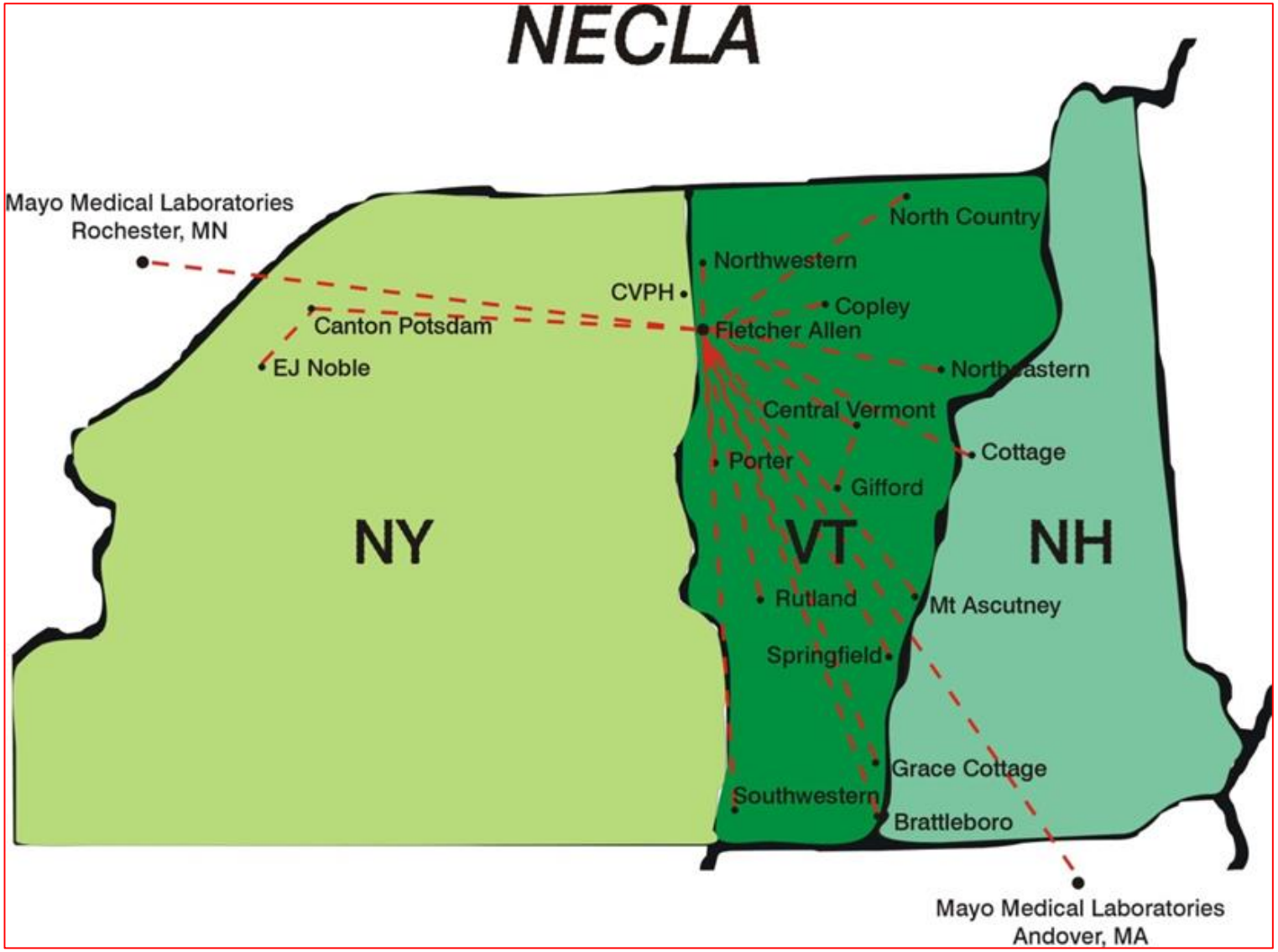
Laboratory Testing Cycle

Your UVMMC Laboratory

- Approximately 2.7 million clinical laboratory tests are performed each year
  - Approximately 1 million specimen tubes are processed for these 2.7 million test
- 200,000 phlebotomy visits
- 22,000 phone calls to our customer service center
- Courier service collecting samples from 240 locations
- 37,350 tissue samples
  - These 37,350 tissue samples required 224, 912 glass slides be prepared and reviewed
- 32,106 Pap tests
- 5,799 cytology (non-pap) cases
- 114 medical autopsy examinations
- 542 Medical Examiner autopsies

Network Map


NECLA
Mayo Medical Laboratories
Rochester, MN
CVPH
Canton Potsdam
EJ Noble
Northwestern
North Country
Copley
Fletcher Allen
Northeastern
Central Vermont
Porter
Gifford
Cottage
NY
VT
NH
Rutland
Mt Ascutney
Springfield
Grace Cottage
Southwestern
Brattleboro
Mayo Medical Laboratories
Andover, MA

Experts in Pathology

- Clinical Pathology
  - Transfusion medicine and histocompatibility
  - Hematopathology and coagulation
  - Flow cytometry
  - Cytogenetics
  - Molecular pathology
  - Chemistry and toxicology
  - Urinalysis
  - Immunopathology
  - Microbiology
  - Point-of-care testing
  - Phlebotomy
- Anatomic Pathology
  - Surgical pathology
    - Multiple organ systems
  - Cytopathology
  - Autopsy pathology
  - Forensic pathology
  - Histology and immunohistochemistry
  - Reproductive medicine
  - Biorepository
  - Electron microscopy

UVMMC Blog Site

https://medcenterblog.uvmhealth.org

Regulatory Agencies

- The College of American Pathologists
- American Association of Blood Banking
- American Society for Histocompatibility and Immunogenetics
- Food and Drug Administration
- Foundation for Accreditation of Cellular Therapy
- New York State Department of Health
- The Joint Commission
- Center for Medicare & Medicaid Services
- American College of Surgeons
- National Radiation Council
- Cytotechnology Programs Review Committee

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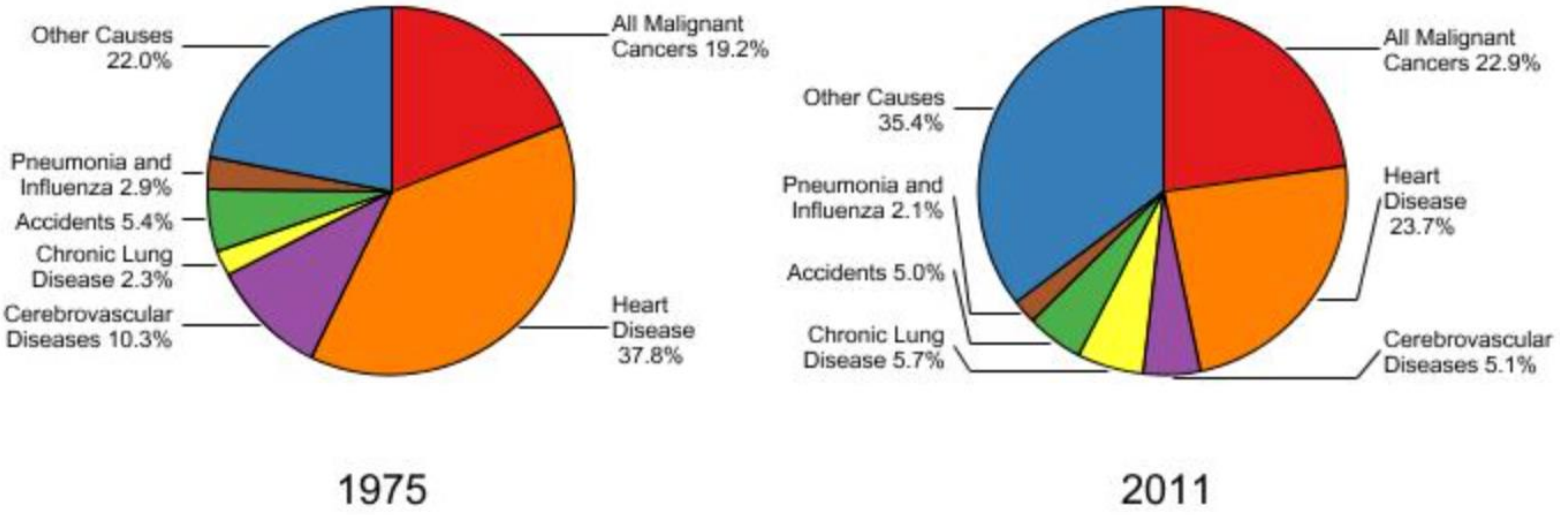
Vitamin CDE

- Vascular
- Infectious / Inflammatory
- Traumatic / Toxic
- Autoimmune
- Metabolic
- Iatrogenic / Idiopathic
- Neoplastic

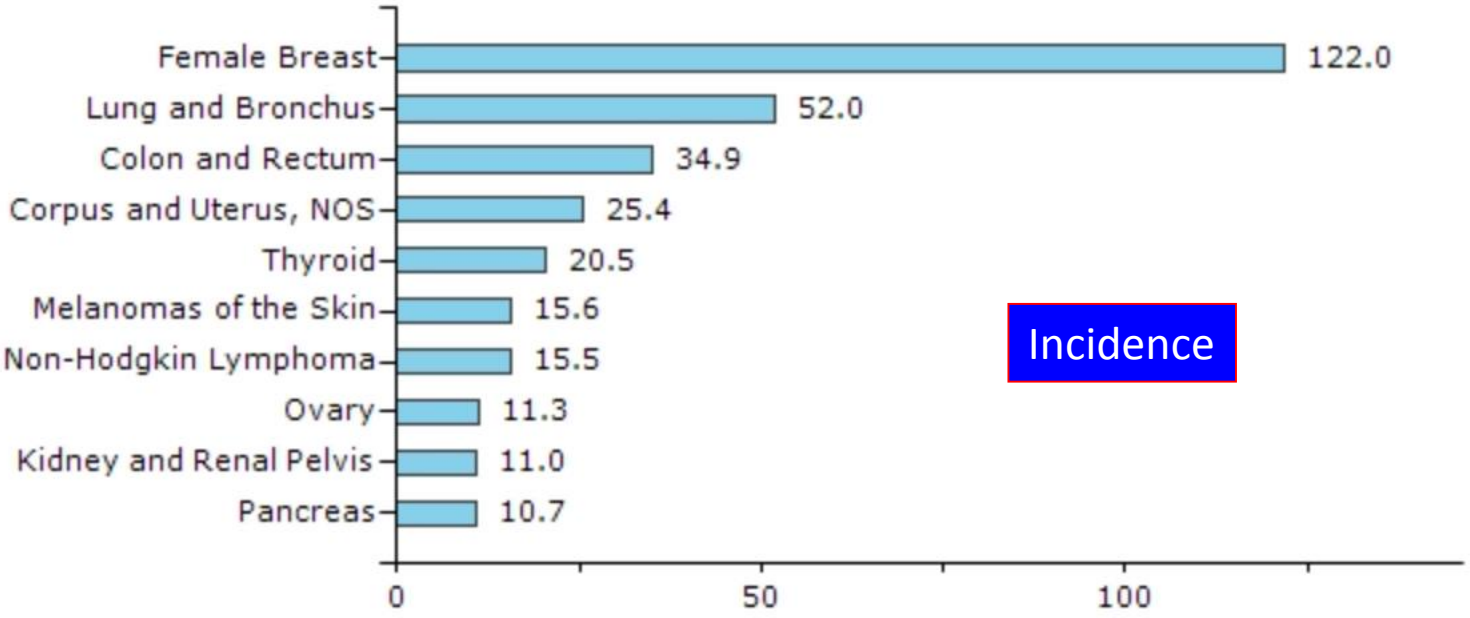
- Congenital
- Degenerative
- Endocrine

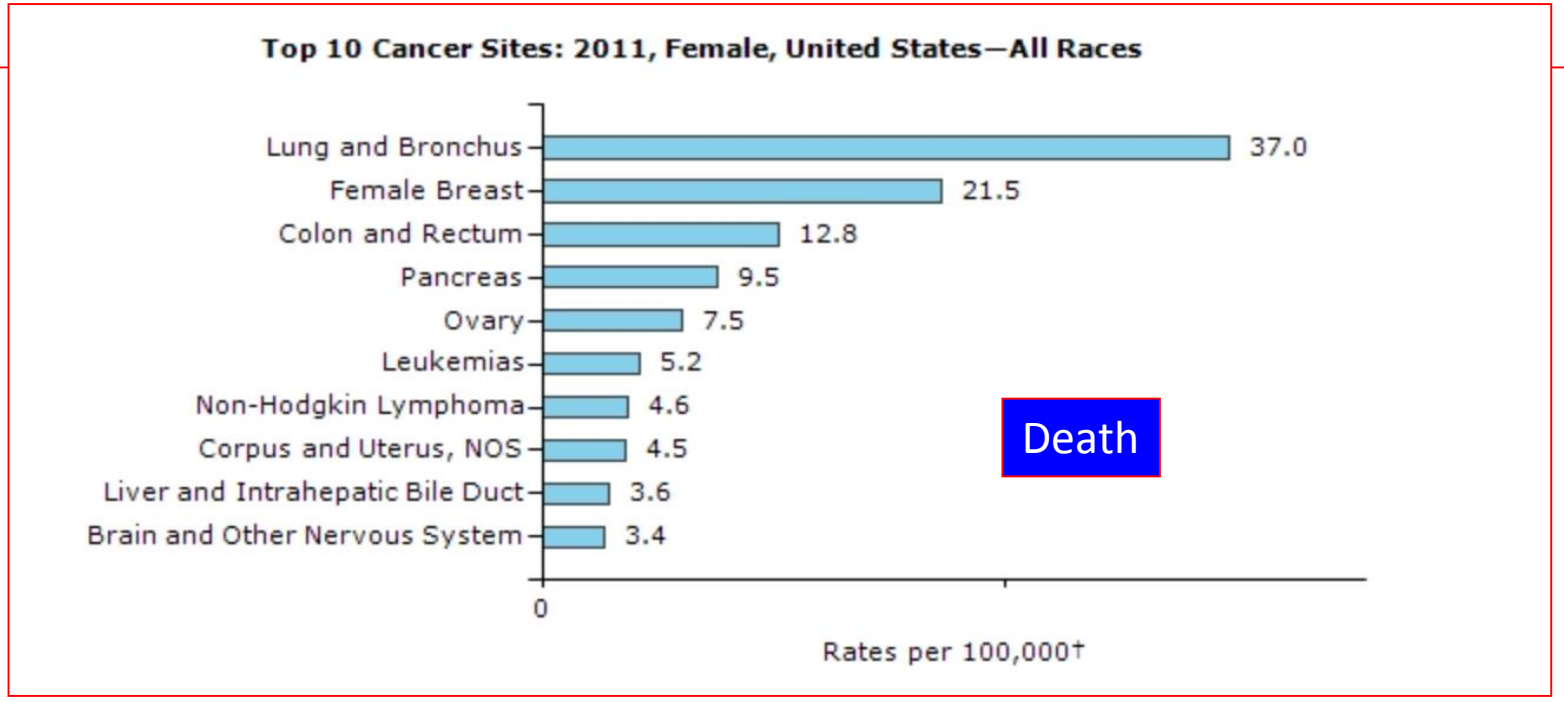
Figure 1.2

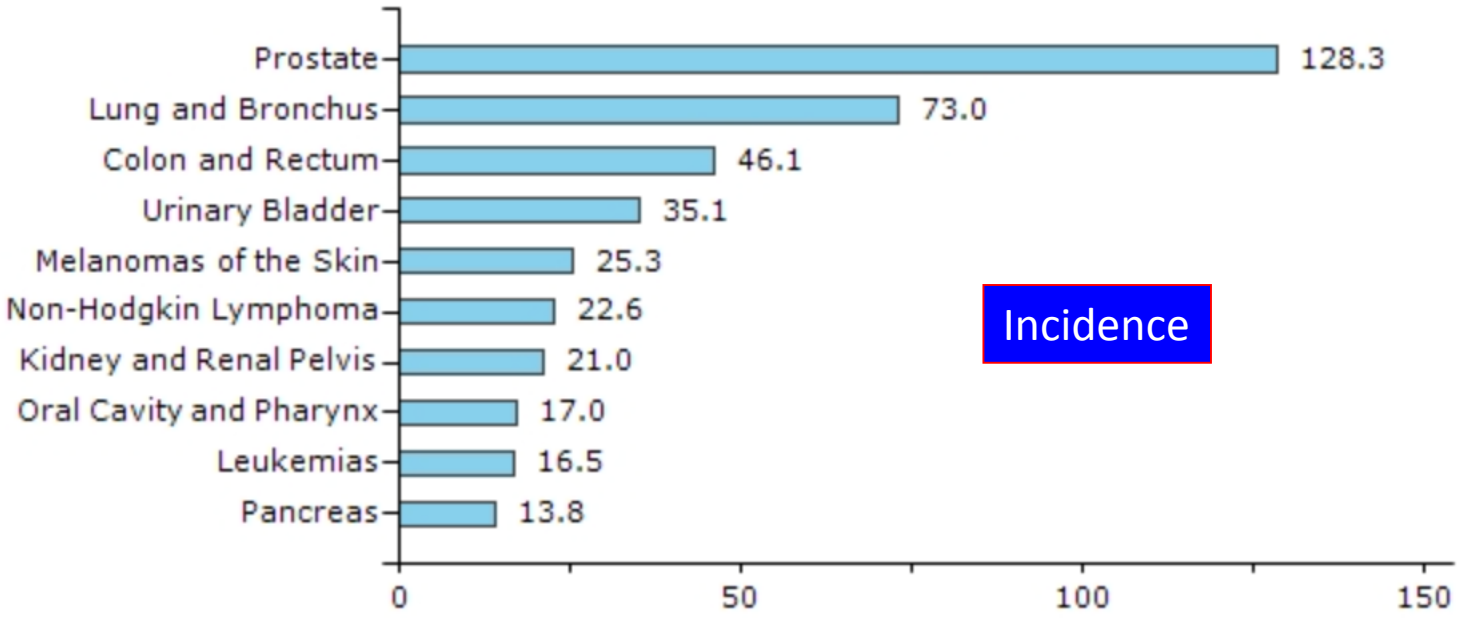
Leading Causes of Death in US, 1975 vs 2011
Percent of All Causes of Death

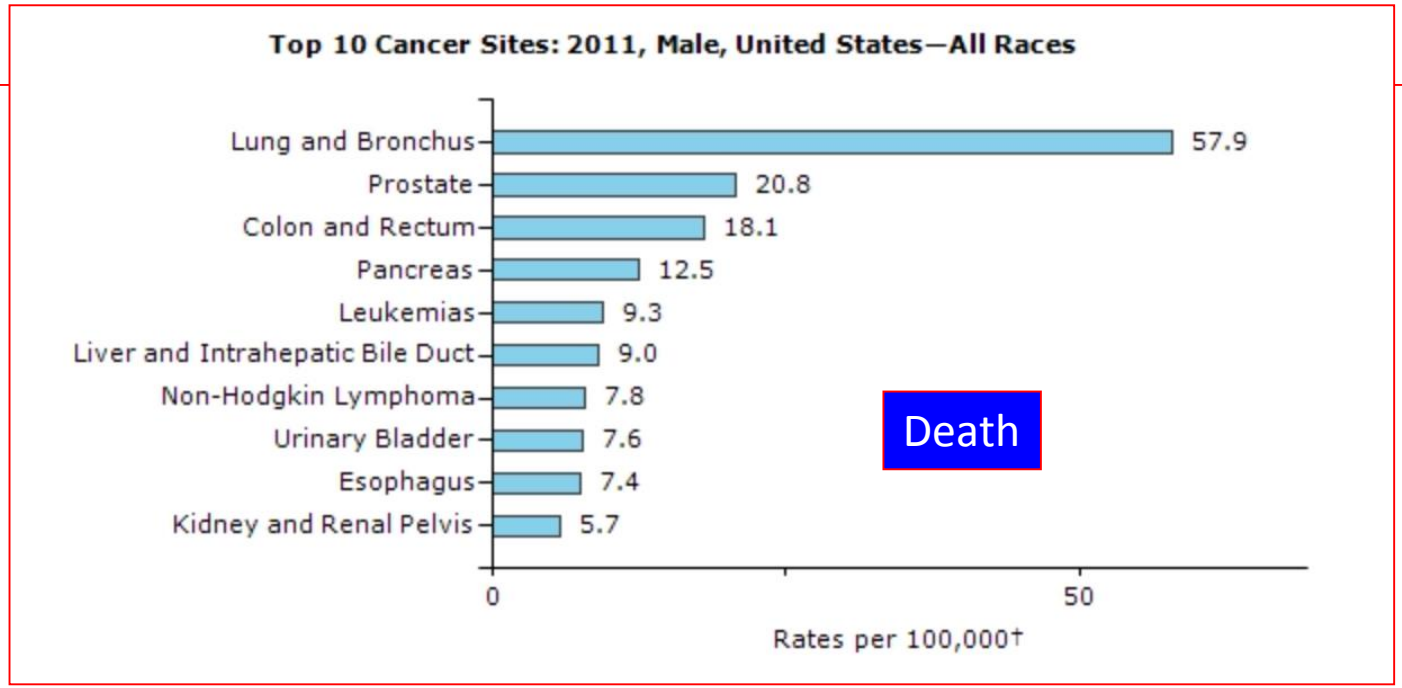


Source: US Mortality Files, National Center for Health Statistics, Centers for Disease Control and Prevention.


Top 10 Cancer Sites: 2011, Female, United States—All Races
Female Breast
Lung and Bronchus
Colon and Rectum
Corpus and Uterus, NOS
Thyroid
Melanomas of the Skin
Non-Hodgkin Lymphoma
Ovary
Kidney and Renal Pelvis
Pancreas
122.0
52.0
34.9
25.4
20.5
15.6
15.5
11.3
11.0
10.7
0
50
100
Incidence


Top 10 Cancer Sites: 2011, Female, United States—All Races
Lung and Bronchus
Female Breast
Colon and Rectum
Pancreas
Ovary
Leukemias
Non-Hodgkin Lymphoma
Corpus and Uterus, NOS
Liver and Intrahepatic Bile Duct
Brain and Other Nervous System
37.0
21.5
12.8
9.5
7.5
5.2
4.6
4.5
3.6
3.4
0
Rates per 100,000†
Death


Top 10 Cancer Sites: 2011, Male, United States—All Races
Prostate
Lung and Bronchus
Colon and Rectum
Urinary Bladder
Melanomas of the Skin
Non-Hodgkin Lymphoma
Kidney and Renal Pelvis
Oral Cavity and Pharynx
Leukemias
Pancreas
128.3
73.0
46.1
35.1
25.3
22.6
21.0
17.0
16.5
13.8
0
50
100
150
Incidence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Lung and Bronchus
Prostate
Colon and Rectum
Pancreas
Leukemias
Liver and Intrahepatic Bile Duct
Non-Hodgkin Lymphoma
Urinary Bladder
Esophagus
Kidney and Renal Pelvis
57.9
20.8
18.1
12.5
9.3
9.0
7.8
7.6
7.4
5.7
0
50
Rates per 100,000†
Death

Neoplasm

- New growth
  - Abnormal mass of tissue
  - Growth exceeds surrounding normal tissue
  - Uncoordinated compared to surround normal tissues
  - Persists in the excessive manner after cessation of stimuli which the change
    - Non-reversible

Neoplasm

- New growth
- Clonal
  - Population of cells arising from a single cell which incurred genetic change (stimuli)
- Derangement of normal growth control mechanisms
- Balance of cell death and cell division is abnormal

Definitions

- Neoplasm
  - Benign
  - Malignant
  - Uncertain potential

Neoplasm- Benign vs. Malignant

Benign

- Remains local
- Does NOT invade adjacent tissues
- Cannot spread
- Cured by removal
- Patient generally survives

Uncertain Malignant Potential

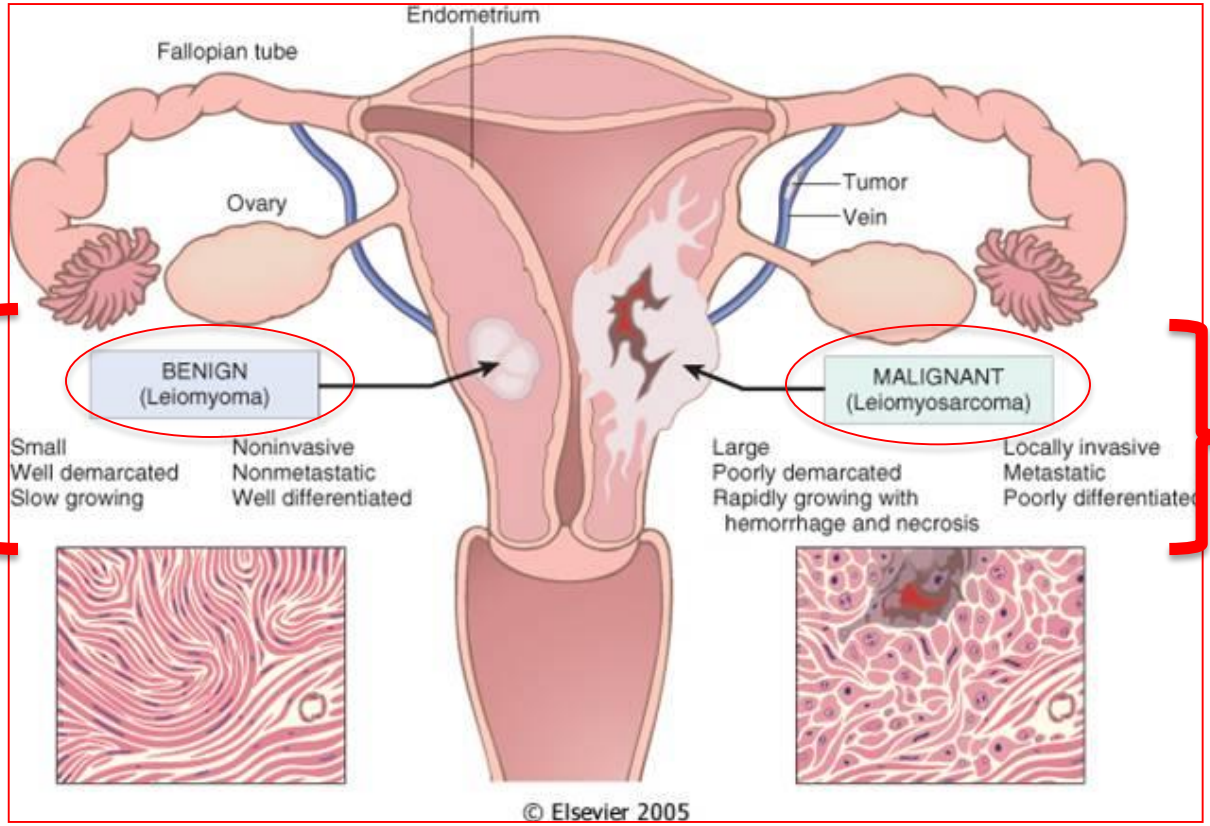
- Unpredictable behavior
- Cannot be classified by histologic features
- Treatment may vary

Malignant

- Invades and destroys adjacent structures
- Can spread to other sites
- May or may not be treatable
- Often causes death (if left untreated)

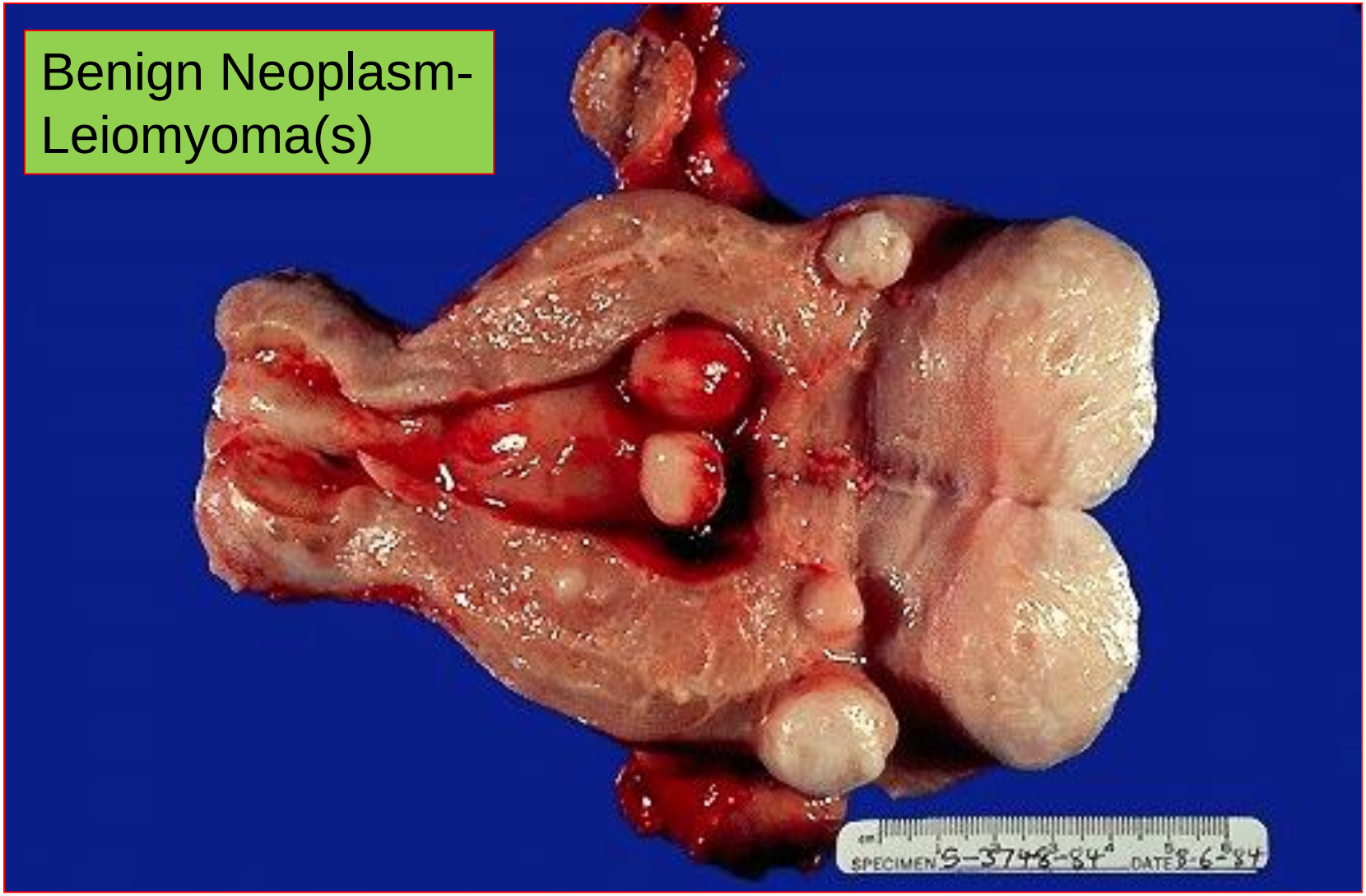
Uterus

Benign Neoplasm



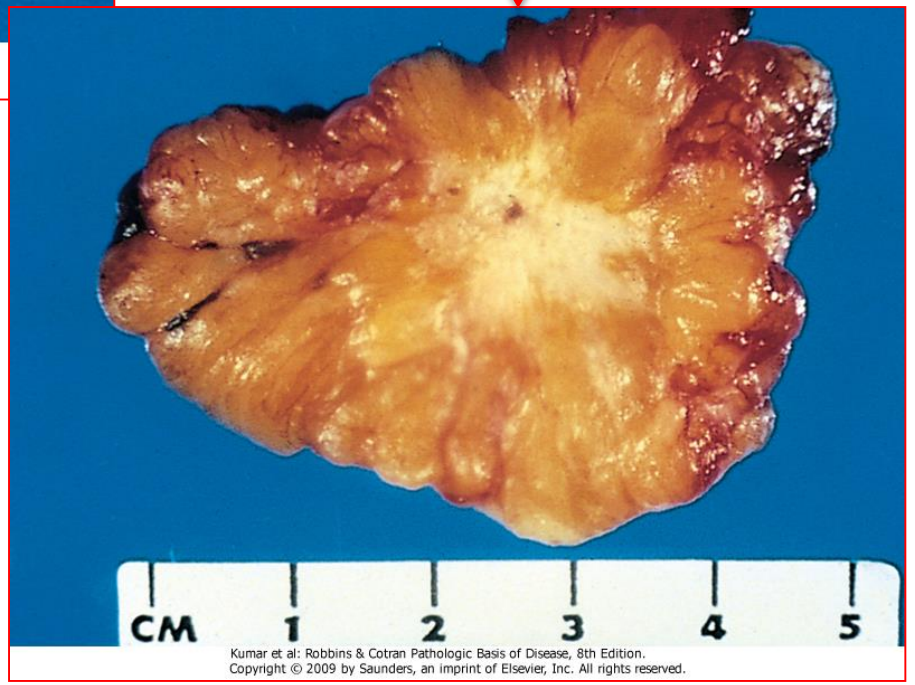
Malignant Neoplasm

Uterus



Breast Tissue- Benign vs. Malignant

Malignant-
Invasive adenocarcinoma

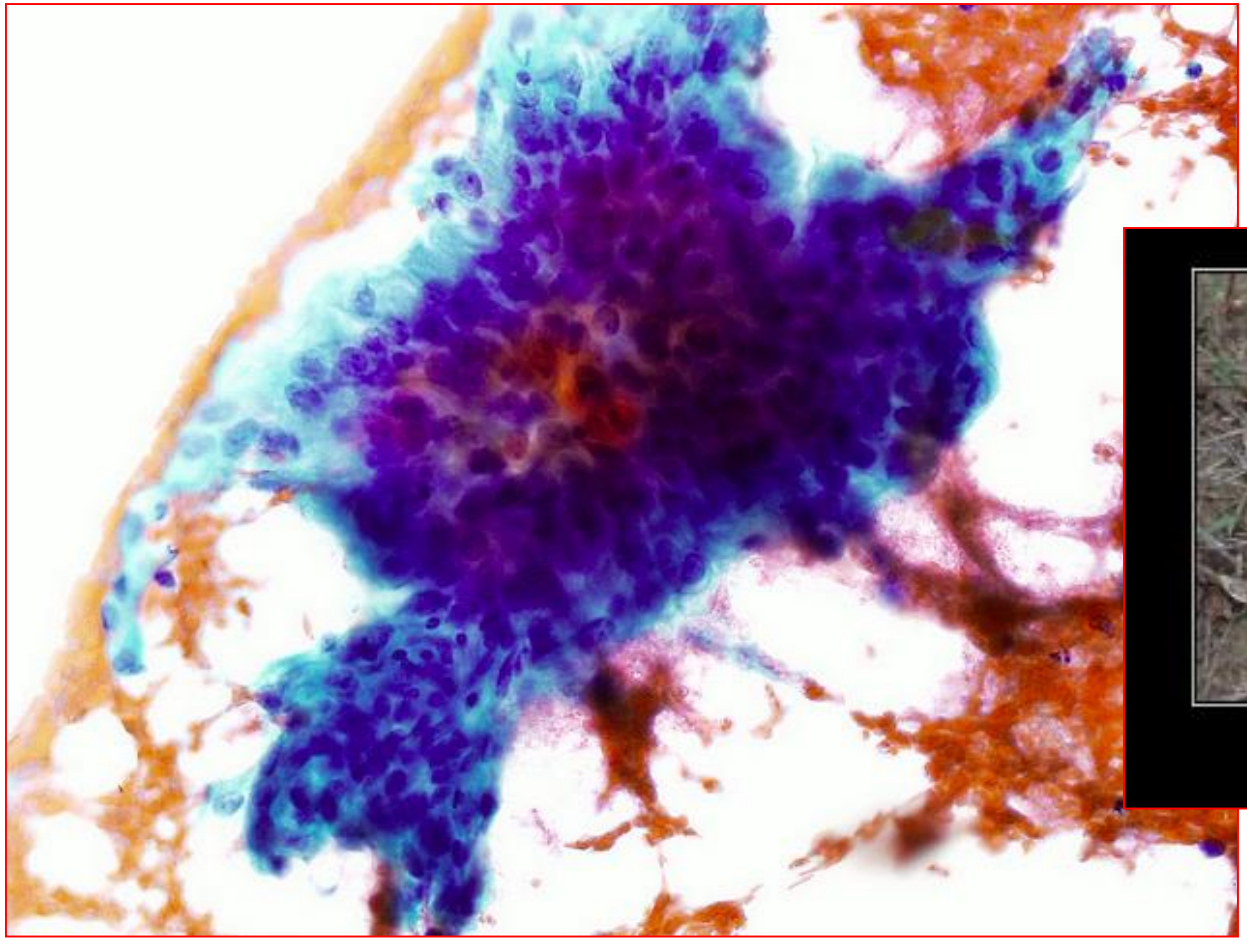


Benign-
Fibroadenoma

Cancer

- The commonly used term for **malignant** neoplasms
- Fits the definition well
  - Caner is Latin for crab
  - "Adheres to any part it seizes upon in an obstinate manner"
    - ? Definition for children?

Cancer Latin for Crab



Adheres to any part it seizes upon in an obstinate manner

Additional Terms Applied to **Malignant** Neoplasms

Terms for **Malignant** Neoplasms

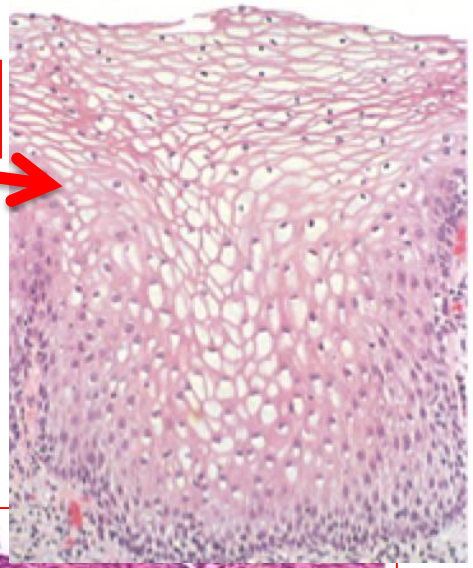
- In-situ vs. Invasive
- Primary vs. Metastatic

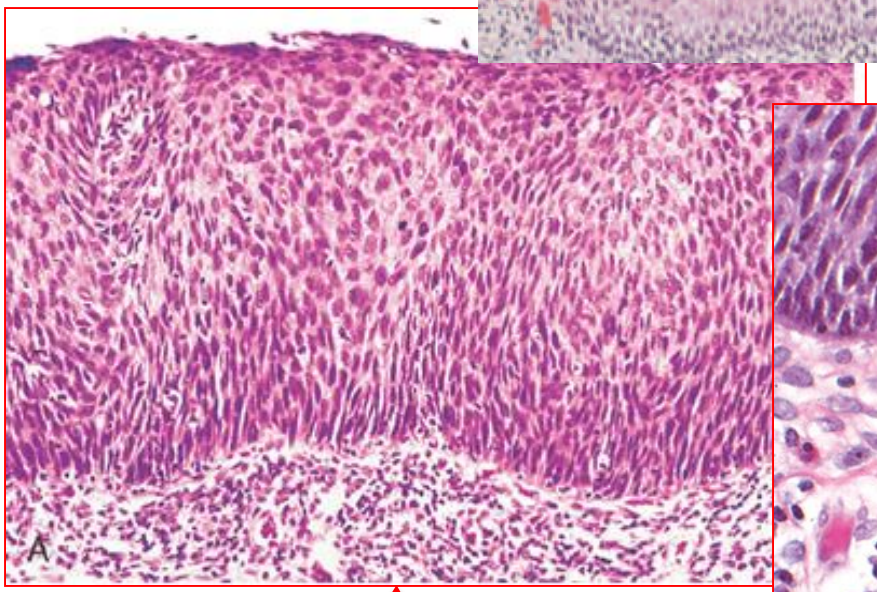
Malignant Neoplasm

- In-situ
  - Does **not** invade the basement membrane
  - Considered pre-invasive cancer
  - **No** capability to metastasize
- Invasive
  - Tumor cells **breach the basement membrane**
  - Grows **into** surrounding tissue
  - Now tumor cells have access to vasculature
    - Ability to **metastasize**

In-situ vs. Invasive Malignant Neoplasm

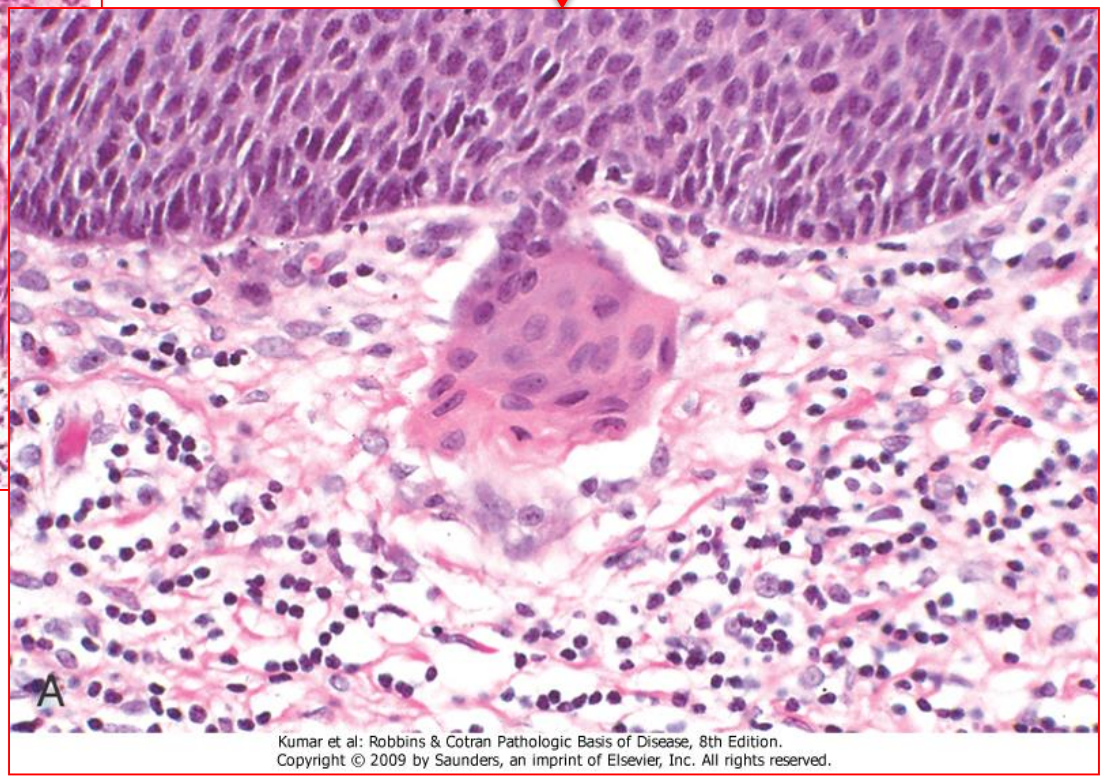
Normal Cervix





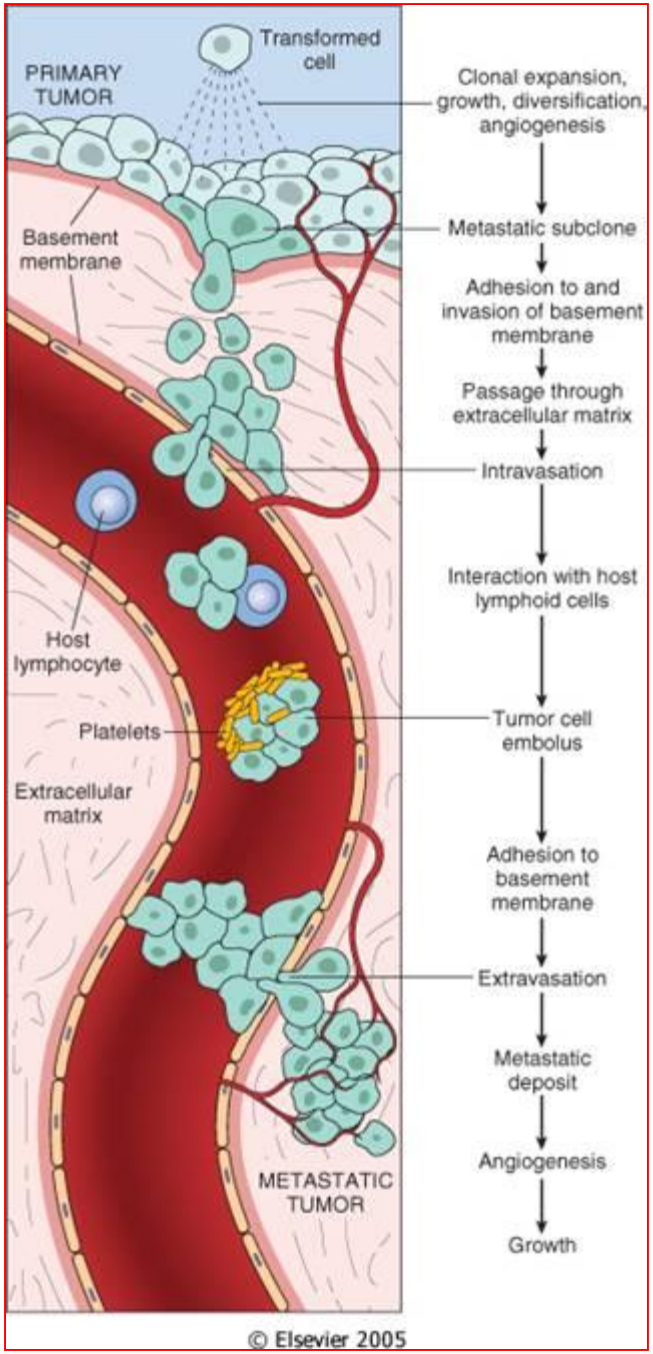
Carcinoma in-situ

Invasive *carcinoma*



Access to Vessels

- Carcinoma in-situ
  - Not invasive
  - Cannot access the vasculature
  - Cannot spread
- Once a tumor is invasive
  - Access to vessels
  - Metastatic spread



Primary vs. Metastatic

- Primary
  - Tumor arising at the site of origin
    - *Carcinoma* of the breast arising in the breast
- Metastatic
  - Spread of tumor to distant sites
    - Lymphatic
    - Hematogenous
    - Seeding body cavity
  - Invasive *carcinoma* of the breast spreading to lung
- Direct extension
  - Neoplasm invades into adjacent organ
    - Prostate *carcinoma* invading into adjacent bladder

What the Mind Does Not Know
The Eyes Cannot See

Pathologic Features of Neoplasms

Gross Features

- Does not mean “icky”
- Features we can see with our naked eye
- Very important
  - First assessment of the specimen to determine benign or malignant
- Can provide information about adjacent tissues
  - Associated pathologies

Gross Features

- Must evaluate
  1. Circumscription of neoplasm
  2. Necrosis within the neoplasm
     - Cystic change
     - Ulceration
  3. Texture and character of neoplasm
  4. Number of neoplasms
     - Metastatic disease
     - Synchronous neoplasms
       - Occurring at the same time

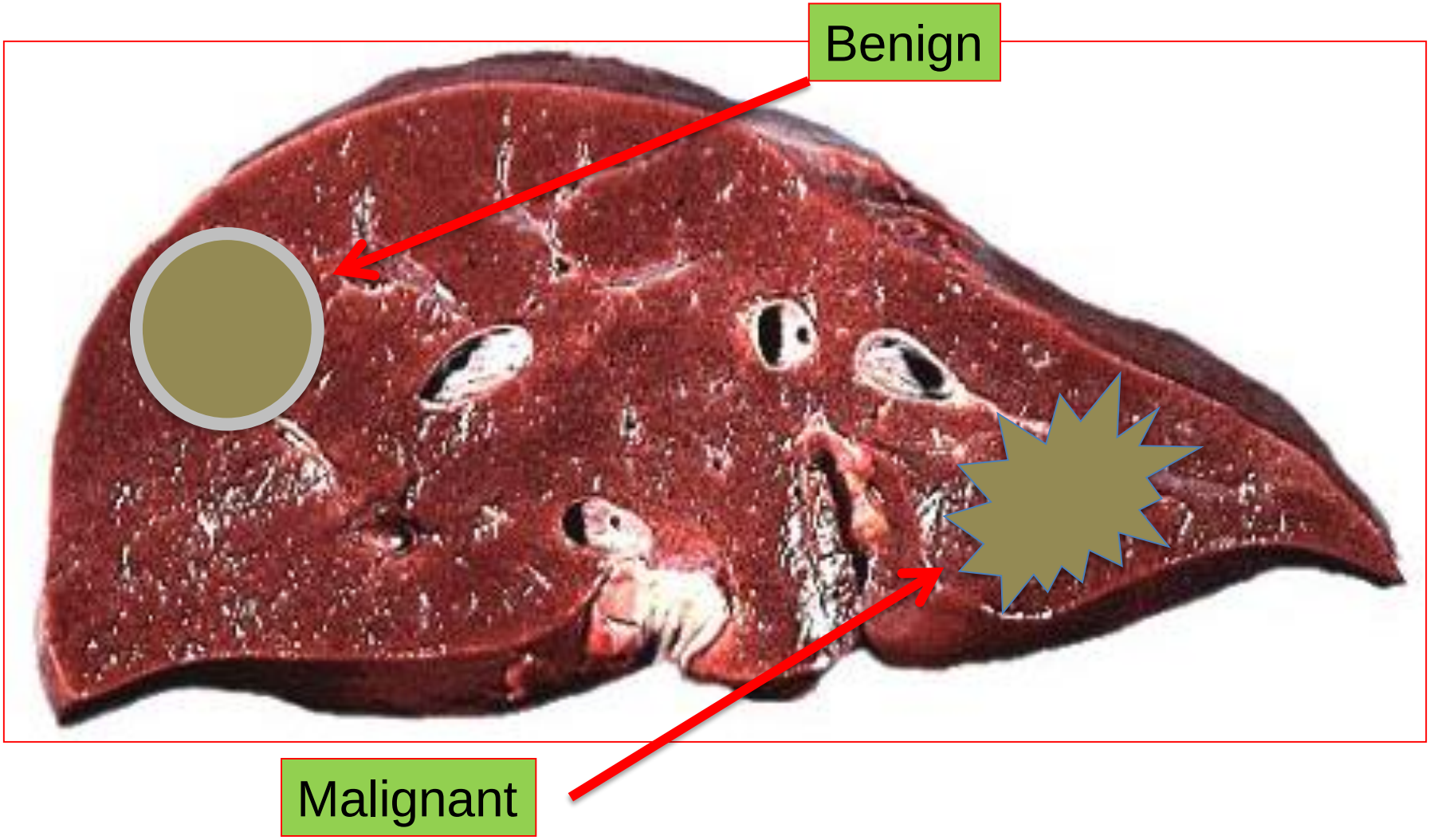
Gross Features

- Circumscription of **Benign** Neoplasm
  - Smooth
  - Circumscribed
  - May have a capsule
  - Can be lobulated
- Low-grade malignancies can have these features
  - DOES **NOT** INVADE INTO SURROUNDING TISSUE

Gross Features

- Circumscription of **Malignant** Neoplasms
  - Irregular borders
  - Finger like projections
  - Remember Cancer=Crab
    - Latin for…
  - Often destroys adjacent tissue

Neoplasm Circumscription

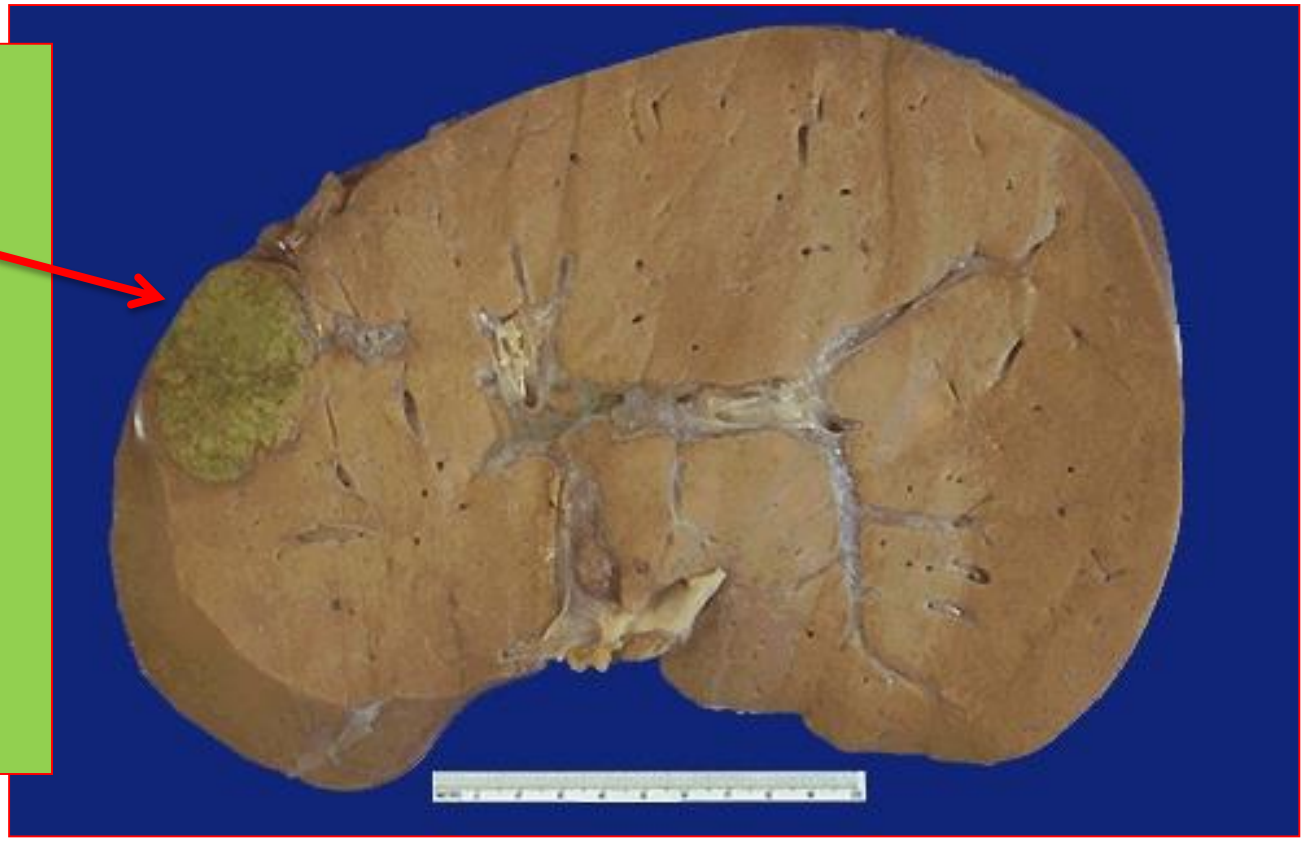


Circumscription of Benign Neoplasm

Liver section with single subcapsular neoplasm.

Smooth, circumscribed border.

Diagnosis:
Hepatic adenoma

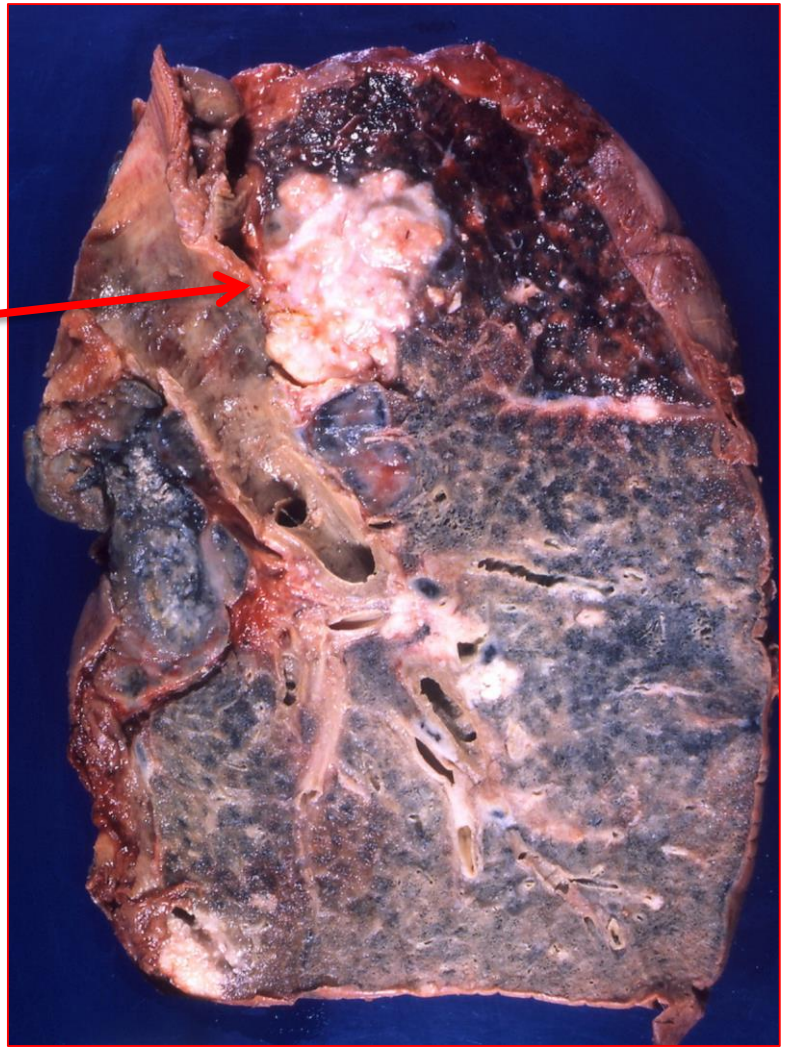


Circumscription of Malignant Neoplasm

Lung with single, large neoplasm.

Irregular circumscription arising from airway

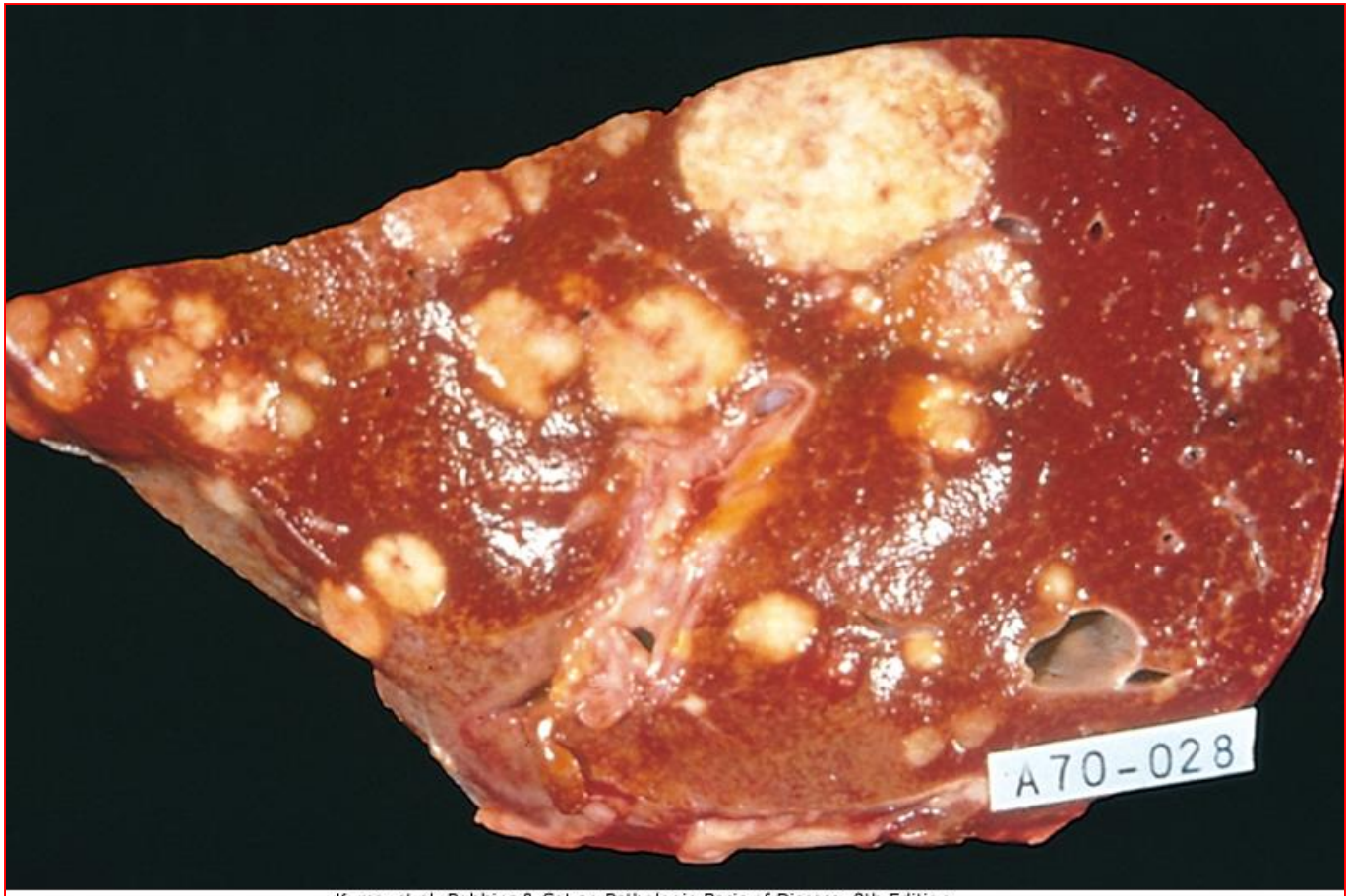
Diagnosis:
Invasive squamous cell carcinoma of the lung



Gross Features

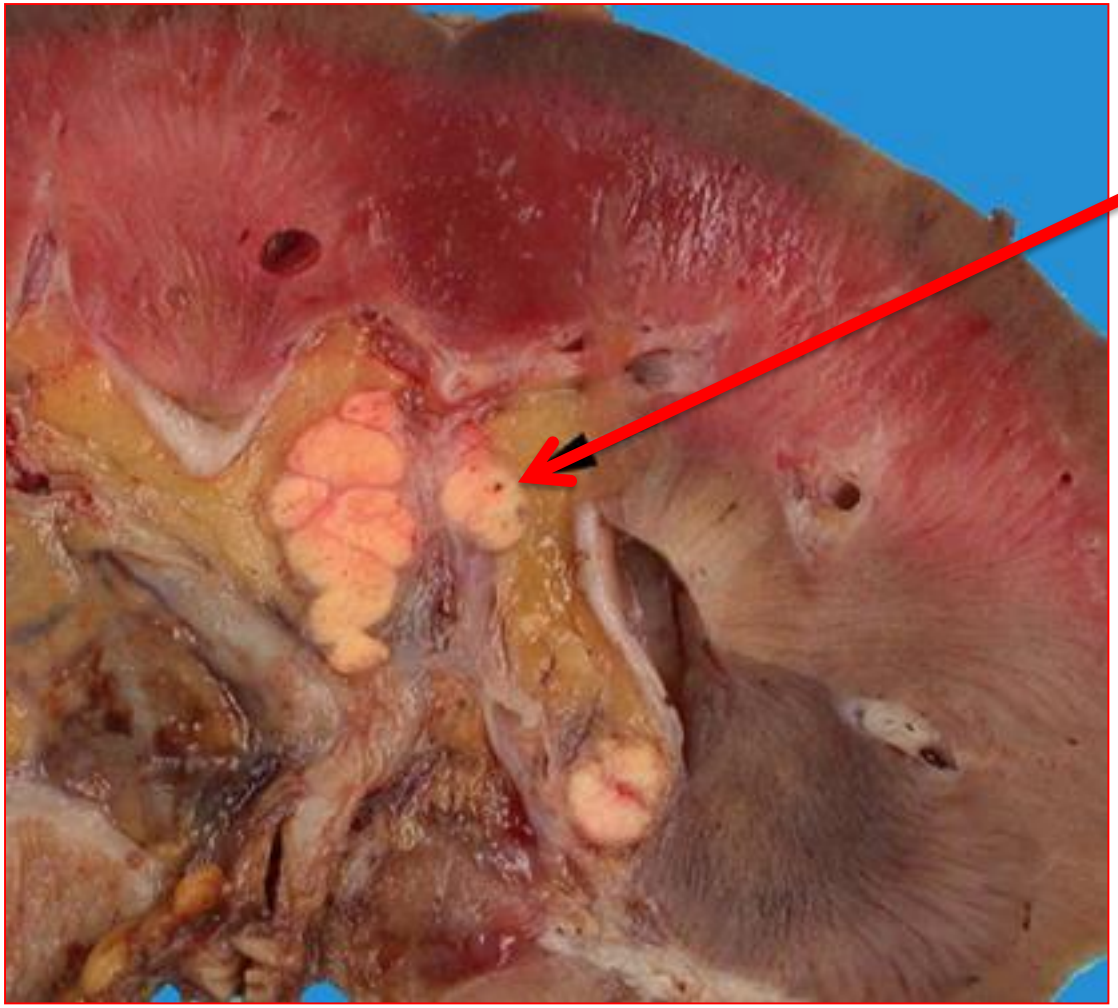
- **Metastasis**
  - Defines malignancy in nearly 100% of neoplasms
  - Seeding of body cavities and surfaces
  - Lymphatic spread
  - Hematogenous spread
- Rare exception includes
    - Benign metastasizing leiomyoma
- ~30% of solid tumors (excluding skin cancer other than melanoma) will have metastasis at presentation

Metastatic Carcinoma to the Liver



Multiple irregular and focally necrotic nodules in the liver. Diagnosis is metastatic carcinoma.

Hematogenous Spread



Renal vein involvement by clear cell renal cell carcinoma of the kidney

Where might the tumor travel?

Gross Features

- Must evaluate
  1. Circumscription
     - Smooth (circumscribed)
     - Irregular (invasive)
  2. Necrosis/Ulceration
     - Very concerning when associated with a neoplasm
  3. Metastasis
     - Seeding a body cavity
     - Lymphatic spread
     - Hematogenous spread

Histologic Features

Histologic Features

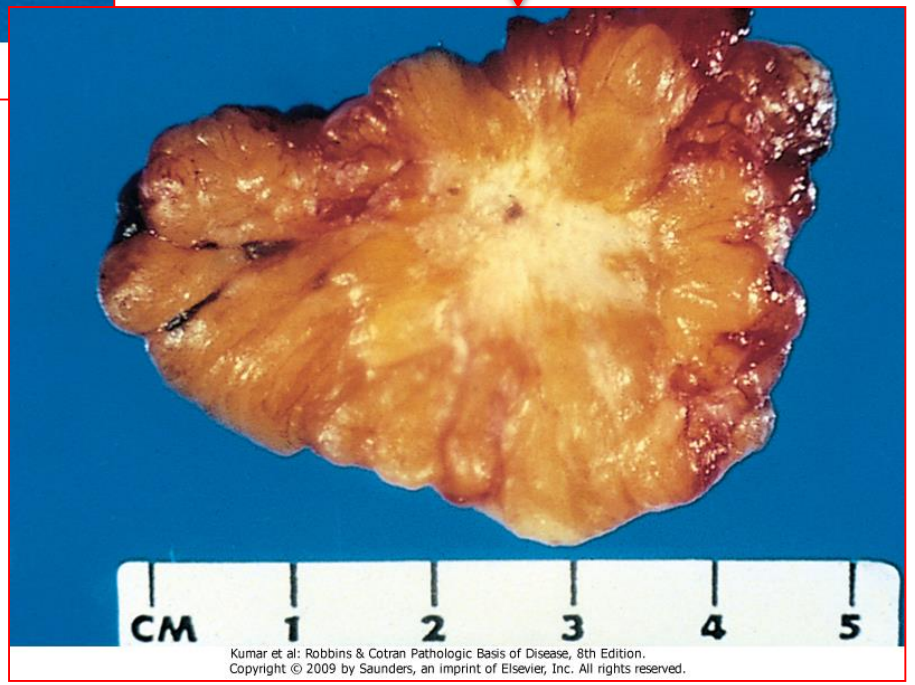
- Features appreciated in tissue sections
  - Biopsy or resection specimens
  - Tissue is fixed in formalin, paraffin embedded, 5 micron section cut, and H&E stains are performed
- Look for architectural and cytologic features to confirm the diagnosis
  - Low to medium power for architecture
  - Medium to high power for cytologic features
- Compare to surrounding, NON-neoplastic tissues

Histologic Features- Low Power

- Invasion
- Loss of normal architecture
- Necrosis
- New structures
- Angiogenesis
- Inflammation

Breast Tissue- Benign vs. Malignant

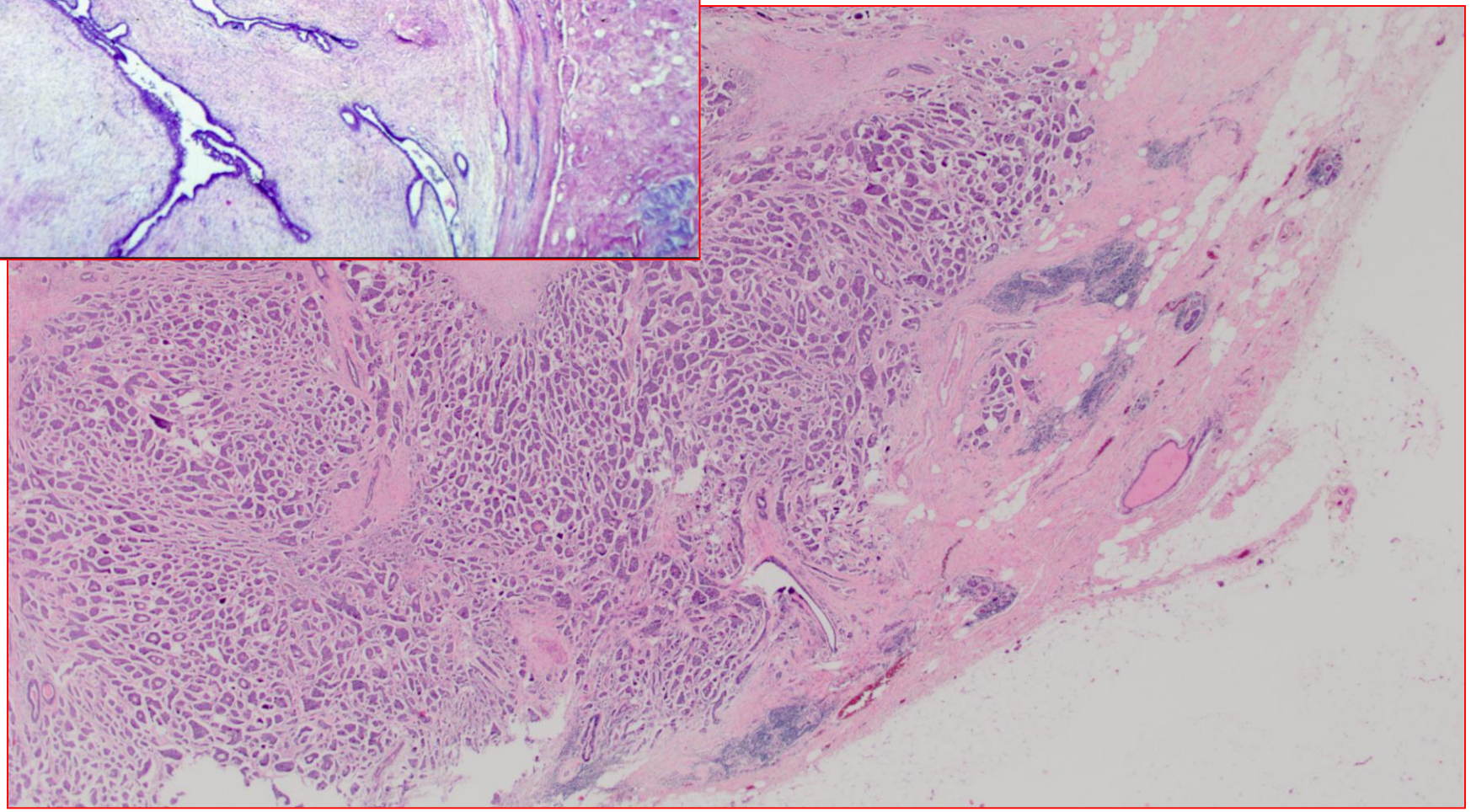
Malignant-
Invasive adenocarcinoma



Benign-
Fibroadenoma

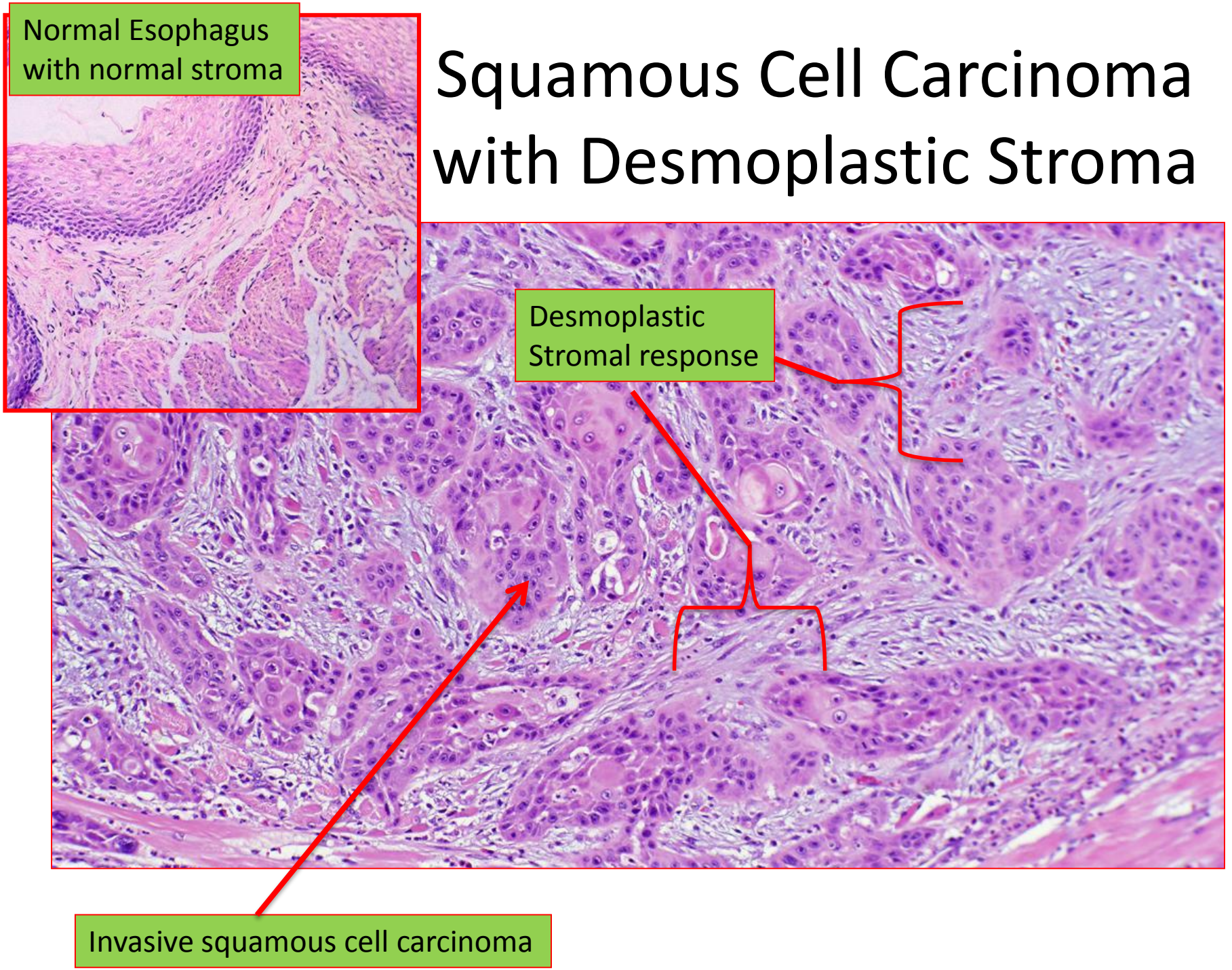
Histologic Evaluation of

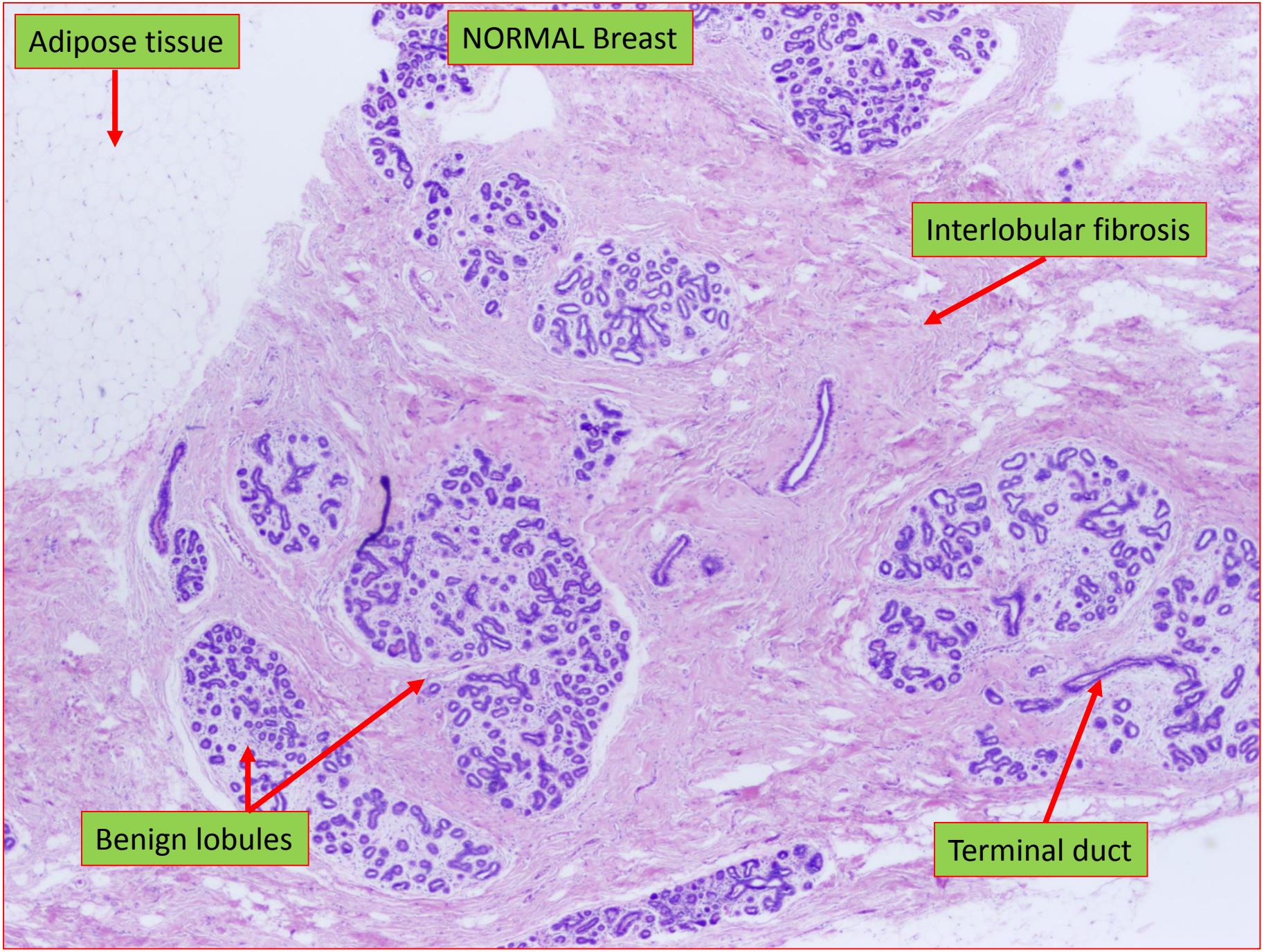
Smooth border- Benign

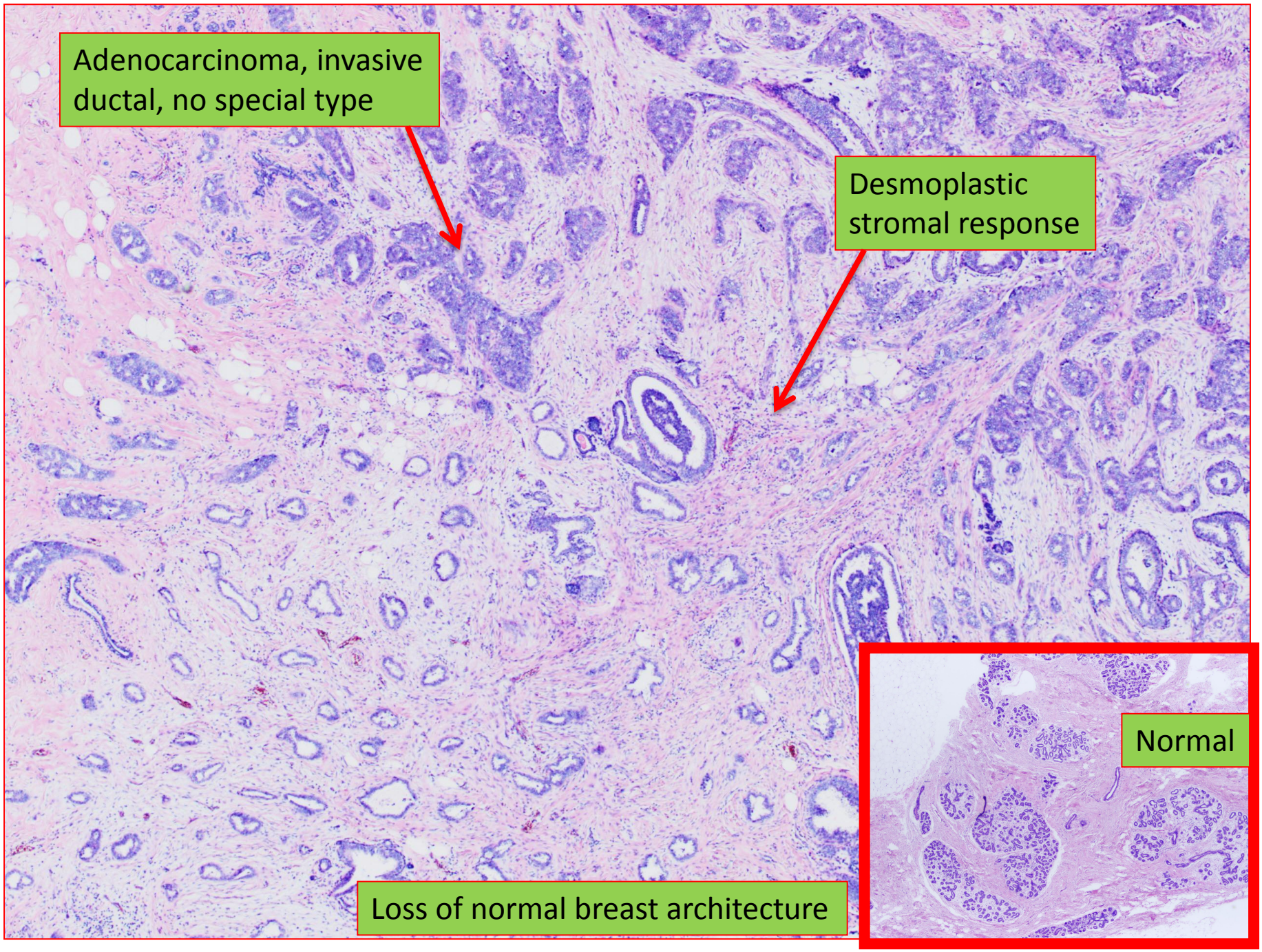


Irregular border of invasion- Malignant

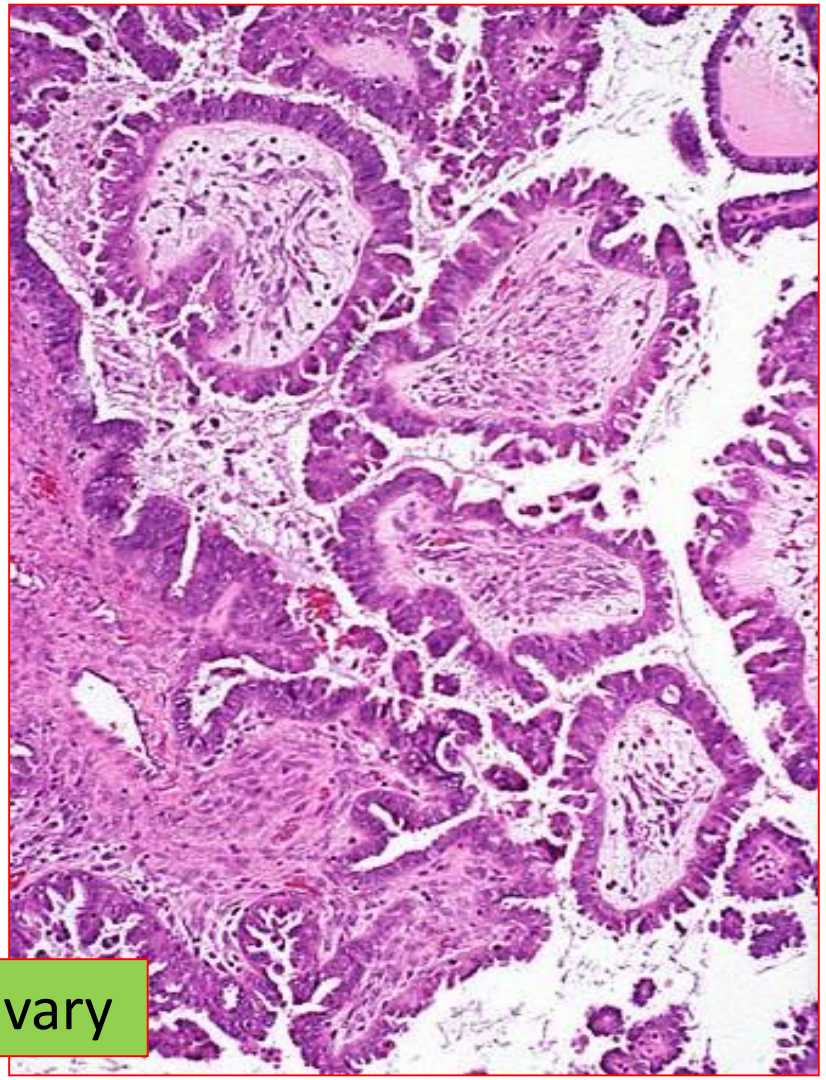
Squamous Cell Carcinoma with Desmoplastic Stroma




Adipose tissue
NORMAL Breast
Interlobular fibrosis
Benign lobules
Terminal duct

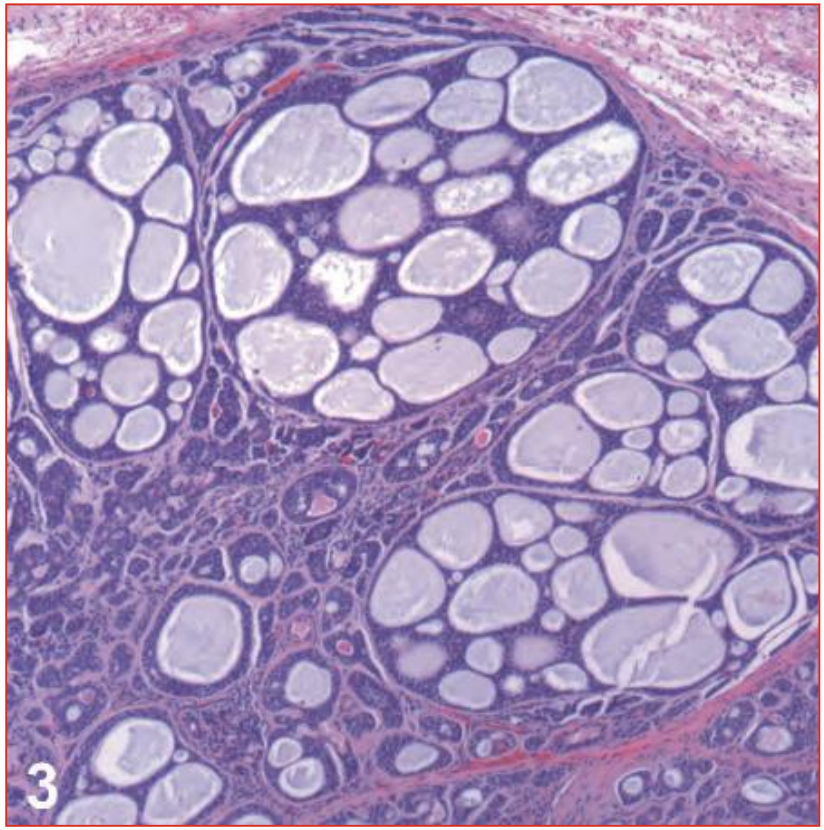

Adenocarcinoma, invasive ductal, no special type
Desmoplastic stromal response
Normal
Loss of normal breast architecture

Papillary Structures



Papillary Serous Carcinoma of the Ovary

Cribriform



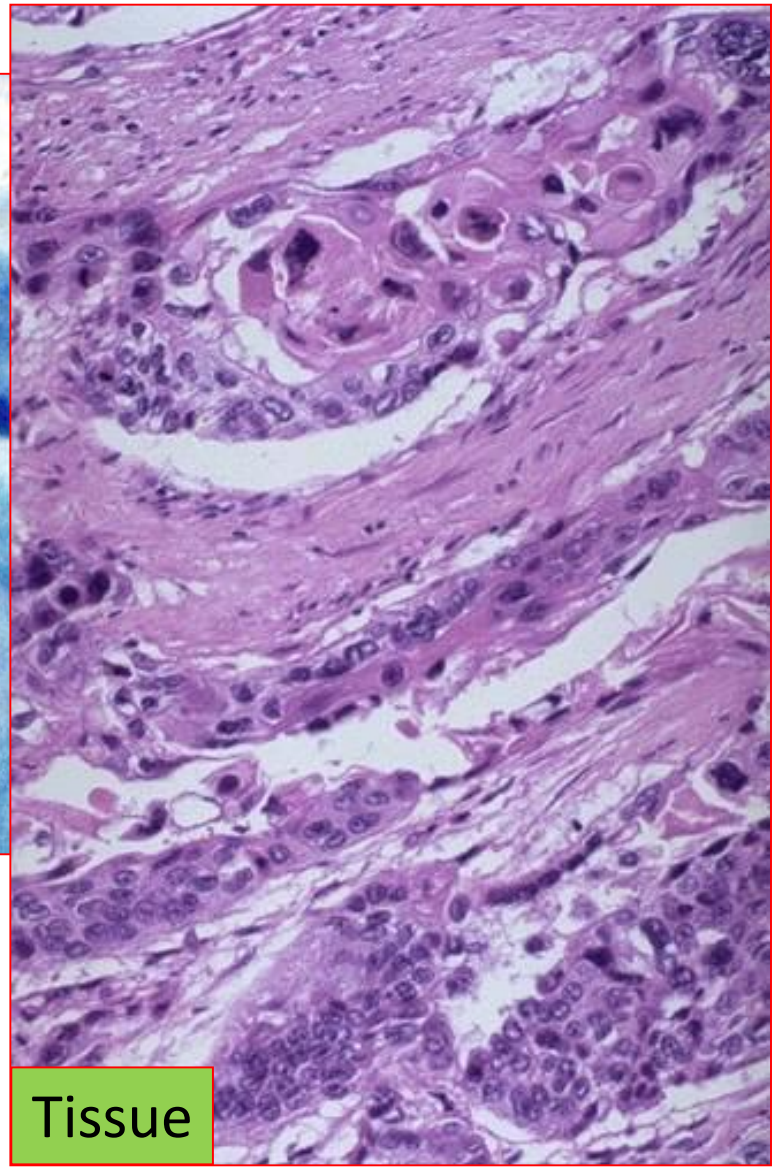
Rigid neolumen (glandular) formation perforated like a colander

Cytologic Features

Cytologic Features

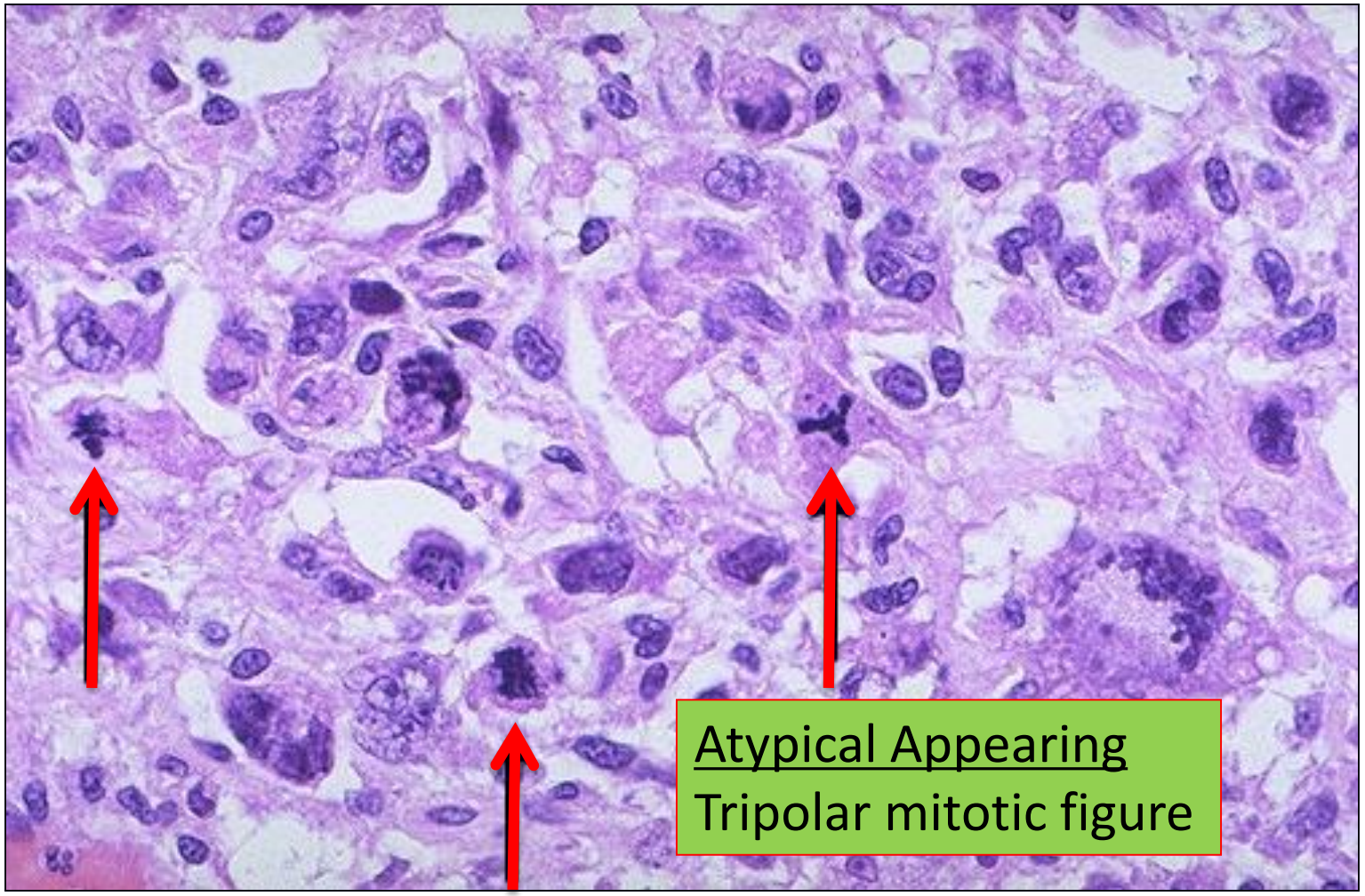
- Study of cells
  - Exfoliative cytology
    - Sputum
    - CSF
    - Urine
    - Pap Test
  - Fine Needle Aspirations (FNA)
- Cells are directly smeared onto slide or processed by thin layer technology

Cytologic Features

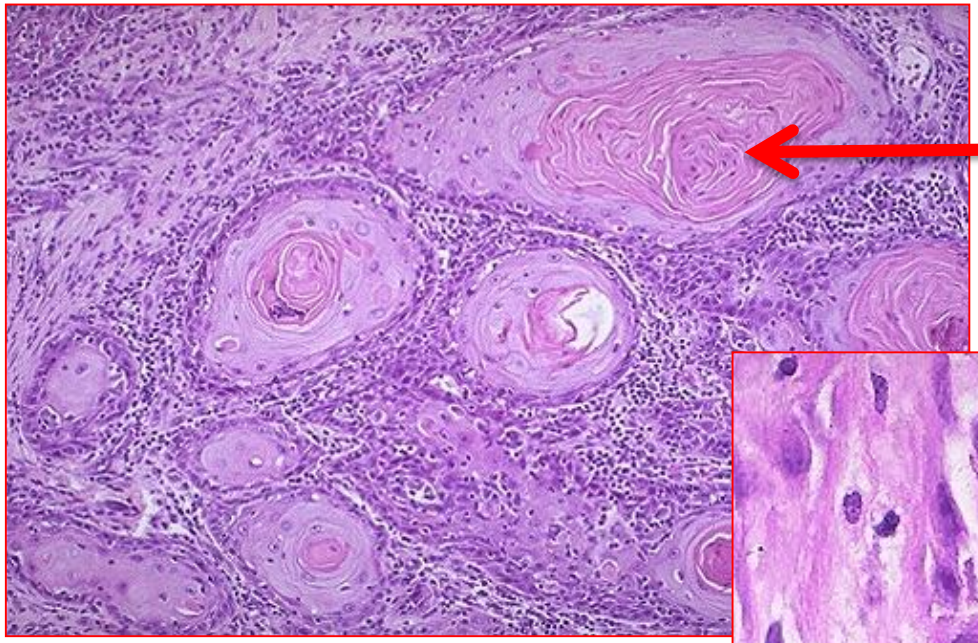


- Pleomorphism
- Increased nuclear-to-cytoplasmic ratio
- Irregular nuclear membranes
- Chromatin clumping
- Hyperchromasia

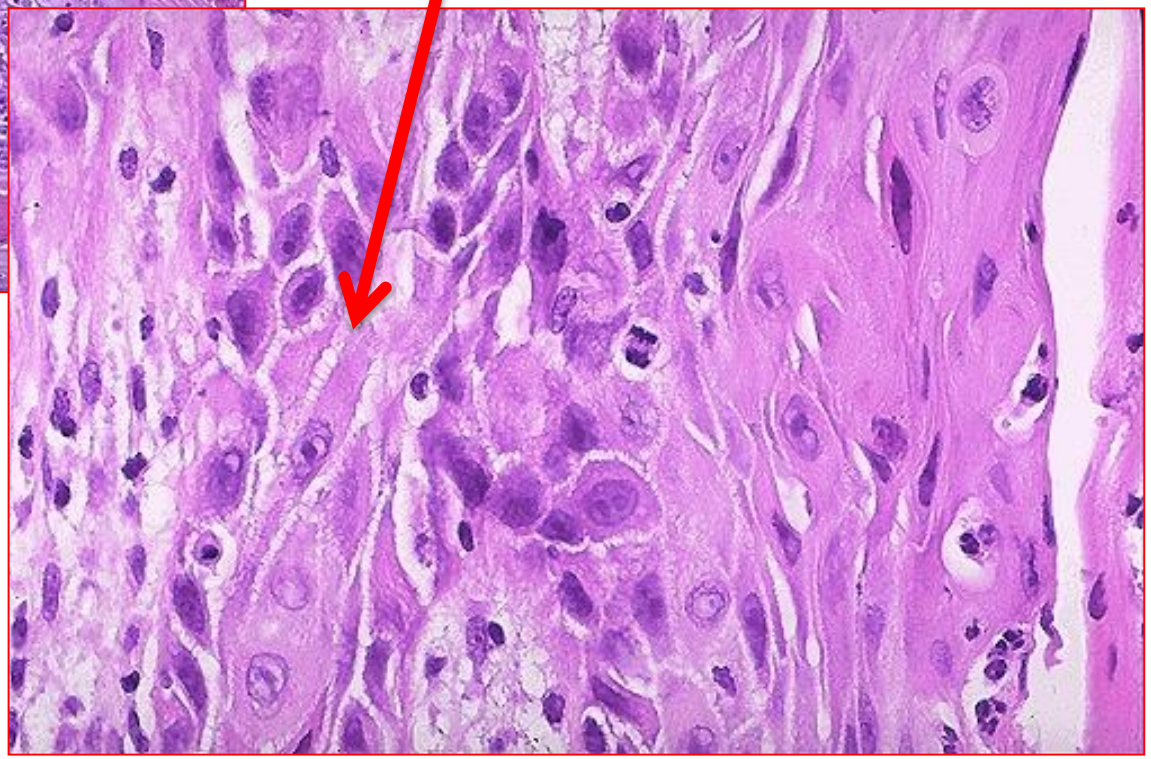
Abnormal Mitoses



Differentiation in Squamous Cell Carcinoma

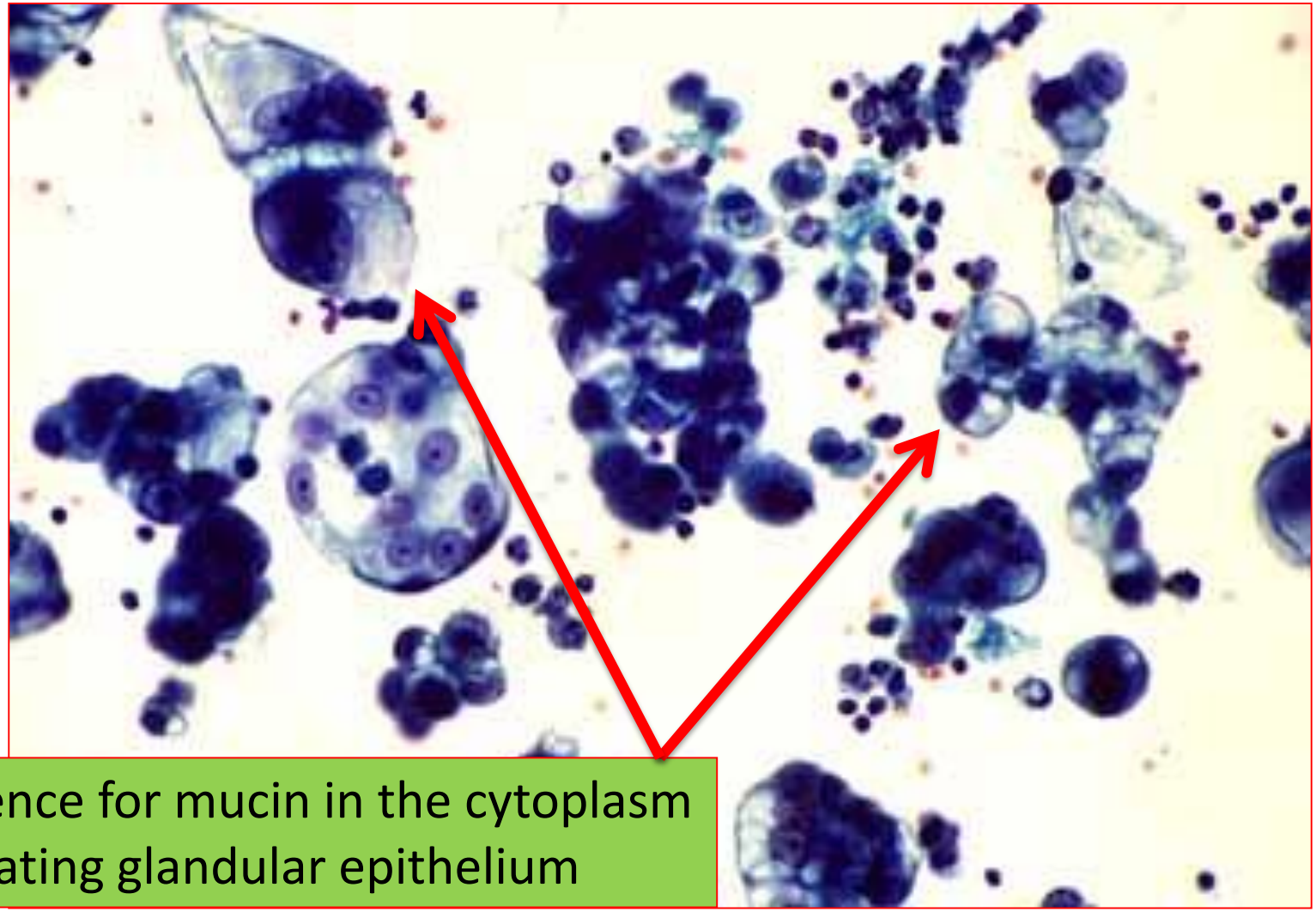


Keratin formation- “keratin pearls” and intracellular bridges



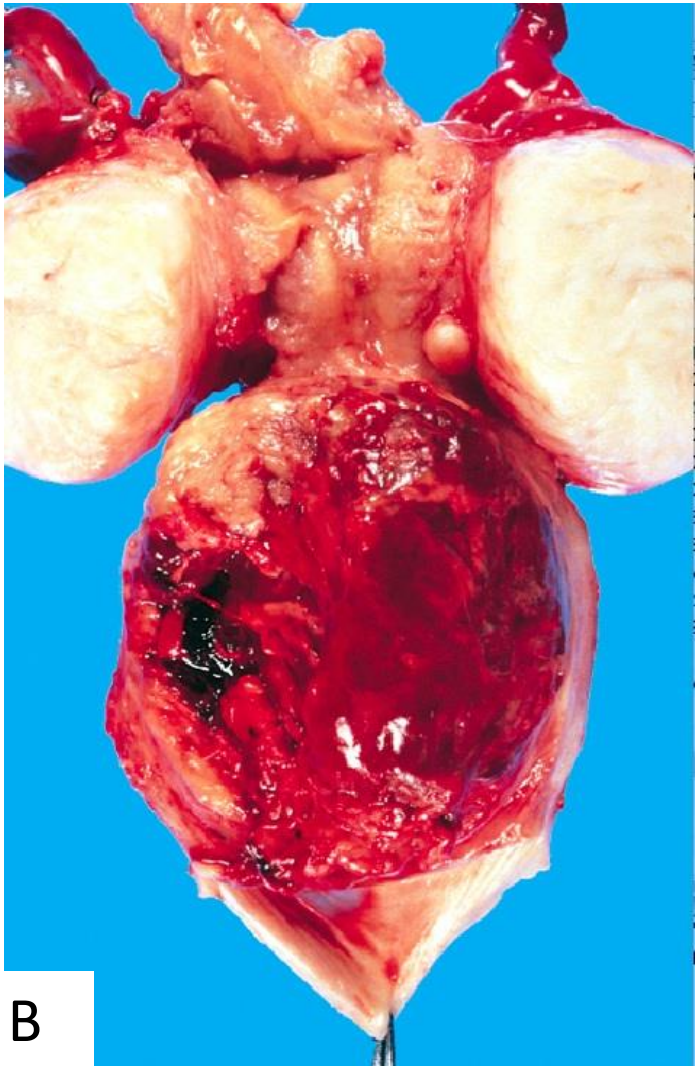
Well-differentiated squamous cell carcinoma

Adenocarcinoma in Ascites



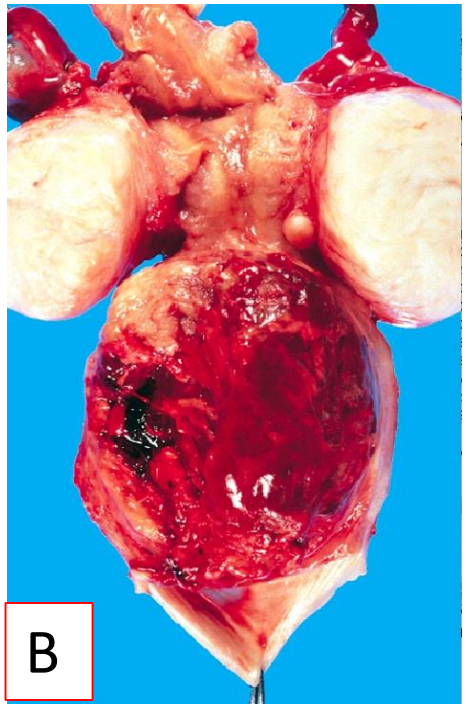
Evidence for mucin in the cytoplasm
Indicating glandular epithelium

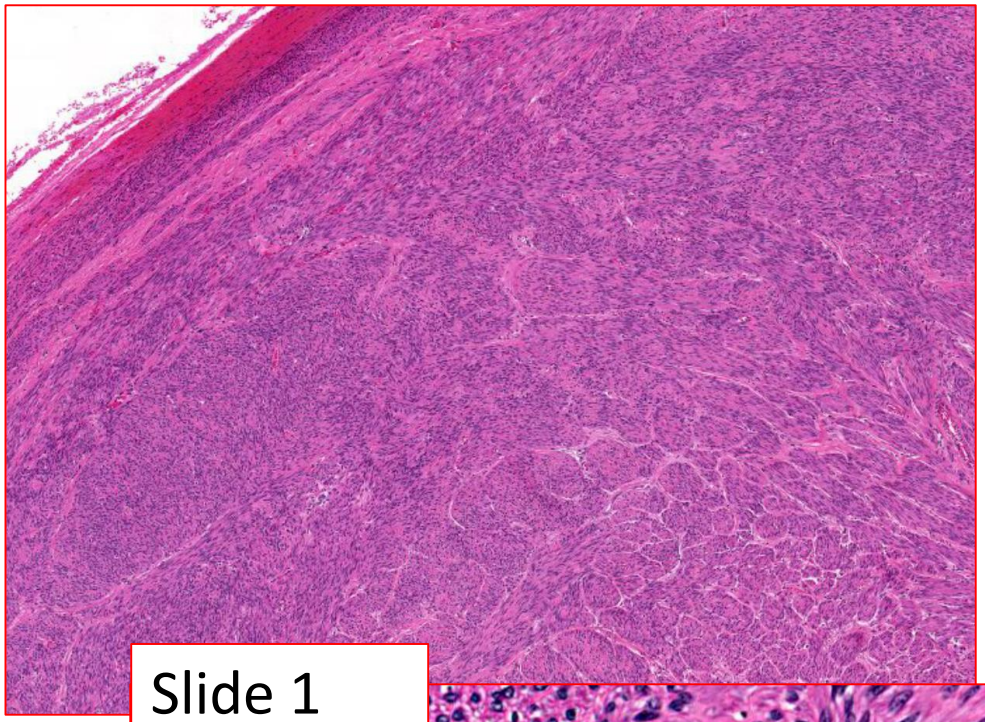
Final Exam



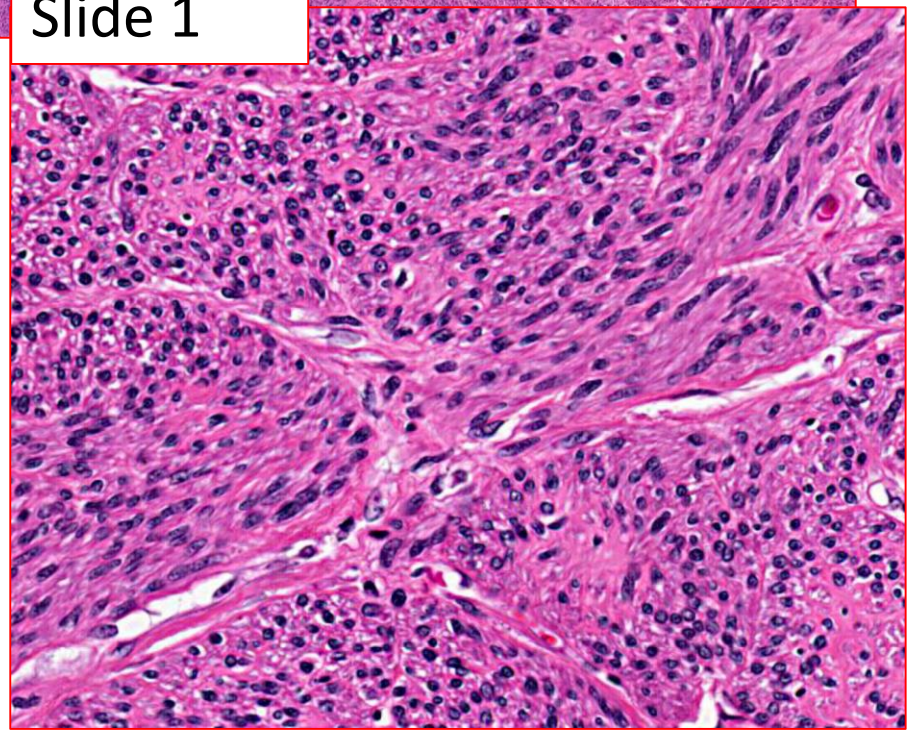
Case 4 and 5- Exercise

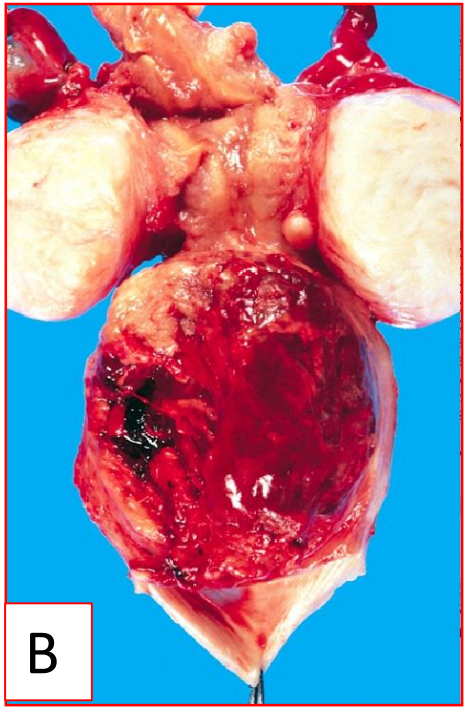
Which histologic slide belongs to Gross A and which slide belongs to Gross B?

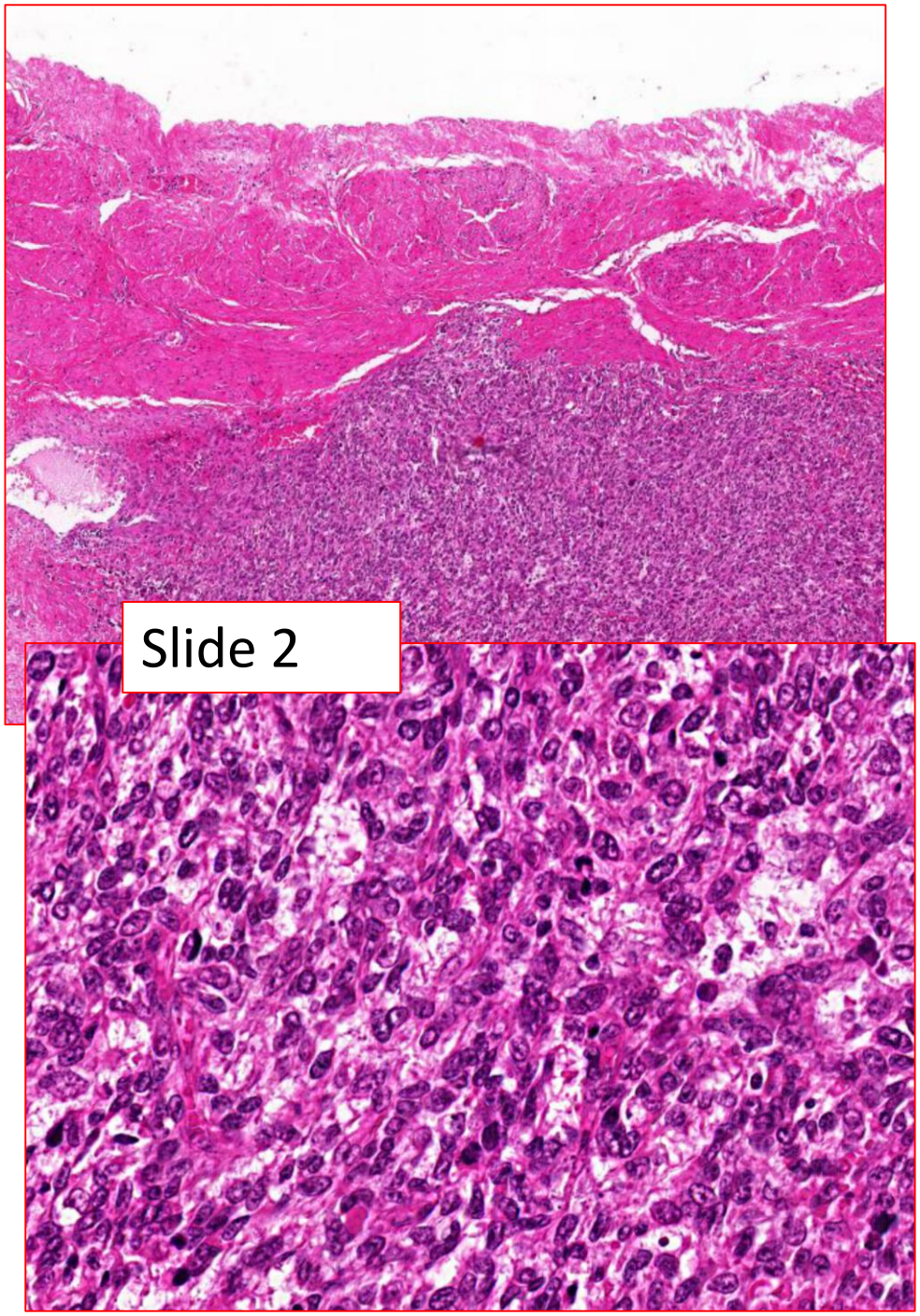




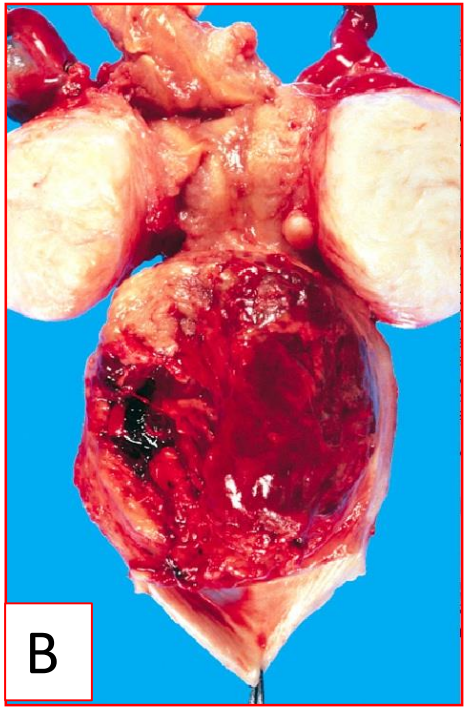
Slide 1






Slide 2


A


B

What is the correct slide-gross specimen combination?

A. Slide 1 with A & Slide 2 with B
B. Slide 1 with B & Slide 2 with A

Objectives

- Describe the scope of practice for pathology and laboratory medicine
- Discuss the *value* of pathology in providing best patient care
- Describe the process and quality systems used to ensure accurate results
- Understand the pathologic features neoplasms
- Describe the “team” of medical professionals

Diagnosing a Patient

It is a TEAM effort

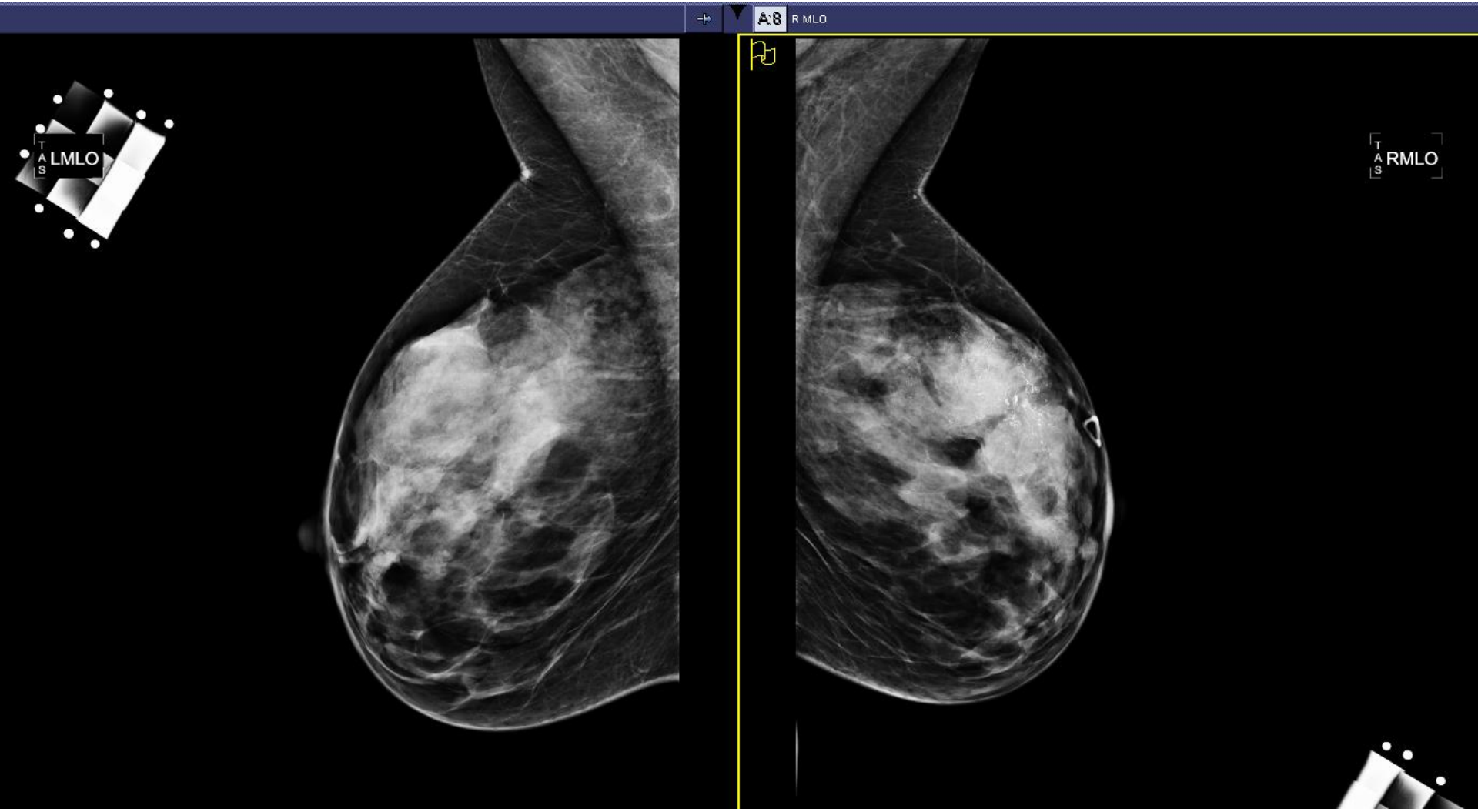
Diagnosis

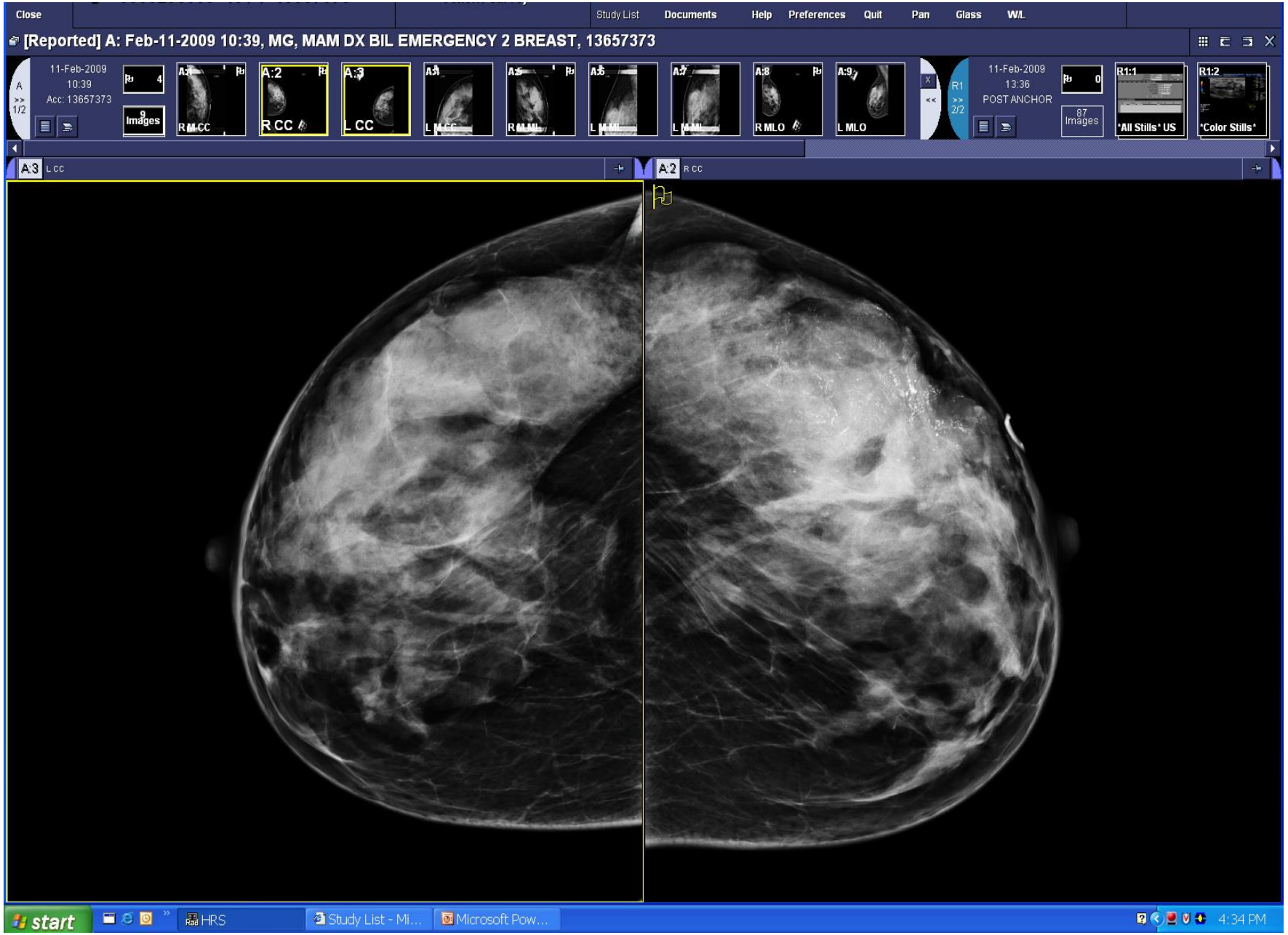
Treatment

Management

Breast Cancer Case Presentation

49-yr-old with newly palpable lump in the right breast


A:8
R MLO
LMLO
RMLO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Study List
Documents
Help
Preferences
Quit
Pan
Glass
W/L
[Reported] A: Feb-11-2009 10:39, MG, MAM DX BIL EMERGENCY 2 BREAST, 13657373
11-Feb-2009
10:39
Acc: 13657373
9 Images
A:2
R CC
A:3
L CC
R MLO
L MLO
11-Feb-2009
13:36
POST ANCHOR
87 Images
R1:1
All Stills US
R1:2
Color Stills
A:3 L CC
A:2 R CC
start
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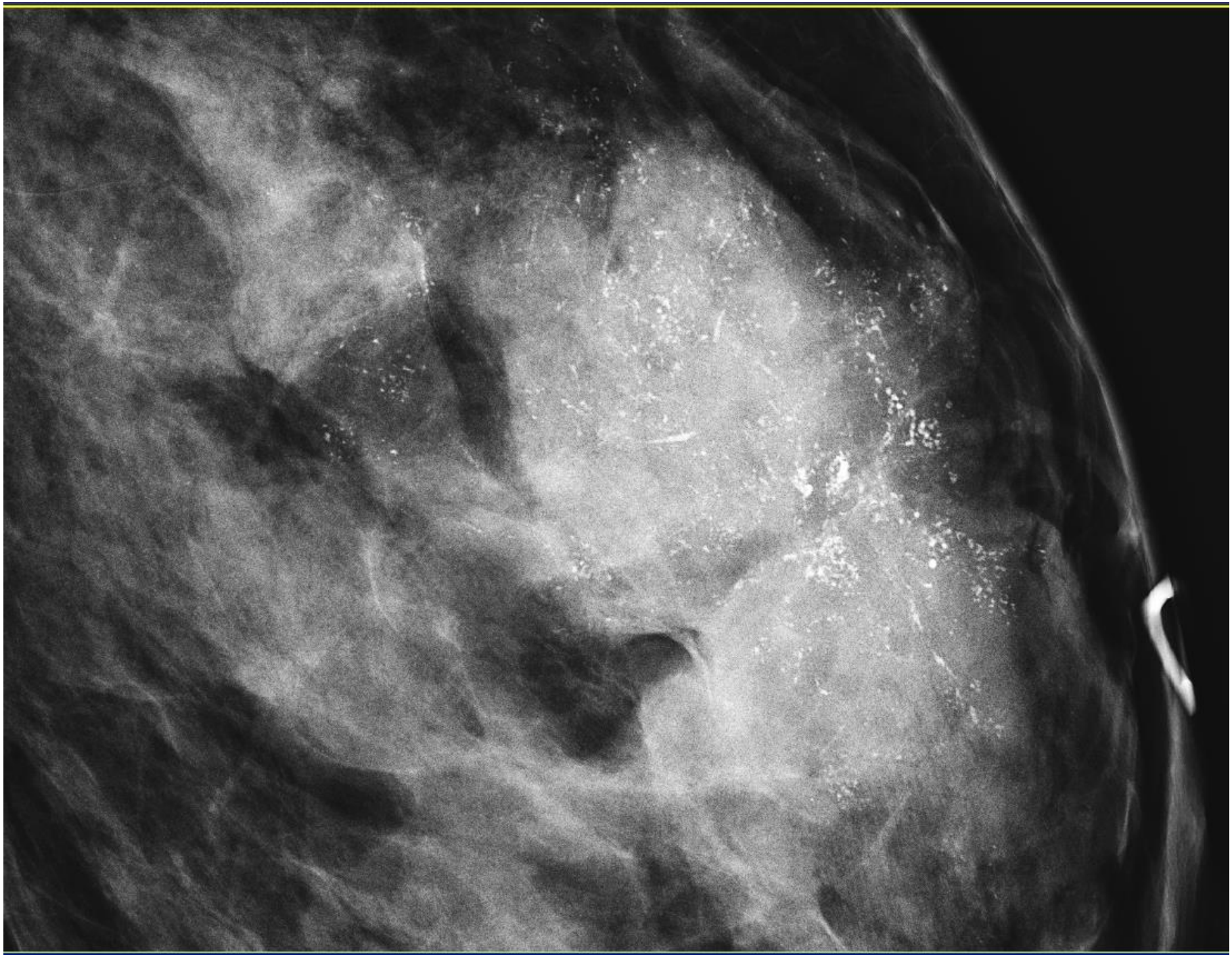
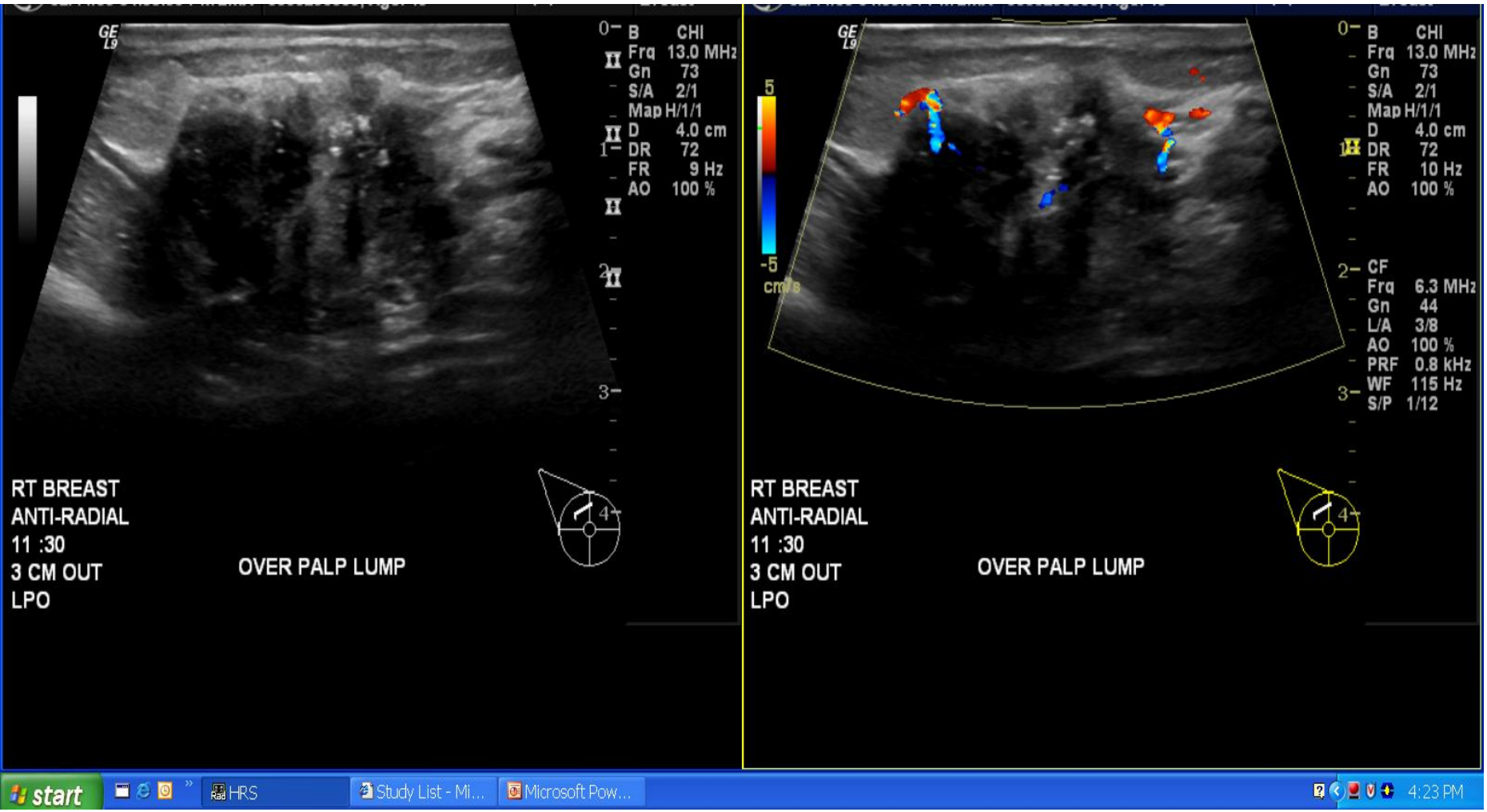
Microsoft Pow...
4:34 PM




GE
L9
B CHI
Frq 13.0 MHz
Gn 73
S/A 2/1
Map H/1/1
D 4.0 cm
DR 72
FR 9 Hz
AO 100 %
RT BREAST
ANTI-RADIAL
11 :30
3 CM OUT
LPO
OVER PALP LUMP
GE
L9
5
-5
cm/s
B CHI
Frq 13.0 MHz
Gn 73
S/A 2/1
Map H/1/1
D 4.0 cm
DR 72
FR 10 Hz
AO 100 %
CF
Frq 6.3 MHz
Gn 44
L/A 3/8
AO 100 %
PRF 0.8 kHz
WF 115 Hz
S/P 1/12
RT BREAST
ANTI-RADIAL
11 :30
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OVER PALP LUMP
start
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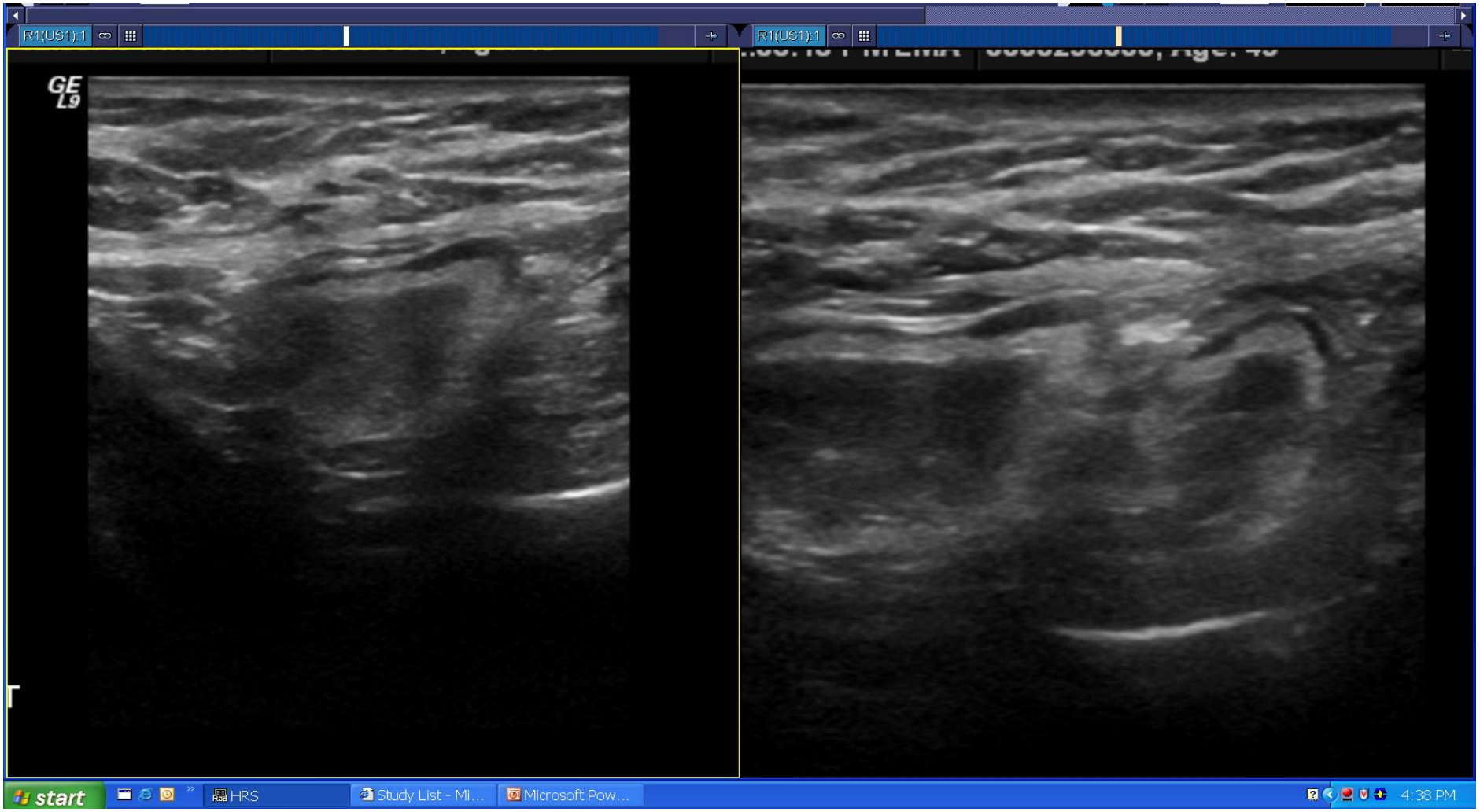
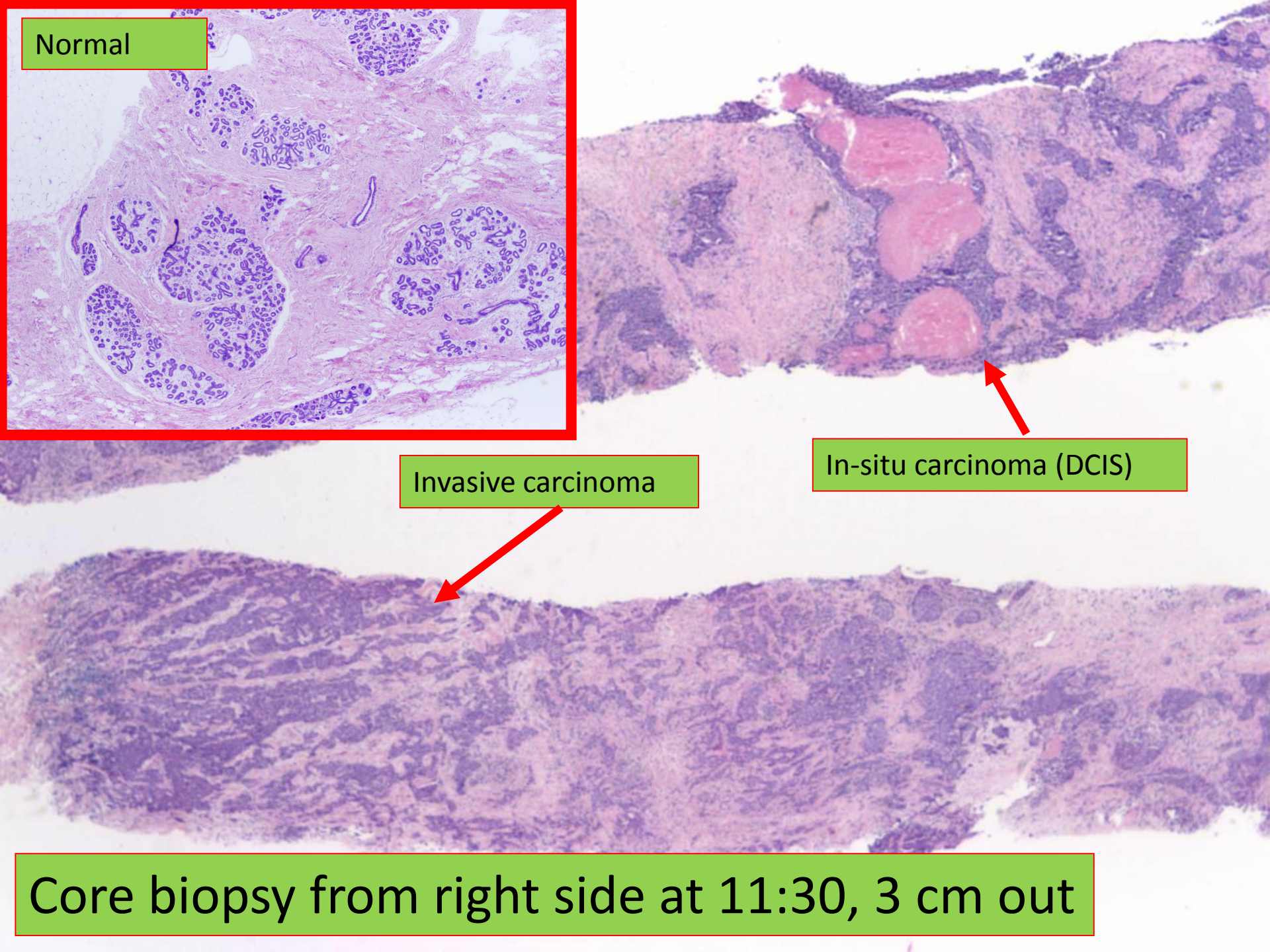
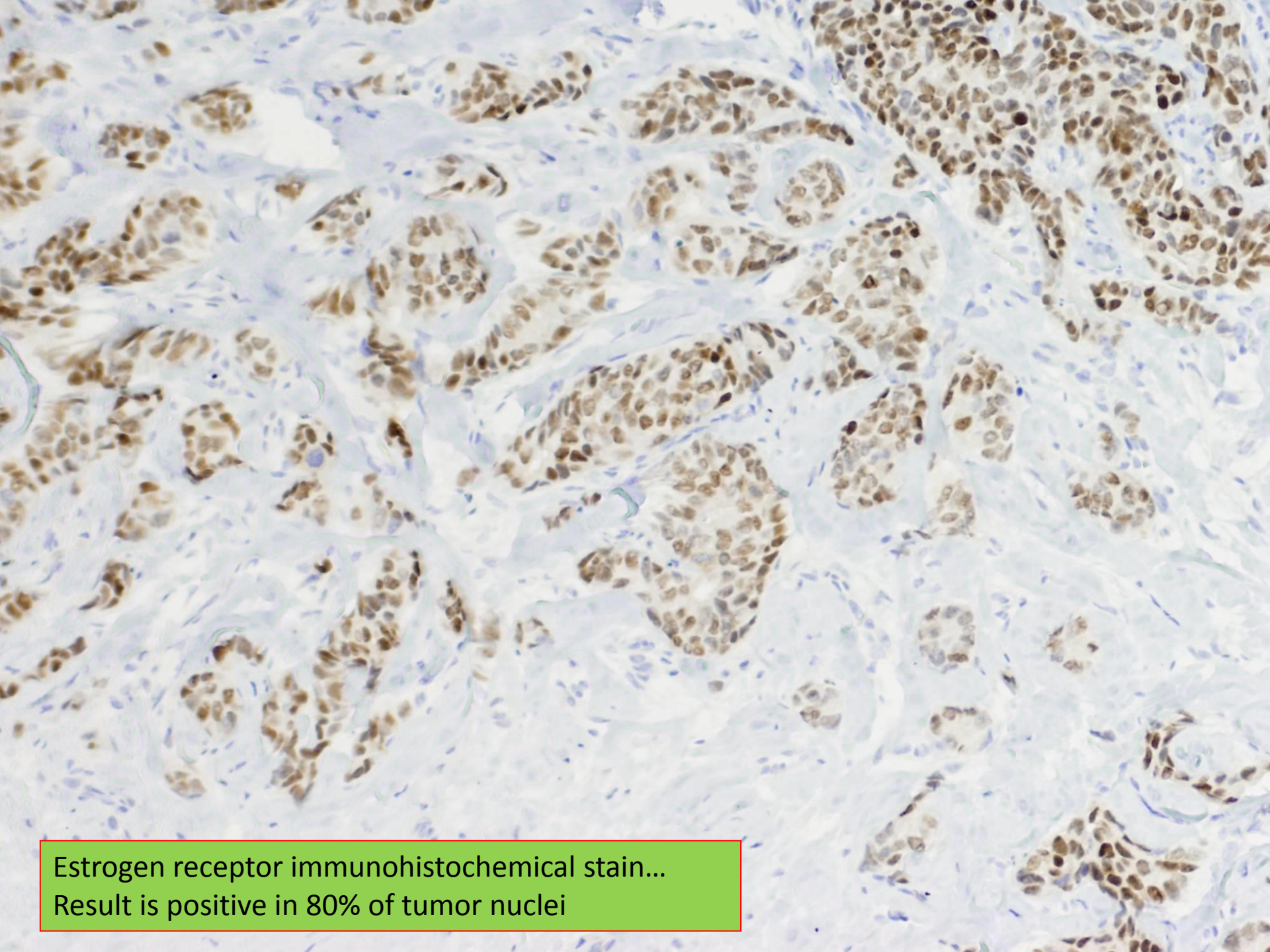
Microsoft Pow...
4:23 PM

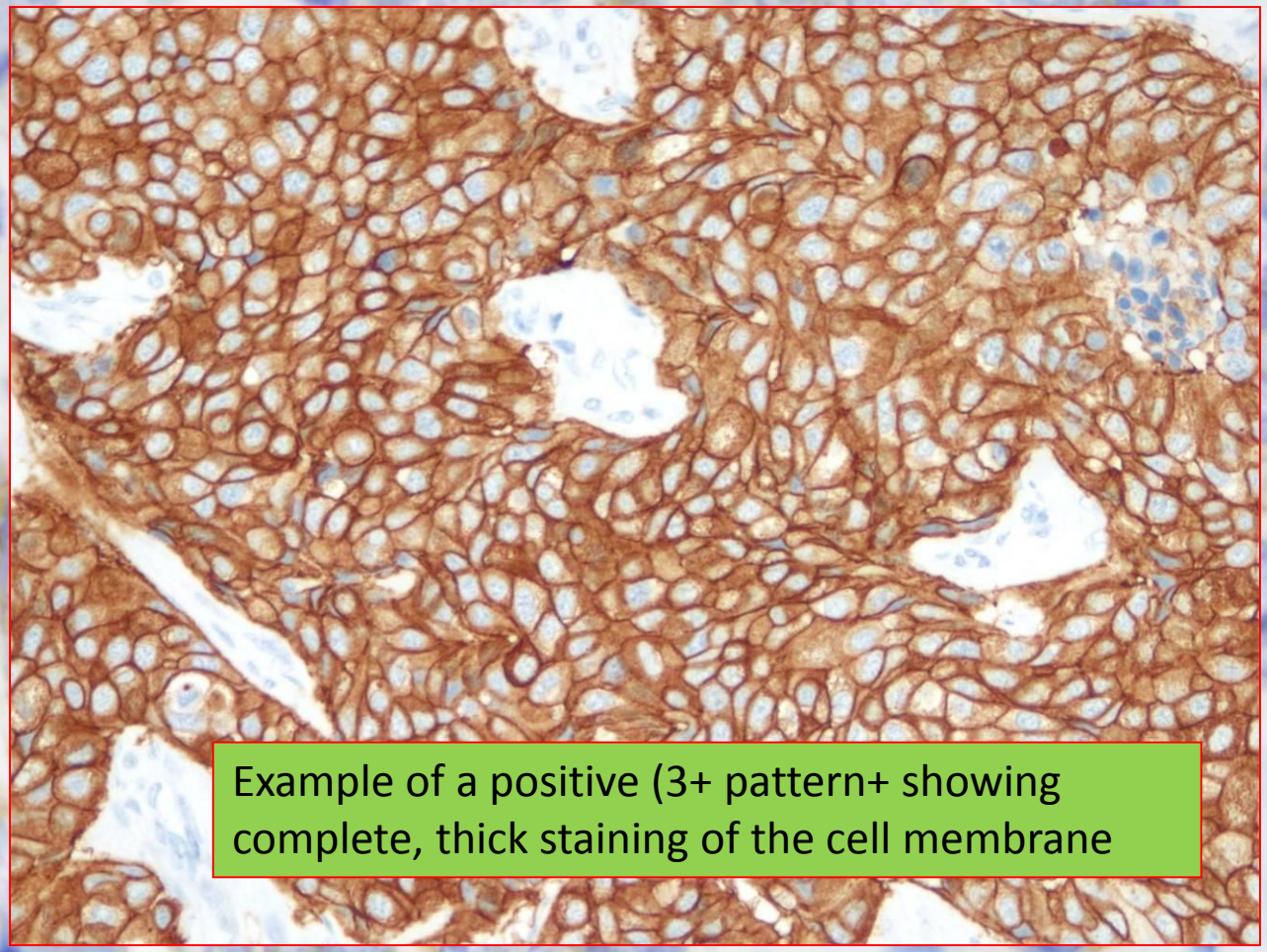

R1(US1):1
GE
L9
R1(US1):1
start
HRS
Study List - Mi...
Microsoft Pow...
4:38 PM



Core biopsy from right side at 11:30, 3 cm out



Estrogen receptor immunohistochemical stain…
Result is positive in 80% of tumor nuclei

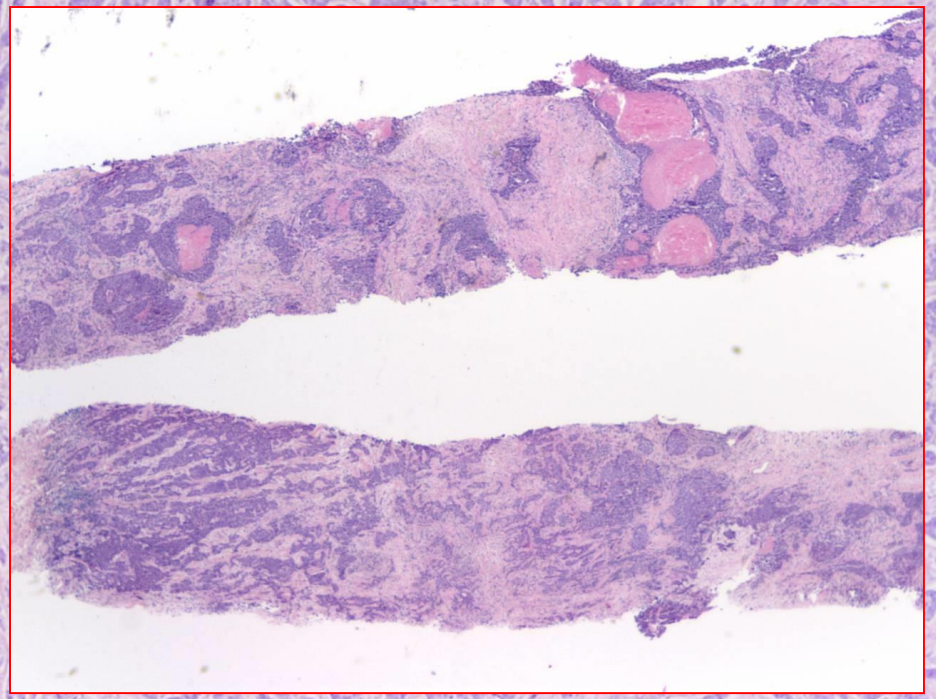


Example of a positive (3+ pattern+ showing complete, thick staining of the cell membrane

Her2/neu immunohistochemical stain…
Result is negative with weak, incomplete membranous (1+ pattern)

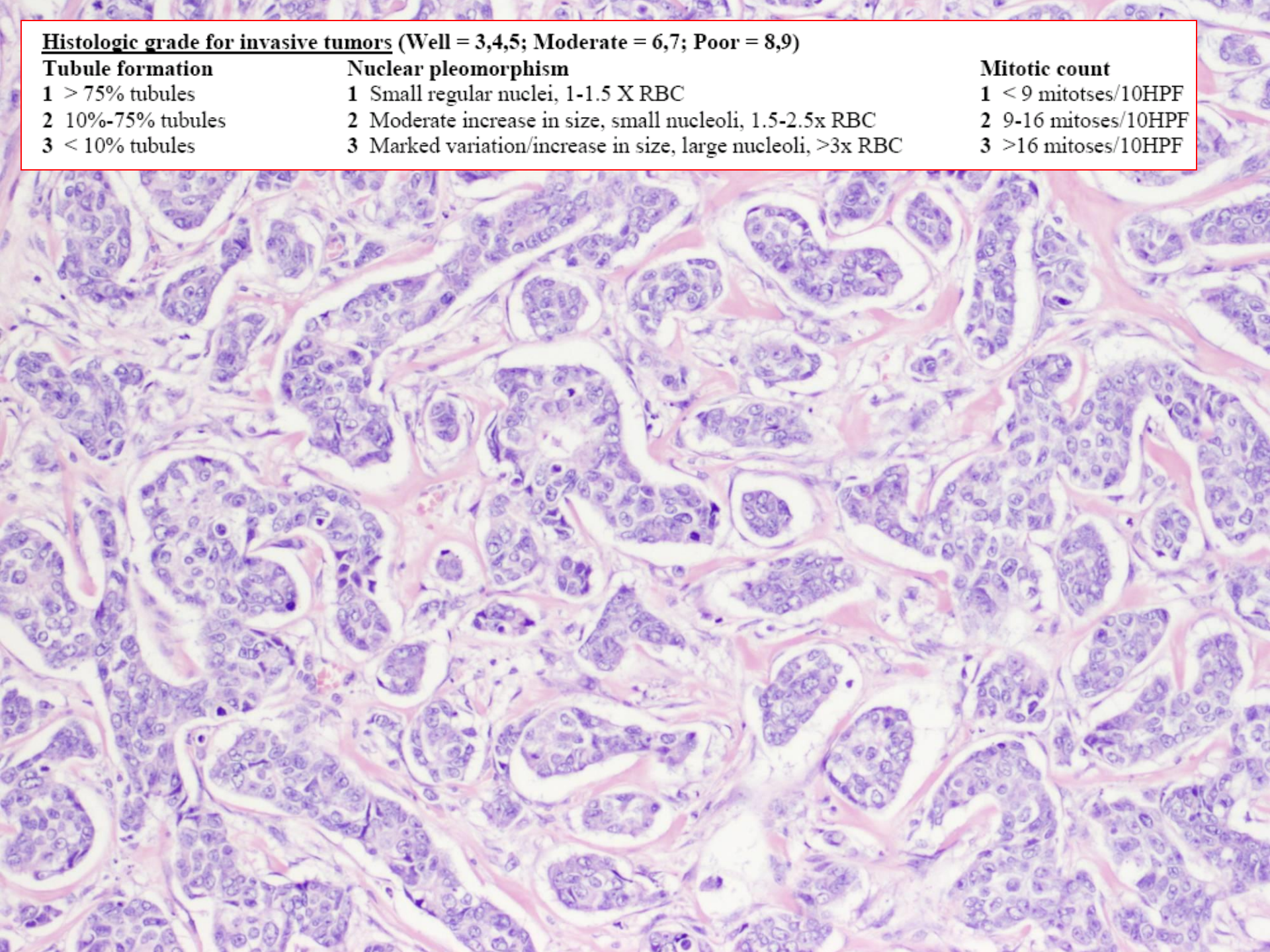
Invasive carcinoma

In-situ carcinoma (DCIS)



Histologic grade for invasive tumors (Well = 3,4,5; Moderate = 6,7; Poor = 8,9)

Tubule formation	Nuclear pleomorphism	Mitotic count
1 > 75% tubules	**1** Small regular nuclei, 1-1.5 X RBC	**1** < 9 mitotses/10HPF
2 10%-75% tubules	**2** Moderate increase in size, small nucleoli, 1.5-2.5x RBC	**2** 9-16 mitoses/10HPF
3 < 10% tubules	**3** Marked variation/increase in size, large nucleoli, >3x RBC	**3** >16 mitoses/10HPF



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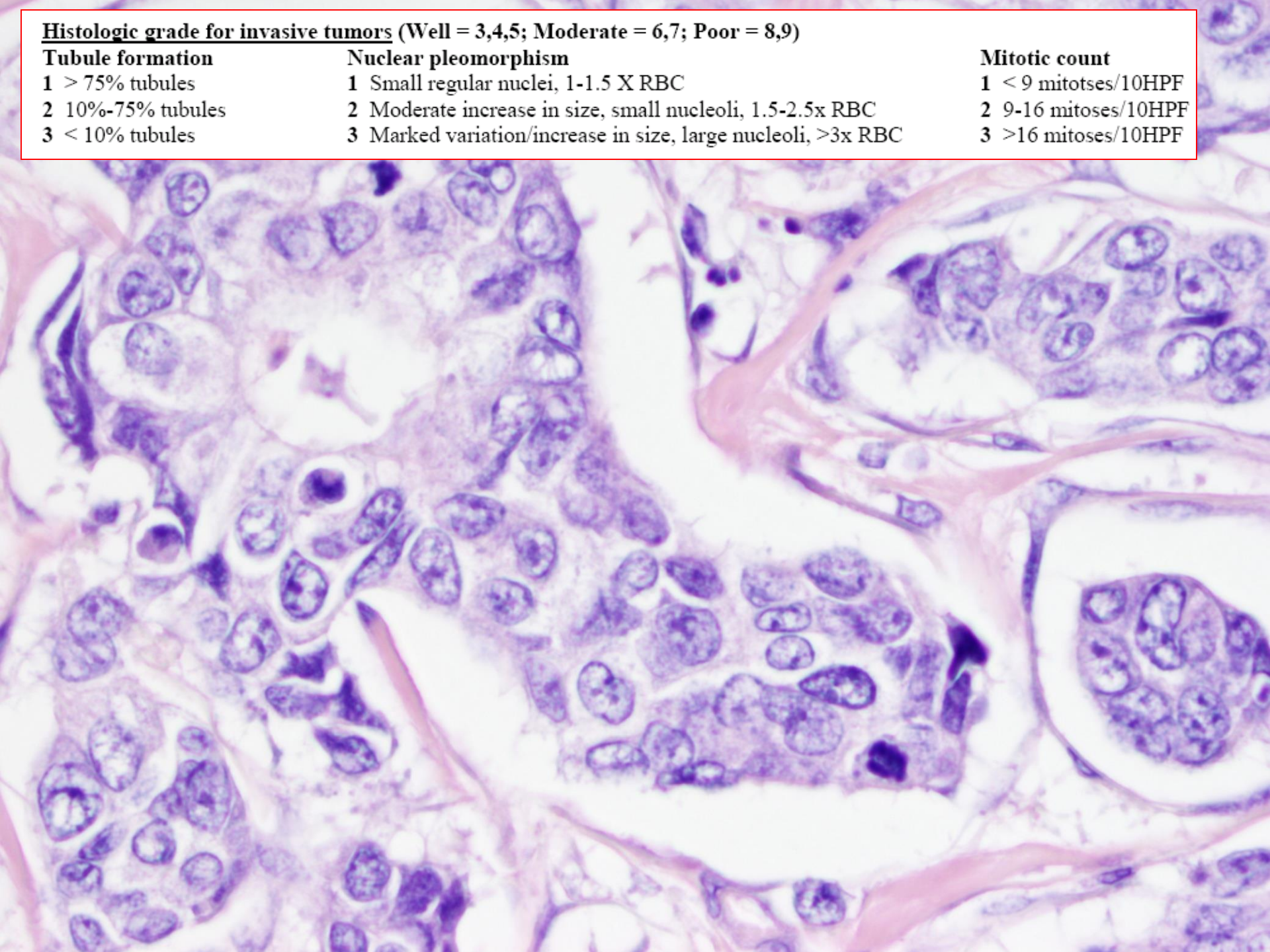
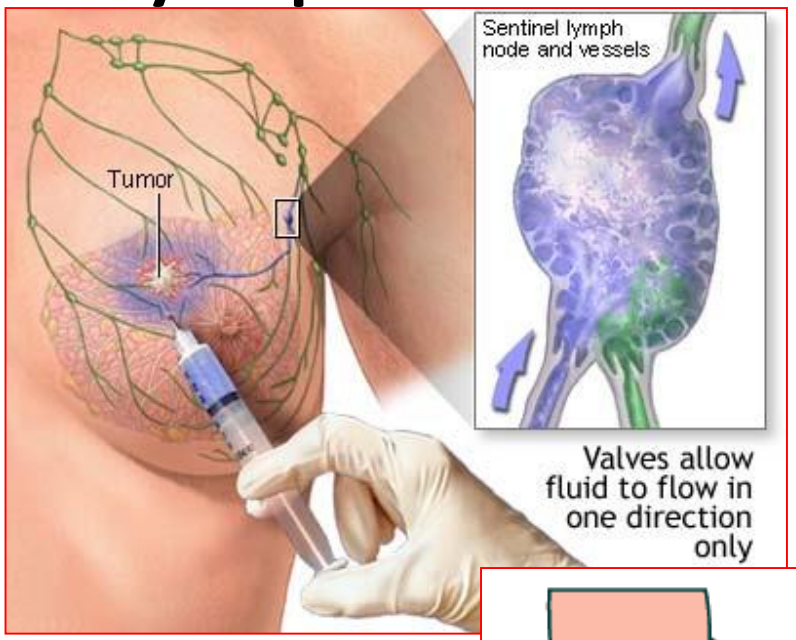
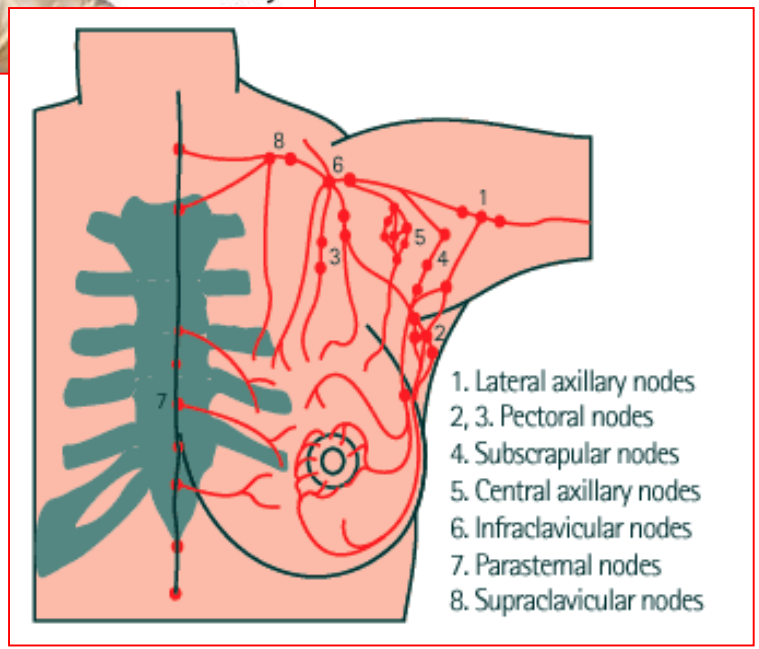



Blue in applied during our gross examination and processing
Tumor distance to margin

Lymphatic Drainage of the Breast

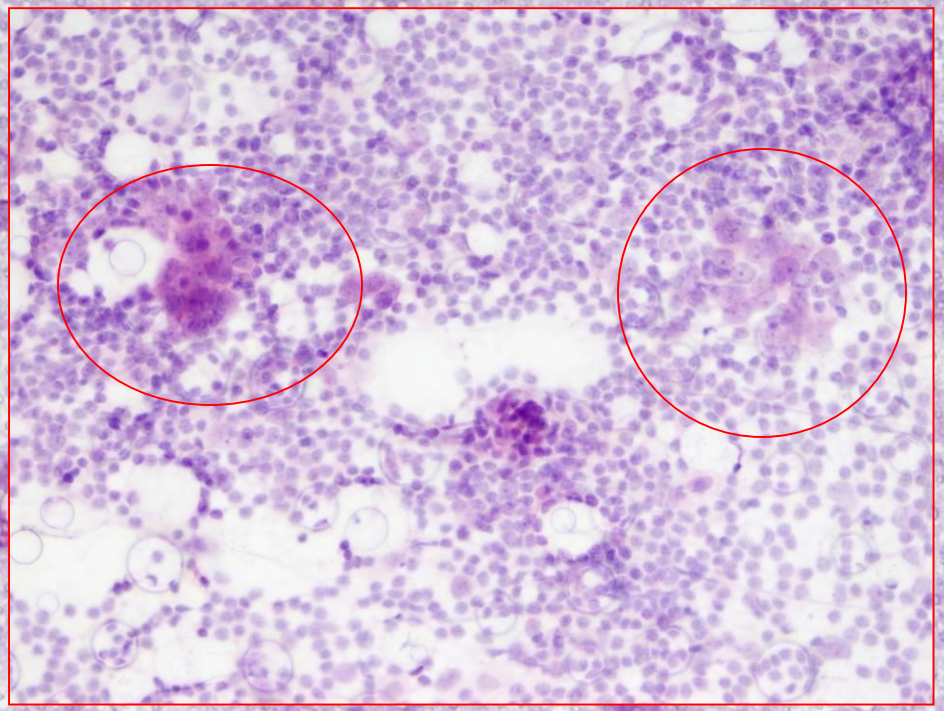




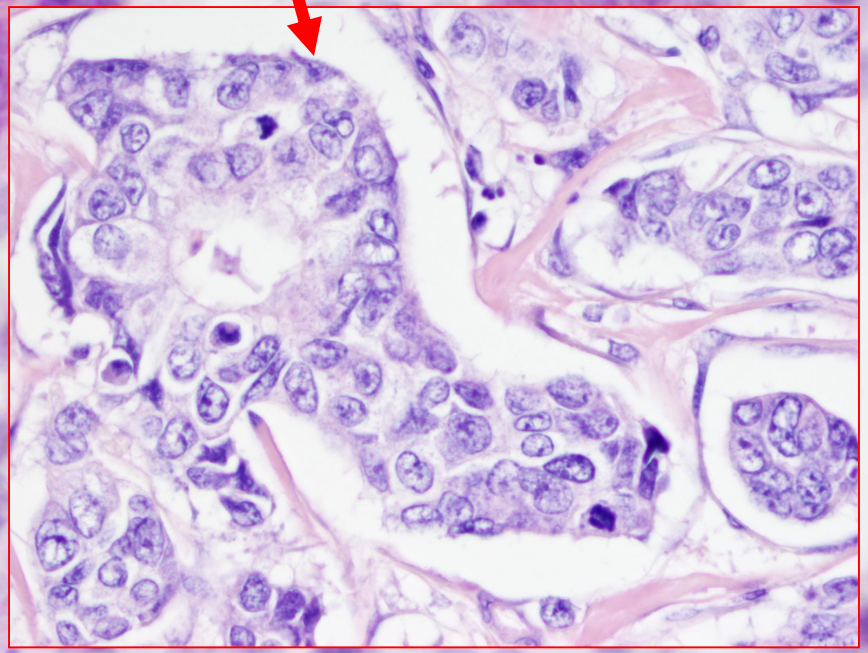
<u>Sentinel lymph node</u> is the first node in a regional lymphatic basin receiving lymph from primary tumor

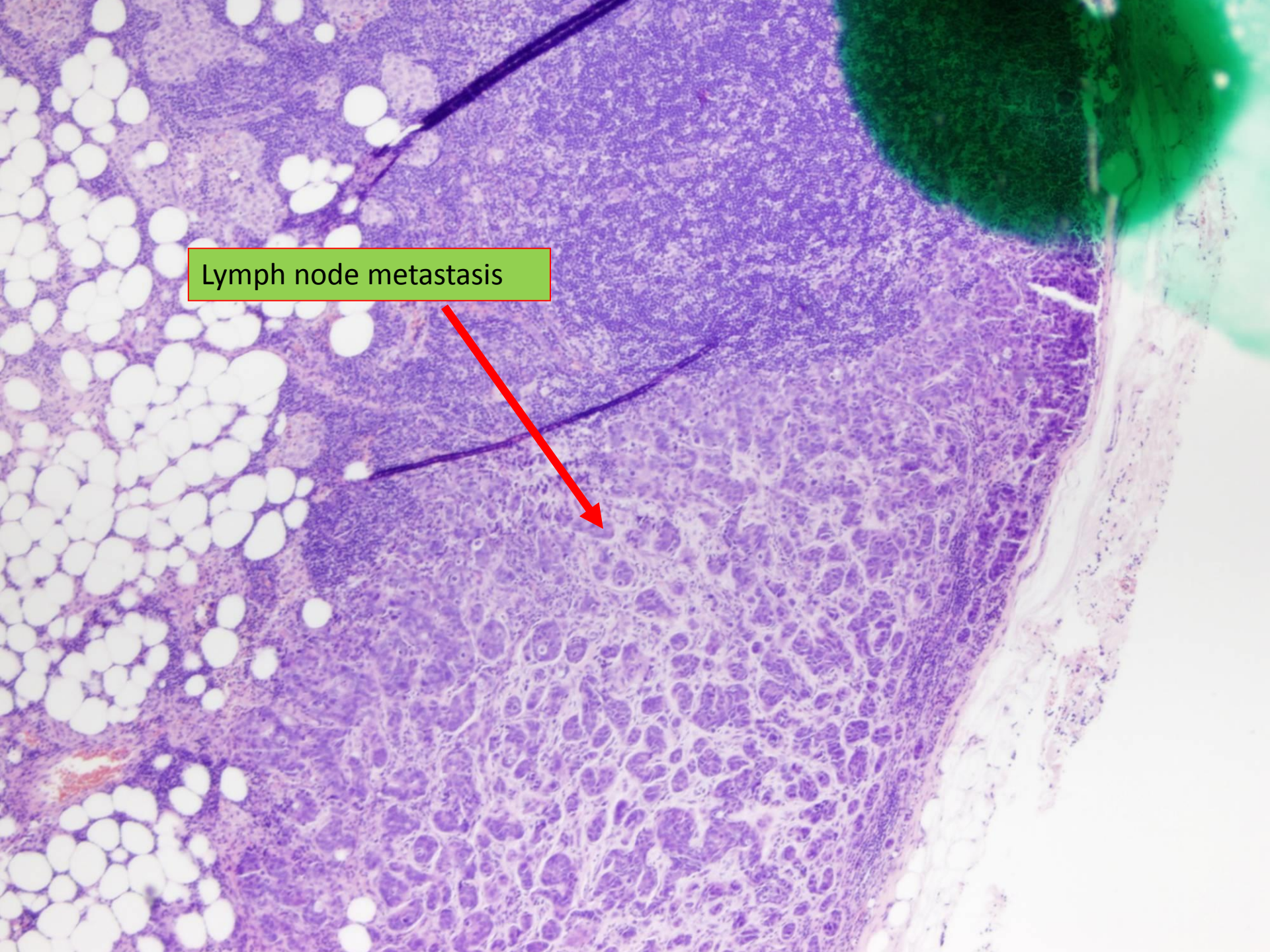
Scrape preparation prepared during surgery- “Intraoperative Consult”

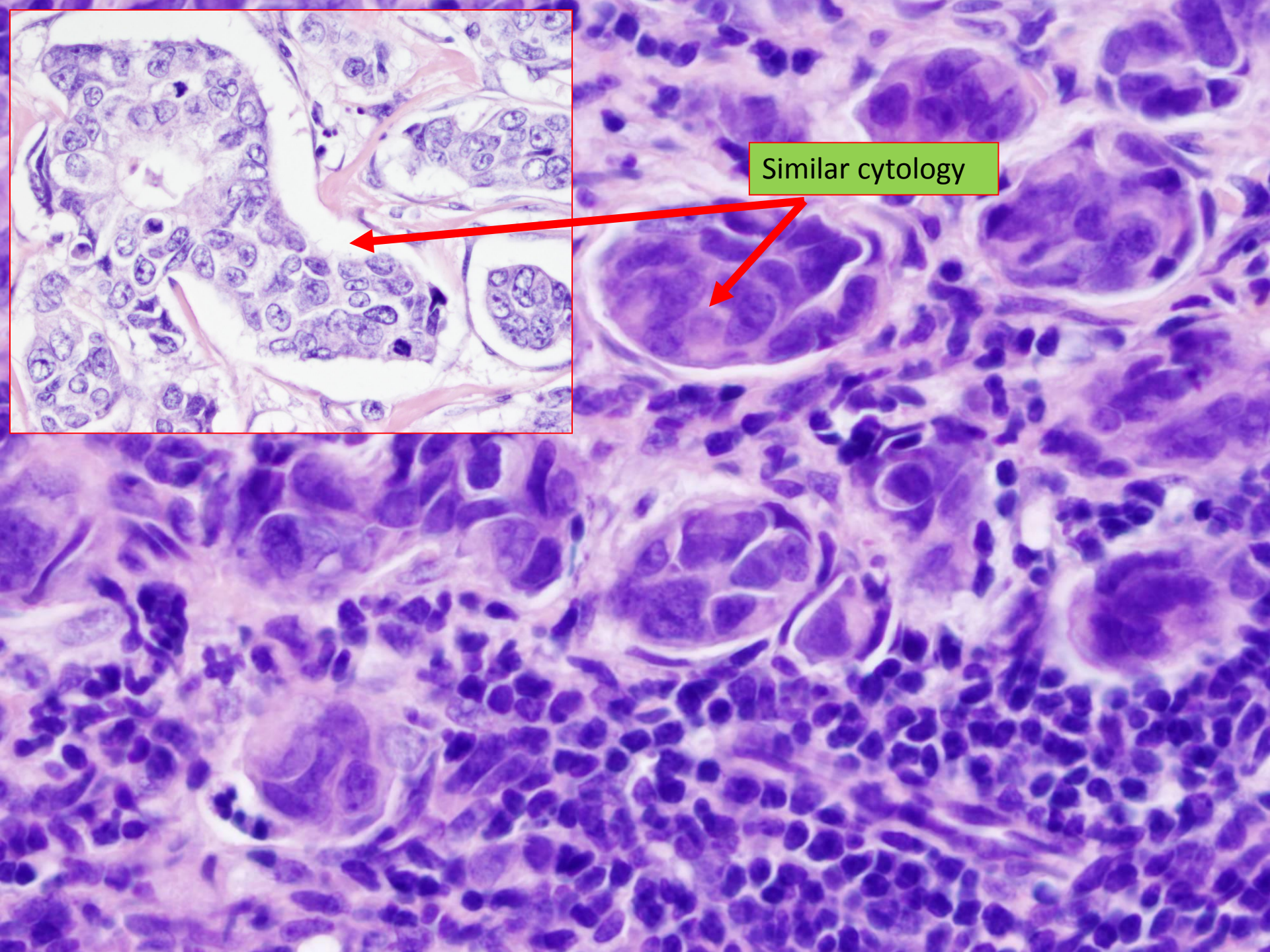
Concerning cells



Similar cytology




Lymph node metastasis


Similar cytology

Synoptic Report for this Carcinoma

Laterality:	Right AJCC (7th edition): pT2 , pN2a
Specimen:	Total mastectomy; sentinel node biopsy; axillary dissection
Tumor Type:	Invasive ductal
Tumor Size:	3.5 x 3.0 x 2.5 cm
Nottingham Combined Histologic Scores:	
Tubules:	3
Nuclei:	3
Mitoses:	3 (actual count 38/10 HPF with field diameter of 0.54 mm)
Total:	9
Differentiation:	Poor
Margins:	Negative (closest margin 4.0 mm, anterior)
DCIS:	Solid and Cribriform pattern, with necrosis, nuclear grade III
% DCIS:	Less than 5%; DCIS also present outside main tumor mass
DCIS margins:	Negative (closest margin 2.0 mm; anterior)
LVI:	Not identified
Lymph nodes:	5/37 (positive/total count); largest metastasis 0.9 mm
ER/PR:	ER positive (80%); PR positive (90%)
Her2:	Negative/ 1+ by immunohistochemistry
	Non-amplified by in situ hybridization; Her2:Chr17 ratio is 1.31

Who is going to care for this patient?

Team Effort

- Primary physician
  - Assess risk
  - Perform physical exam
    - Detect an abnormality
- Radiologist
  - Perform and review imaging
  - Perform biopsy
- Pathologist
  - Diagnose disease
  - Provide information to surgeon

Team Effort

- Surgeon
  - Counsel patient on treatment options
  - Consider other diagnostic tests
  - Perform cytoreductive surgery
- Pathology
  - Diagnose disease
  - Provide staging and prognostic information
- Medical and Radiation Oncologists
  - Counsel patient on treatment options
  - Consider other prognostic tests
  - Treat the disease
  - Manage the patient

Team Effort

- Nursing
  - Coordinate patient care
  - Follow-up on diagnostic and prognostic testing
  - Counsel patient
- Geneticist
- Nutritionist
- Primary physician
  - Continue to monitor and care for patient’s disease
  - Prevent further disease
  - Educate the patient and family

Thank you for attending Community Medical School