FNA Cytology of Metastatic Malignancies of Unknown Primary Site

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Pathologic Diagnosis of Metastasis

- Smaller specimens, less invasive techniques
- FNA cytology is highly accurate
- Determine primary site
  - No previous history of malignancy
  - Prior pathology not available
  - Unpredictable pattern of metastasis
- Accurate Dx → modify patient management

Metastatic Malignancies of Unknown Primary Site (MUP)

- 8th most common malignancy
- 5-10% of all non-cutaneous malignancies
- Up to 15% of new referrals to hospital based oncology centers
- Standard panel of multi-agent chemotherapy
- Poor prognosis. Median survival ≈ 4-12 mo.

Metastases of Unknown Primary Site

Definition: Bx confirmed. 1º site not found after rigorous, but limited initial clinical and radiographic evaluation

- careful Hx, physical exam, lab, x-rays, etc..

Is Workup of MUP Necessary?

- Optimal management may be organ-specific, and rely on accurate determination of primary site
- Inability to ID a primary → major clinical challenge
  - Patient anxiety:
    - ? Inadequate evaluation by physician
    - ? Prognosis improved if primary is found

Cost Effectiveness of Pathologic Workup

- Extensive radiological exams & serum tumor markers – often unsuccessful in finding 1º site
- Pathologic evaluation (including extended IHC panel) is more cost effective than clinical workup

	Cost per patient	*Success rate*	*Theoretical cost-effectiveness ratio*
Clinical tests alone	$ 18,000 *	20 %	$ 250,000
IHC panel**	$ 2,000	70 %	$ 2,900

* *excluding physician charges*

** *panel of 6 tests*

Wick et al 1999

Cost Effectiveness of Pathologic Workup $_2$

- Overutilization occurs in individual cases or by individual pathologists
  - Too many Ab's in 30% of cases
  - Unnecessary IHC in 10% of cases

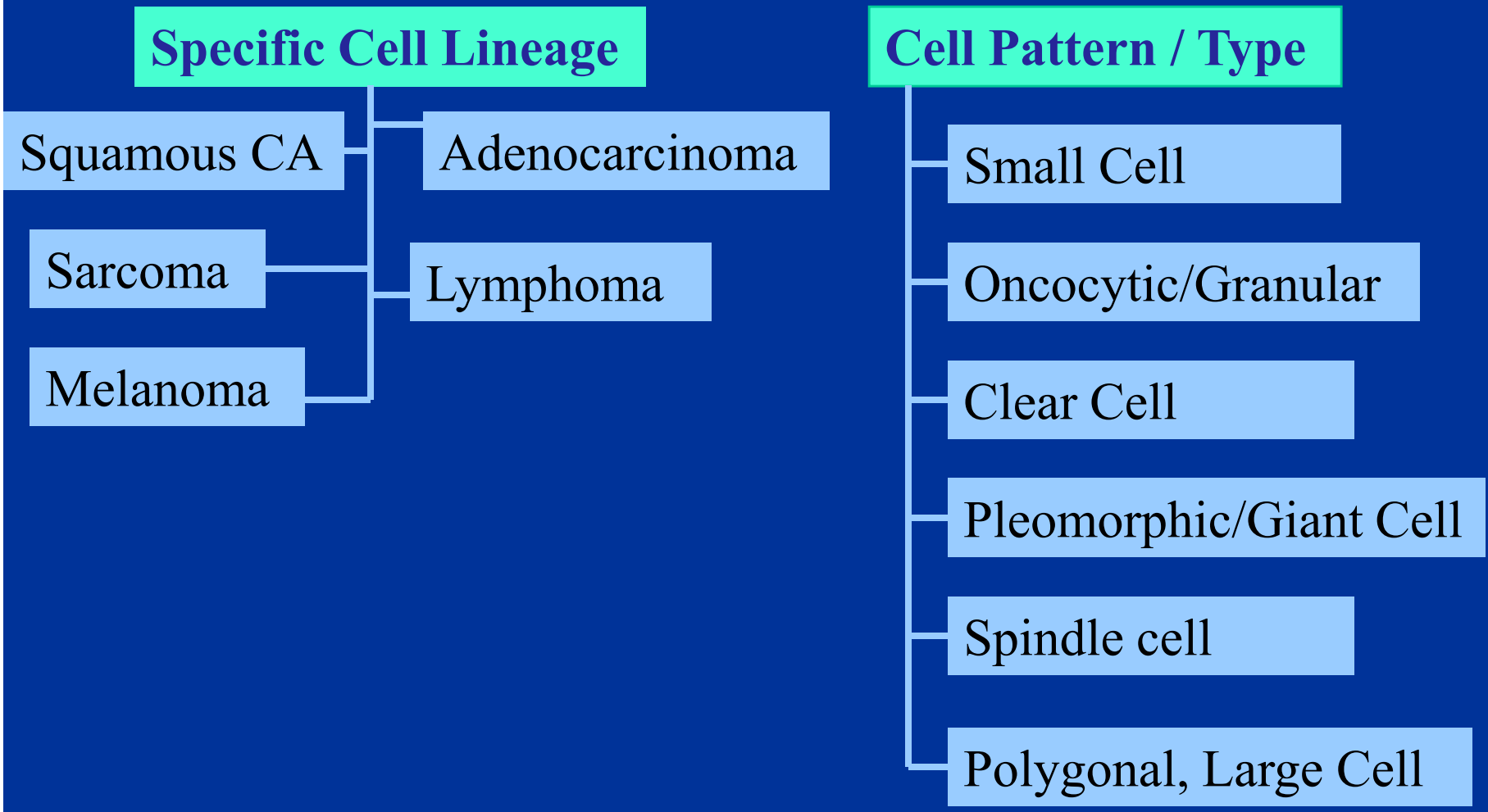
FNA Diagnosis of MUP
A Clinico-pathologic approach

1. Cytomorphologic features
2. Ancillary studies: IHC
3. Clinical patterns of metastases

FNA Diagnosis of MUP [2]
A Clinico-pathologic approach

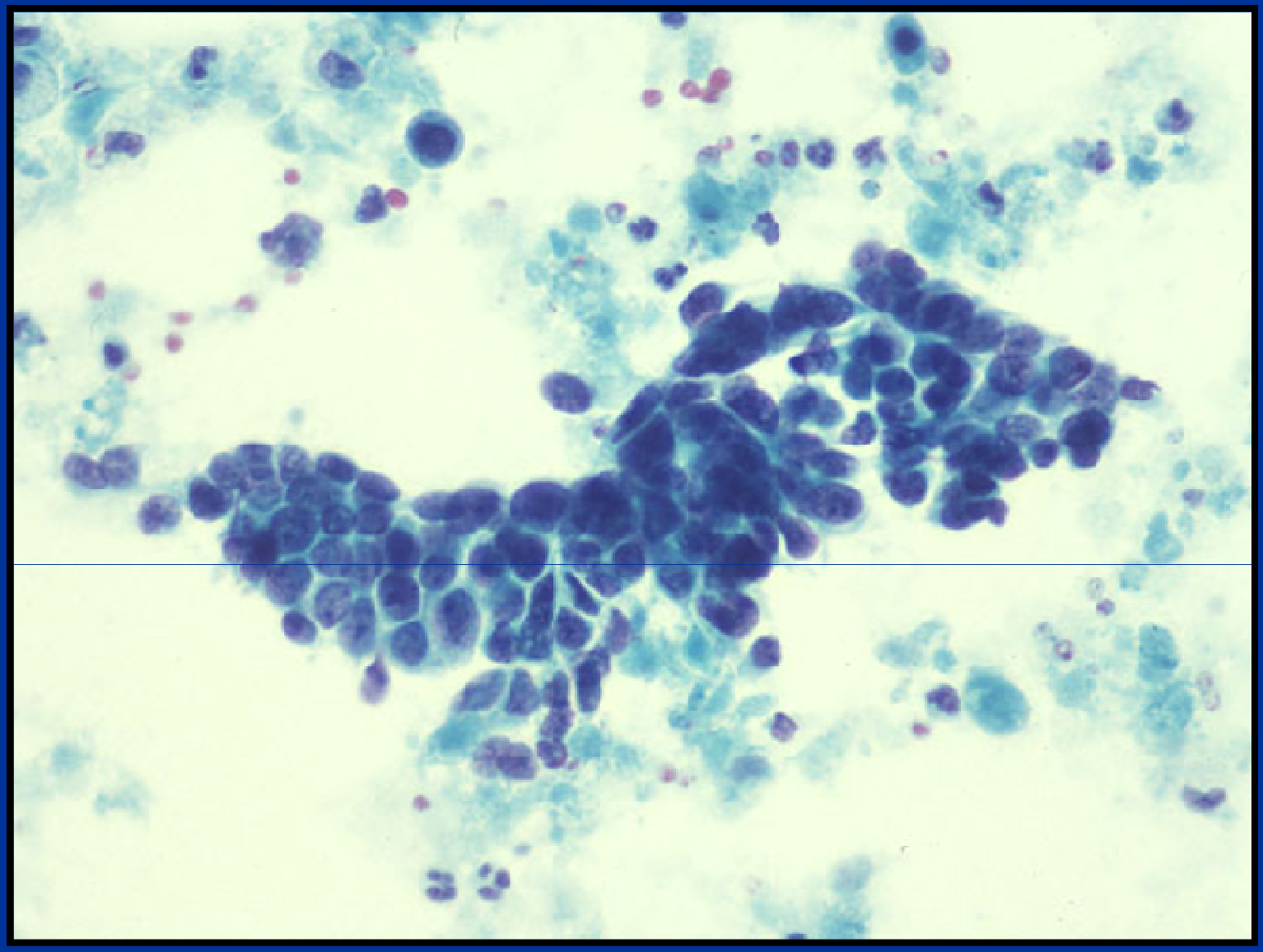
1. Cytomorphologic features
   - *Histologic types* (specific cell lineage): adenoca, squamous ca, melanoma, etc.
   - *Morphologic patterns* (non specific cell lineage): small cell, large cell, oncocytic, spindle, etc.
2. Ancillary studies: IHC
3. Clinical patterns of metastases

CYTOMORPHOLOGIC PATTERNS OF MUP



Case 1

- CT guided FNA biopsy of a kidney mass in a 68 year old woman.



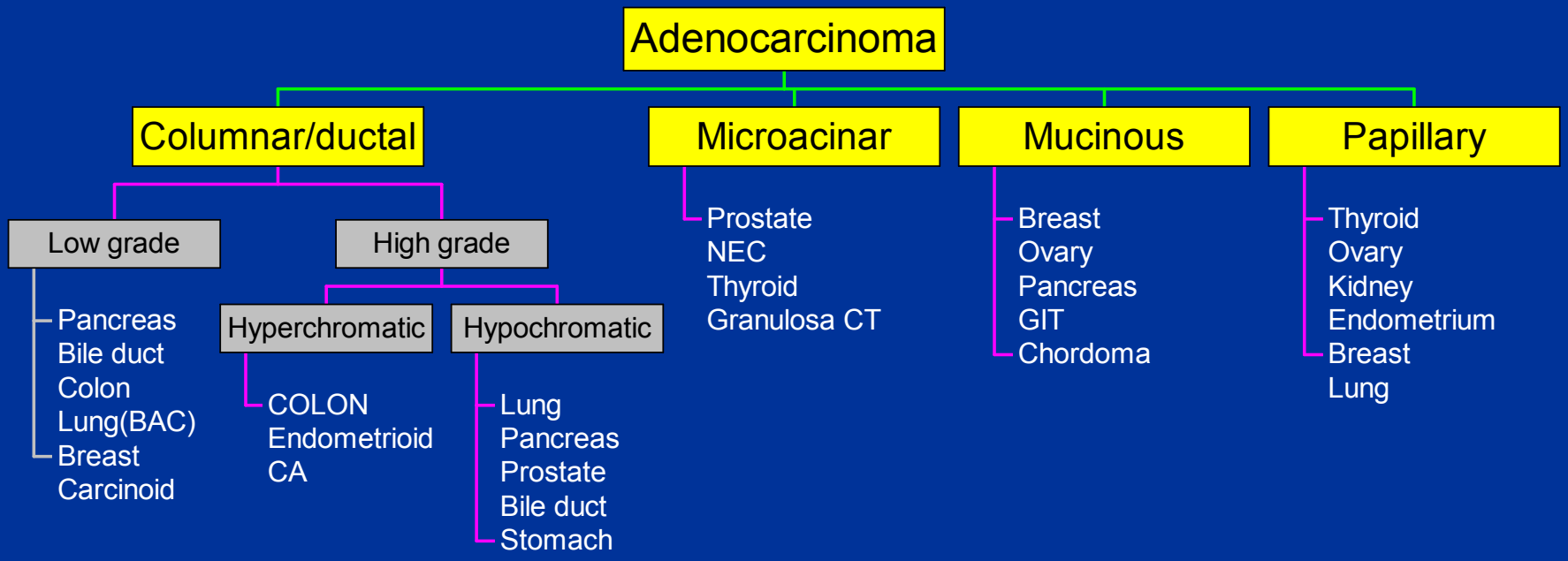
Diagnosis: Metastatic adenocarcinoma.

A lung primary was subsequently found

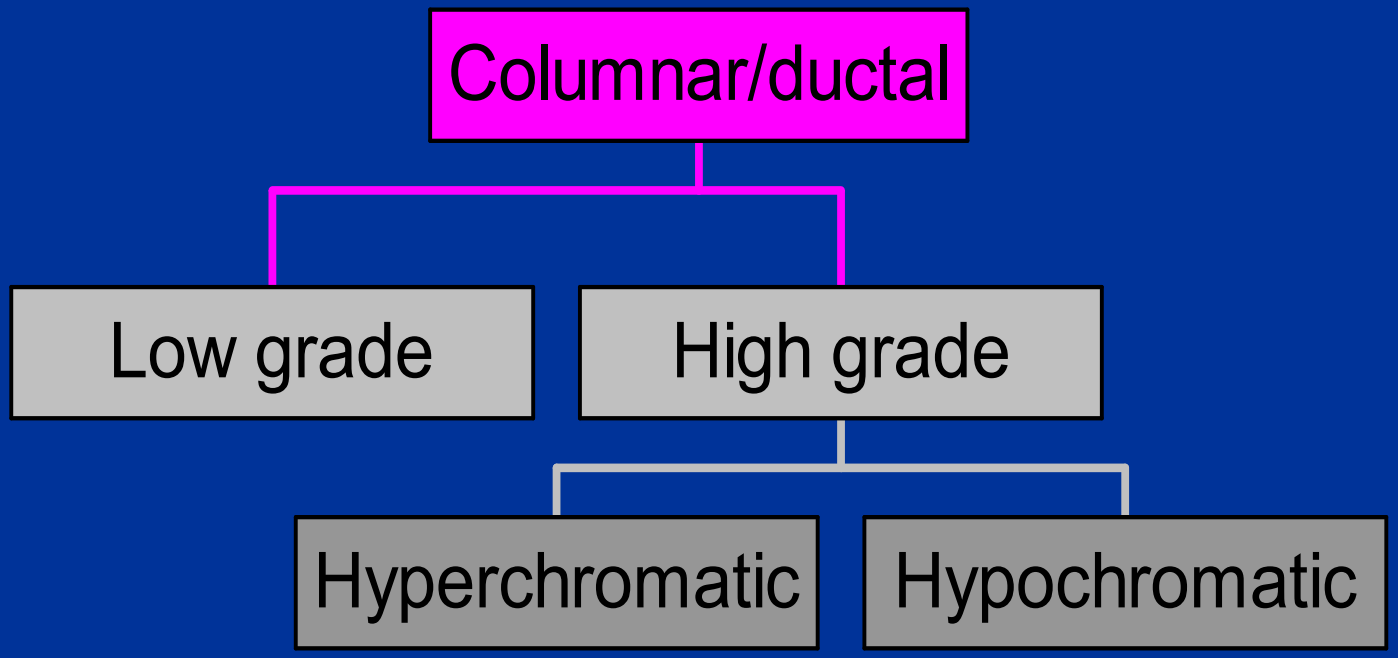
Adenocarcinoma

- Most common MUP (60%)
- W-M differentiated adenocarcinoma → median survival ≈ 3-6 months
- Lung & pancreas: most common (40%)
  - GI tract
  - Liver
- Nonspecific diagnosis → 1° vs. MET

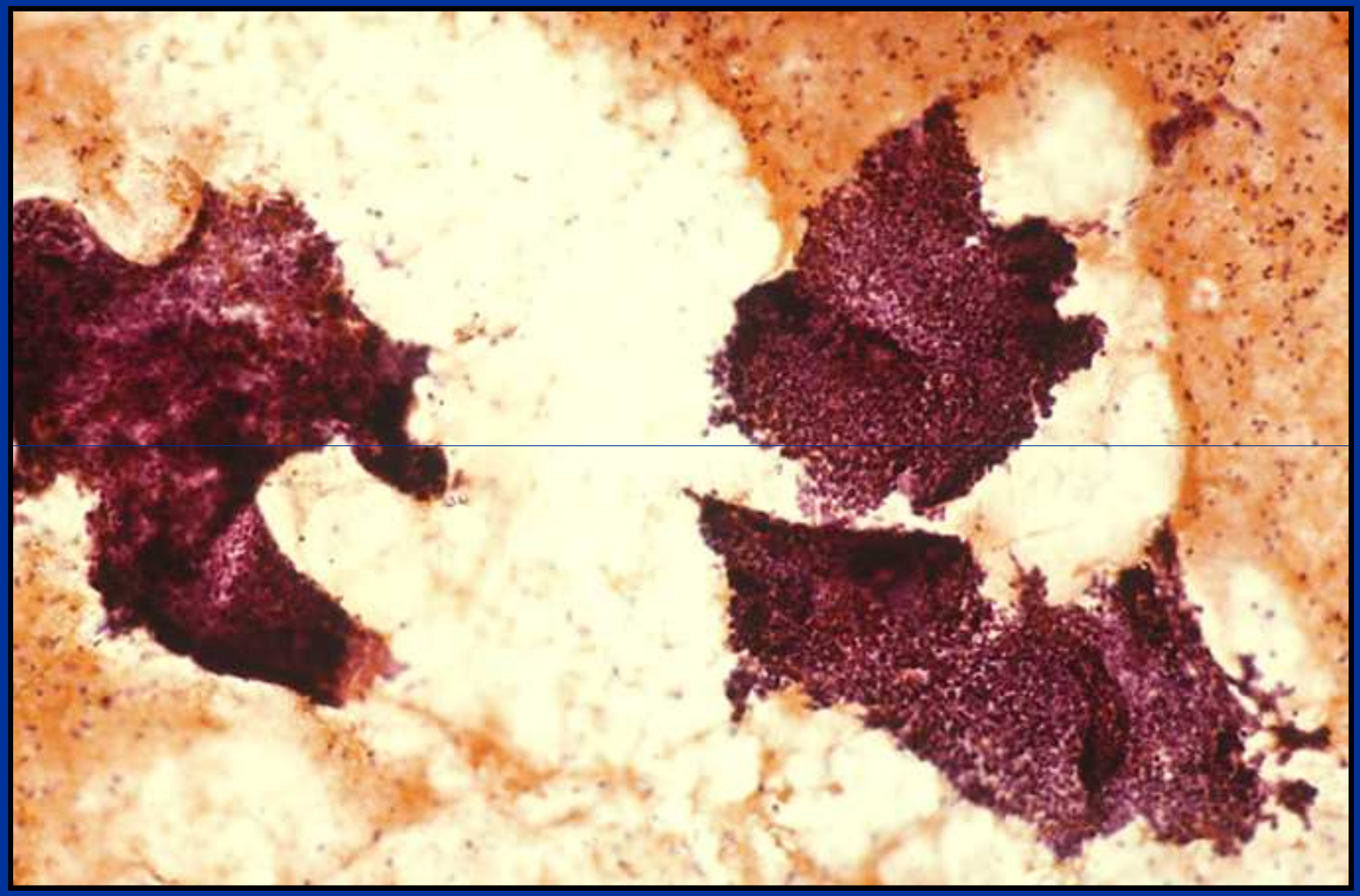
Morphologic Patterns of Differentiated Adenocarcinoma (W-M)



Adenocarcinoma

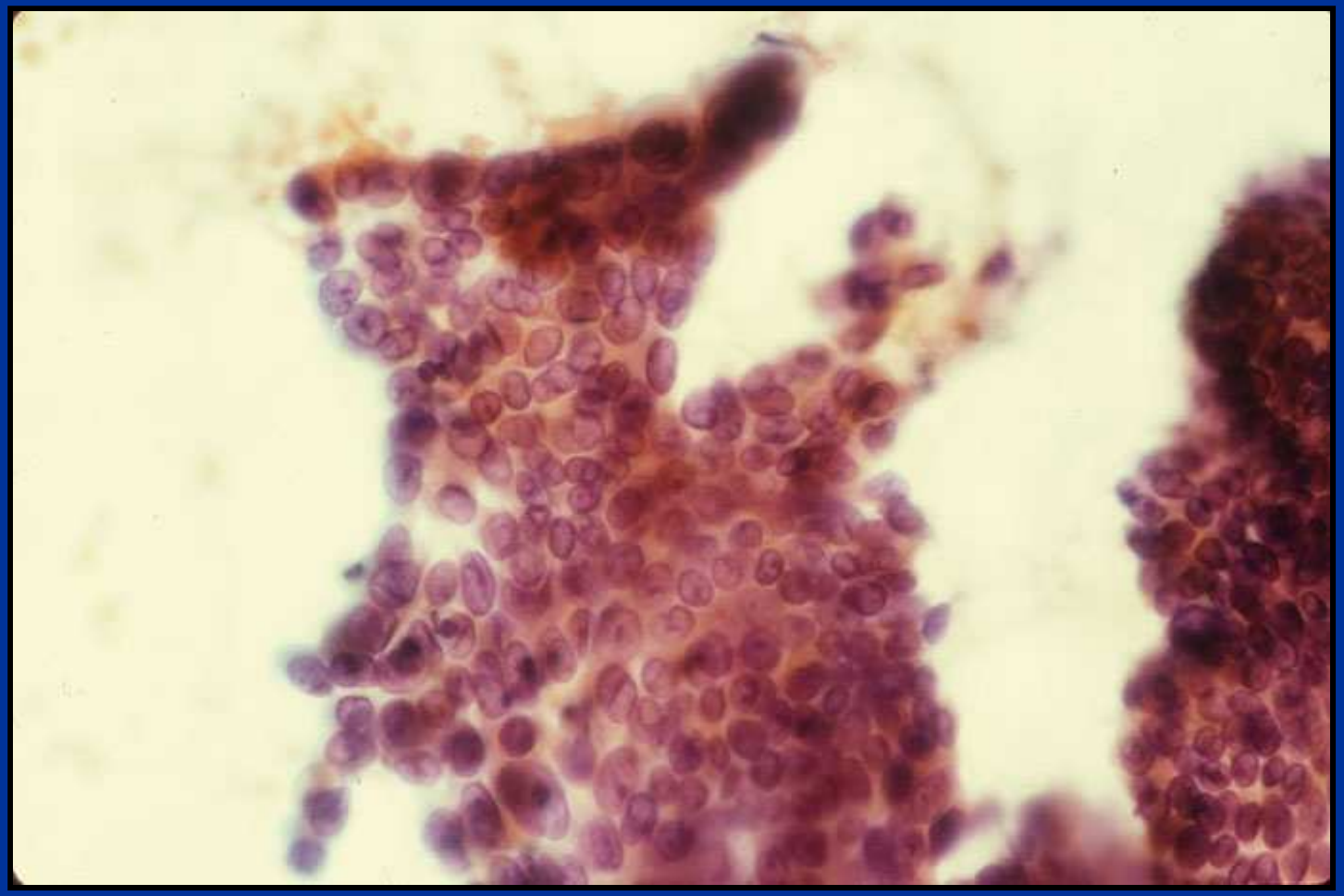


Adenocarcinoma: Low Grade Columnar/ductal



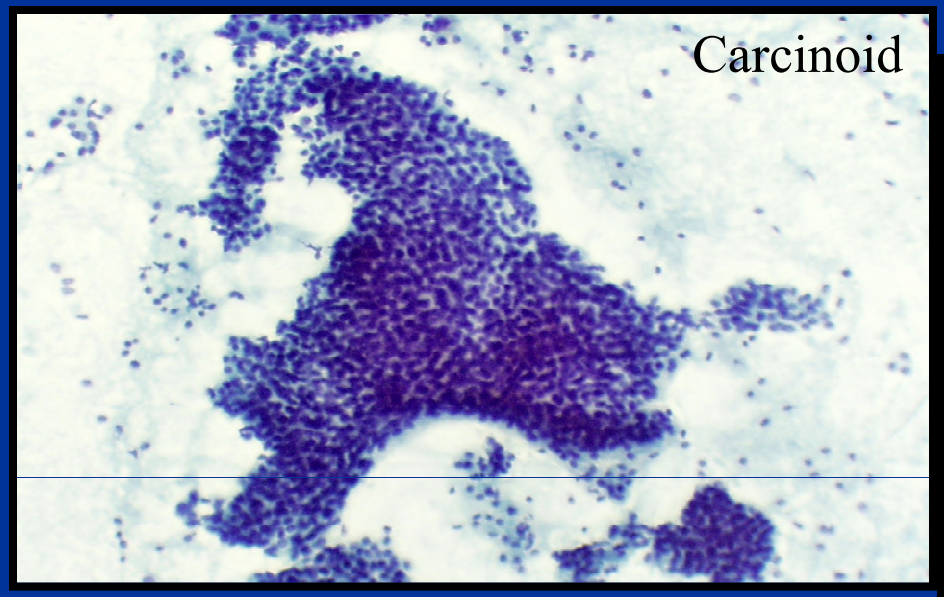
- Cohesive clusters and geographic flat sheets

Low Grade Columnar/Ductal

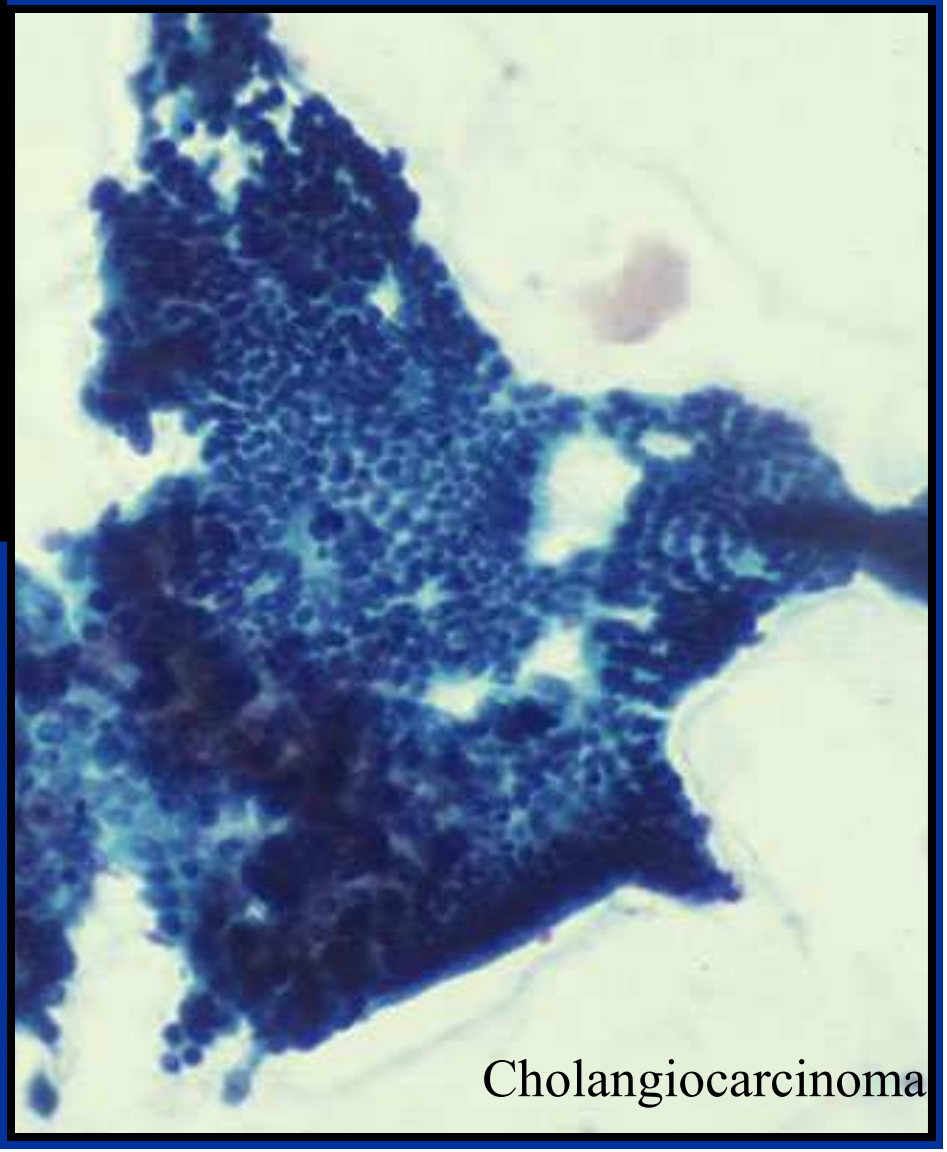


- Uniform cell population with bland appearance
- Low N/C ratio, finely granular chromatin, small nucleoli
- Round to elongated nuclei, luminal borders

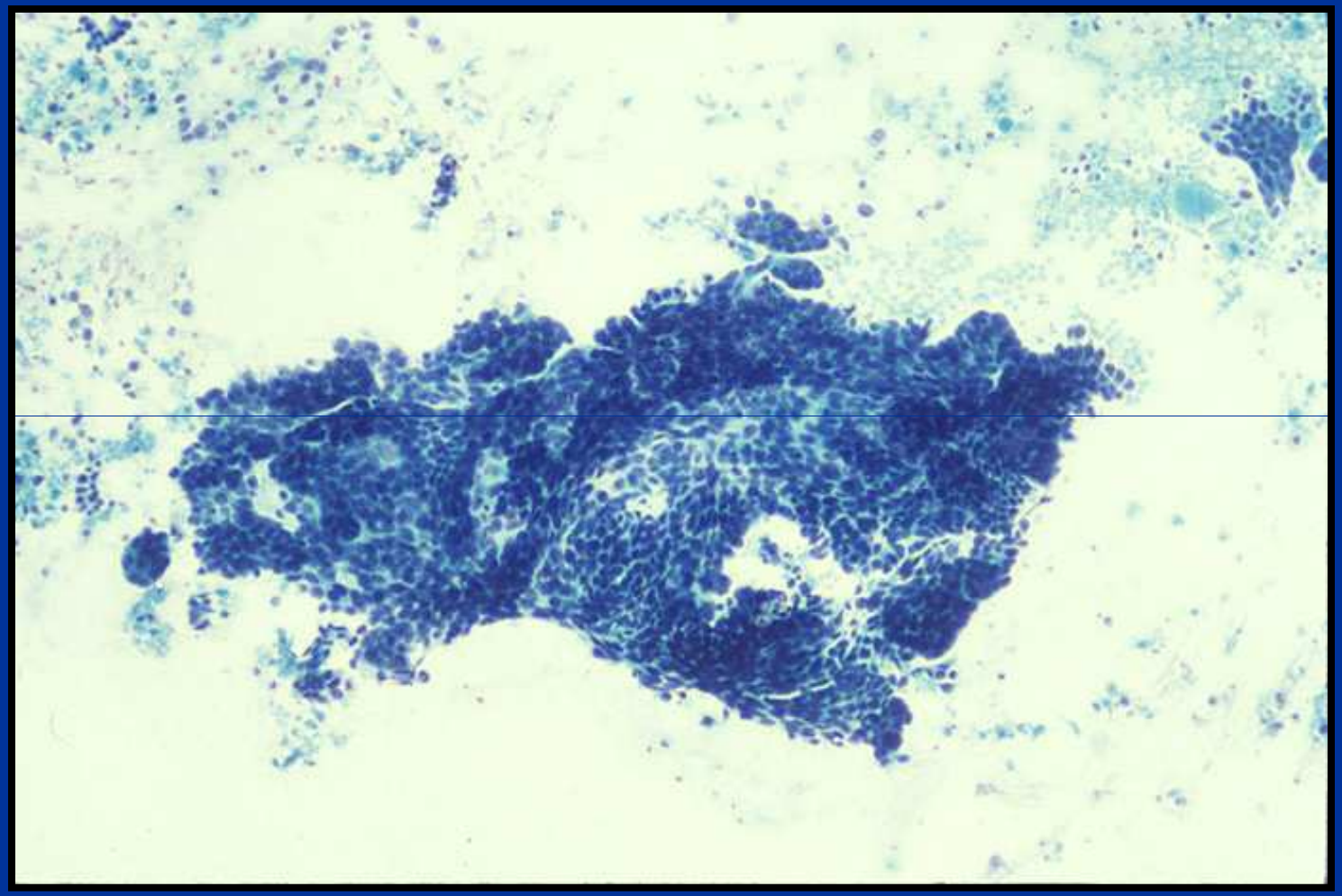
Low Grade Columnar/Ductal Adenocarcinoma



- Pancreas
- Breast
- Bile duct
- Lung (BAC)
- Colon
- Carcinoid

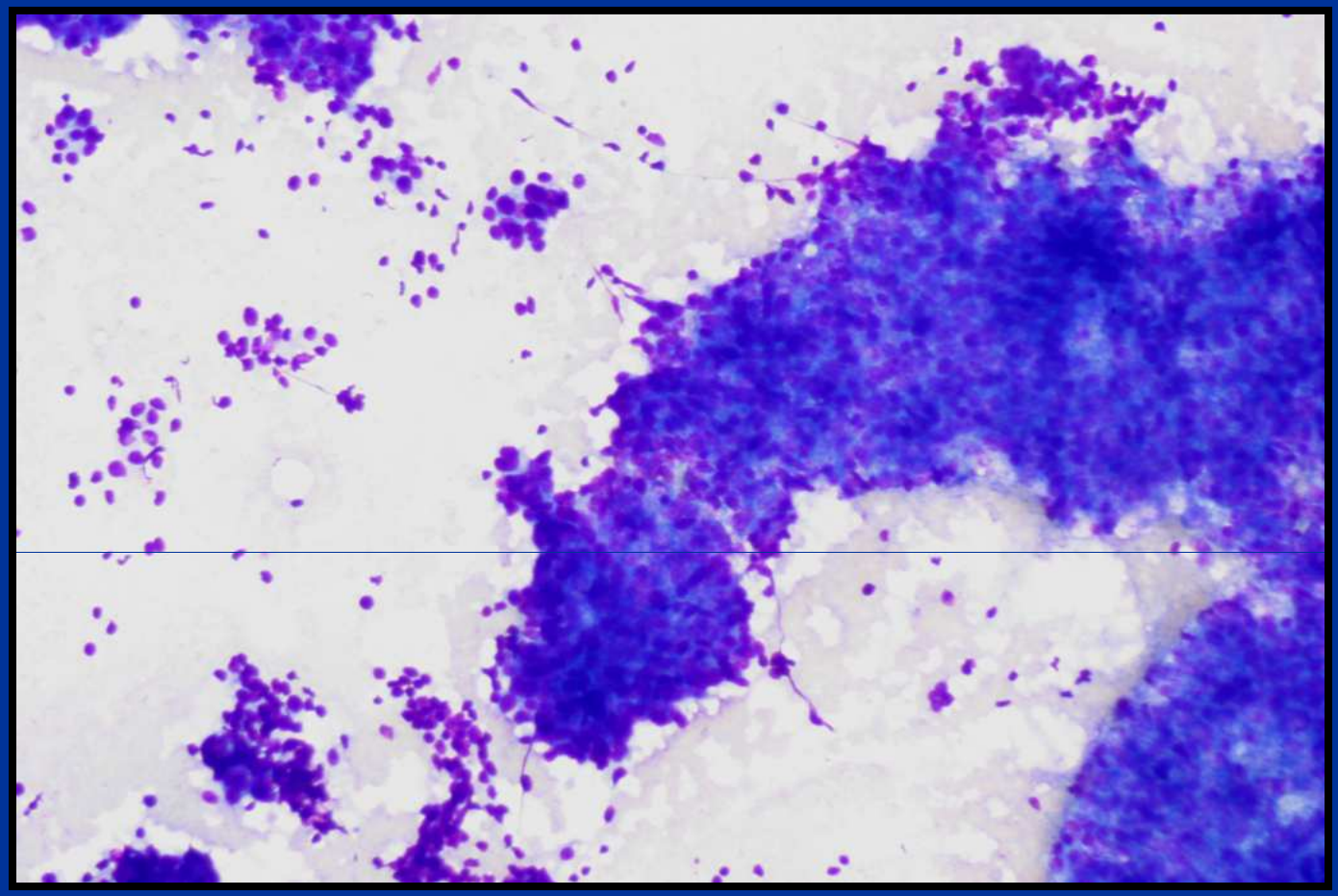


High Grade Columnar/Ductal Adenocarcinoma



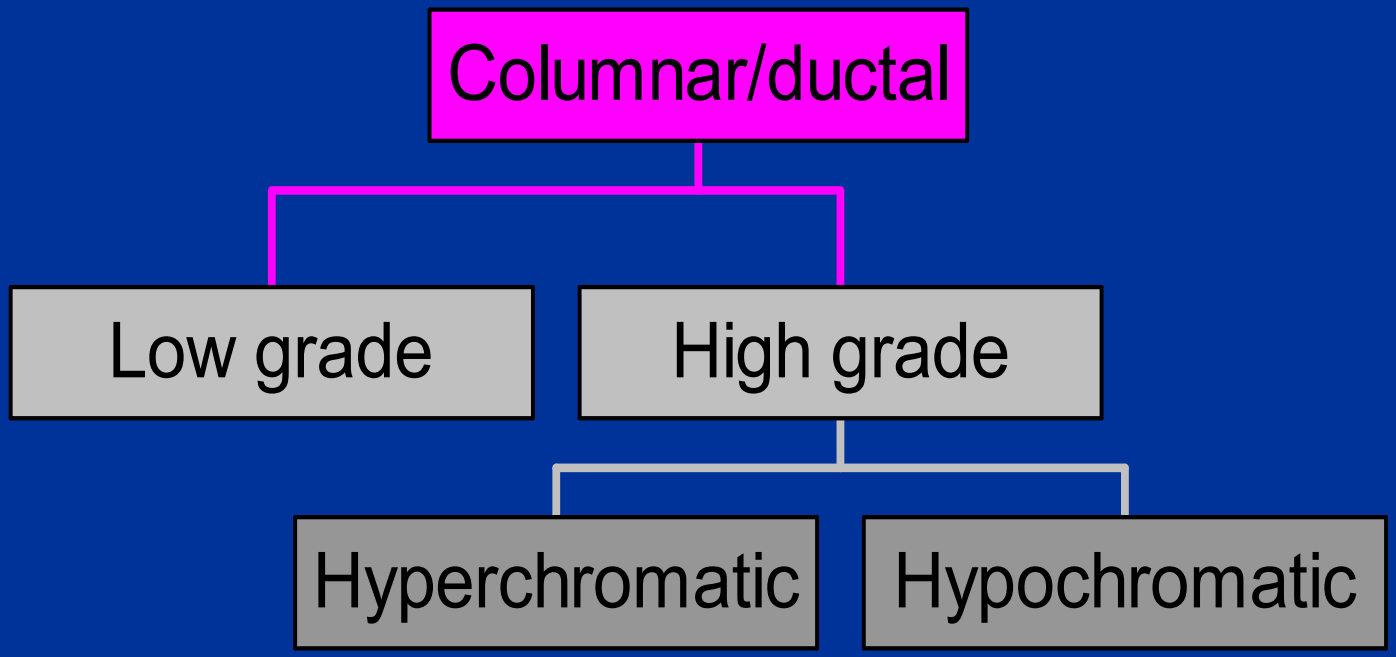
- Cohesive clusters and flat sheets

High Grade Columnar/Ductal Adenocarcinoma



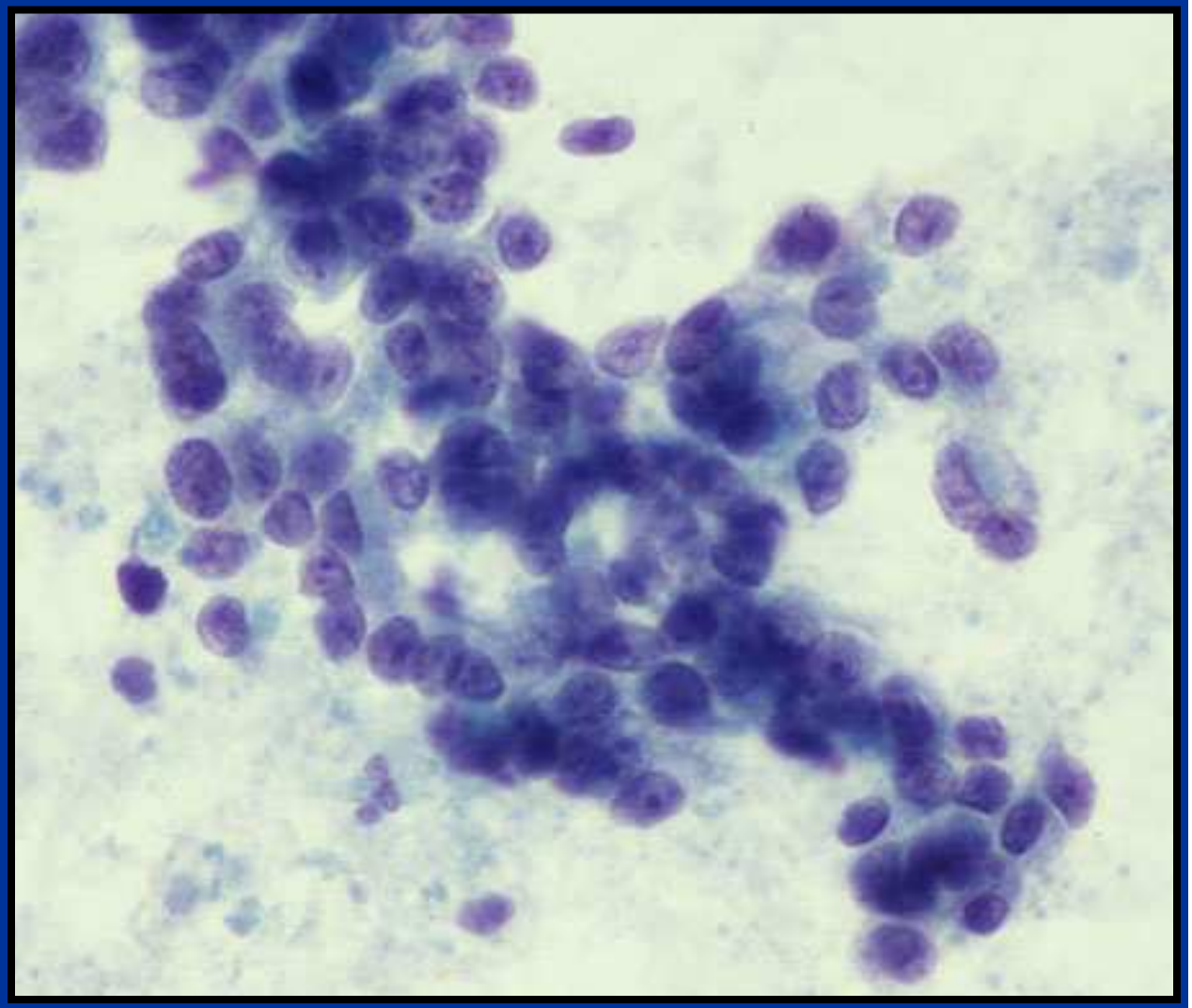
- Nuclear overlapping, haphazard arrangement, significant pleomorphism.
- Acinar formation may bee seen.

Adenocarcinoma



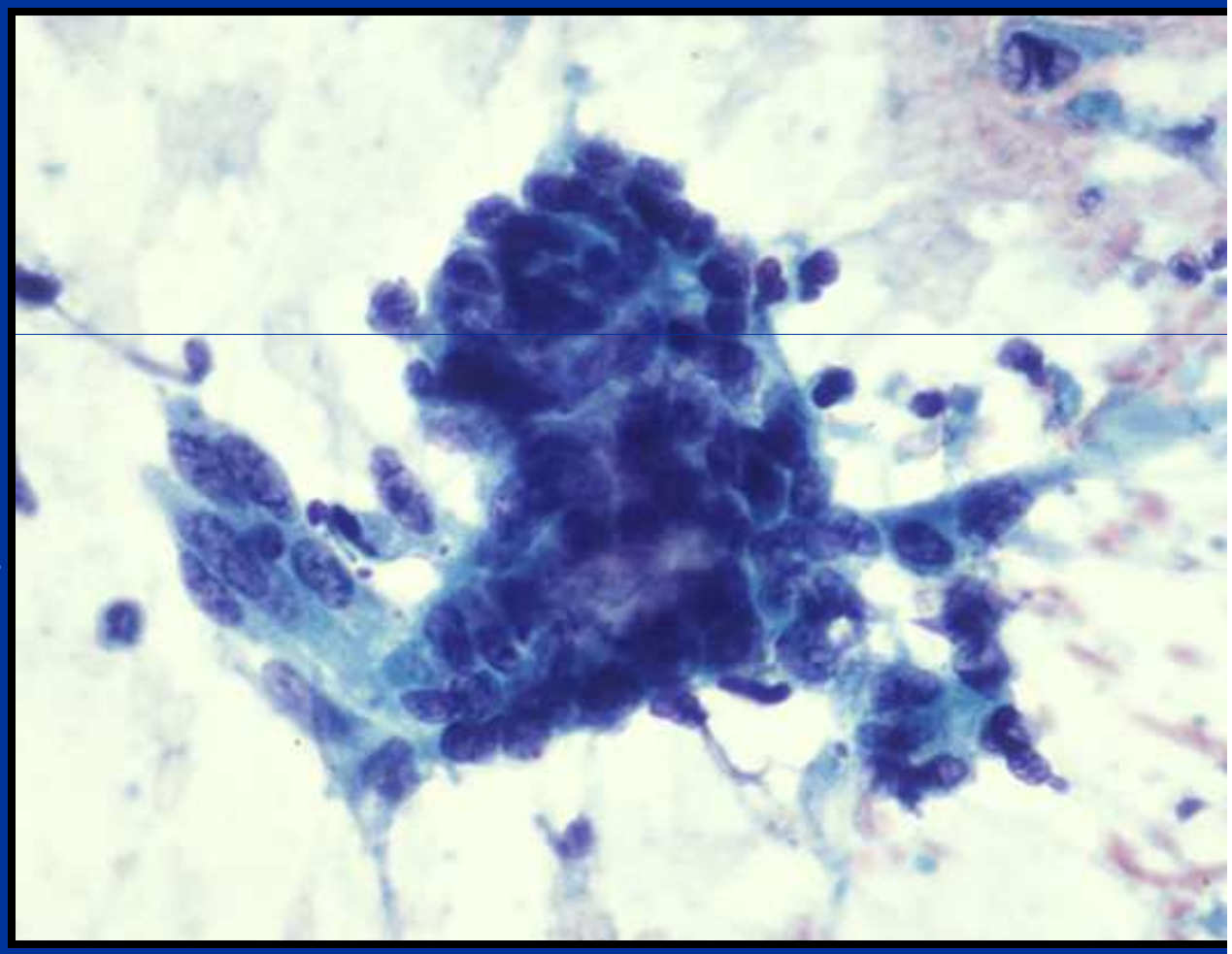
High Grade Columnar/Ductal Adenocarcinoma

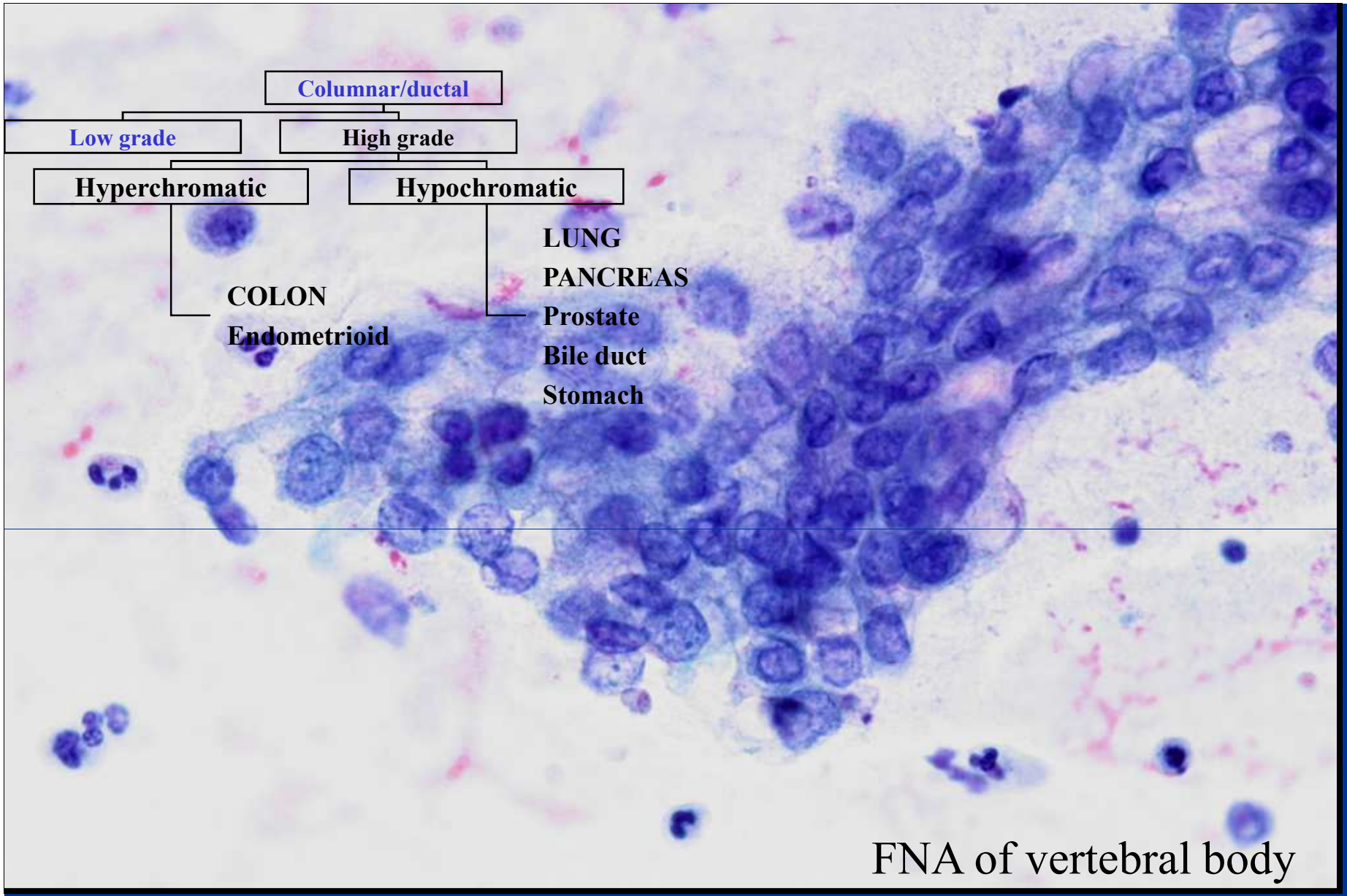
- *Hypochromatic*
  - Lung
  - Pancreas
  - Bile duct
  - Prostate
  - Stomach



High Grade Columnar/Ductal Adenocarcinoma

- *Hyperchromatic*
  - COLON
  - Endometrioid CA (endometrium, ovary, cervix)
  - Bile duct

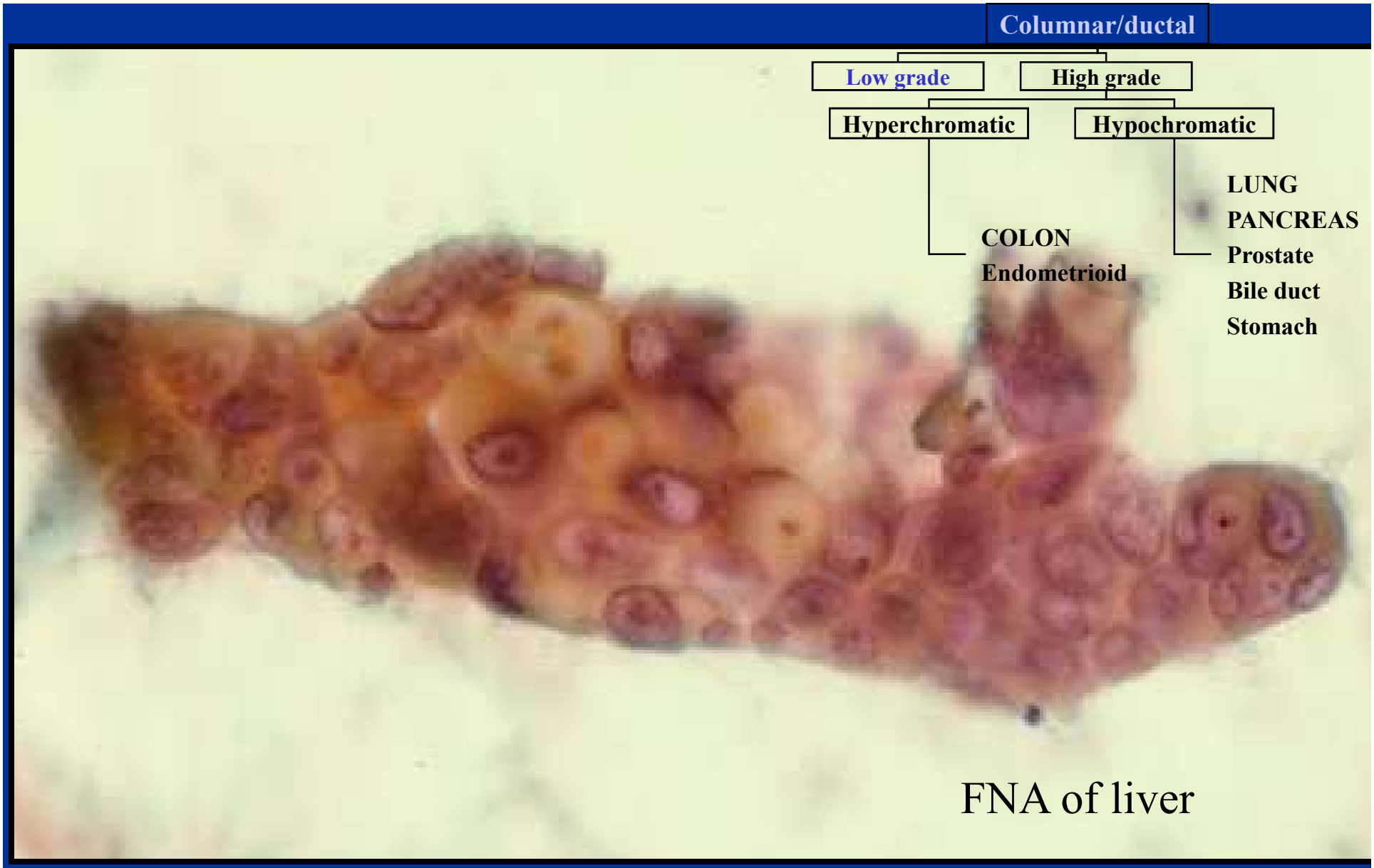




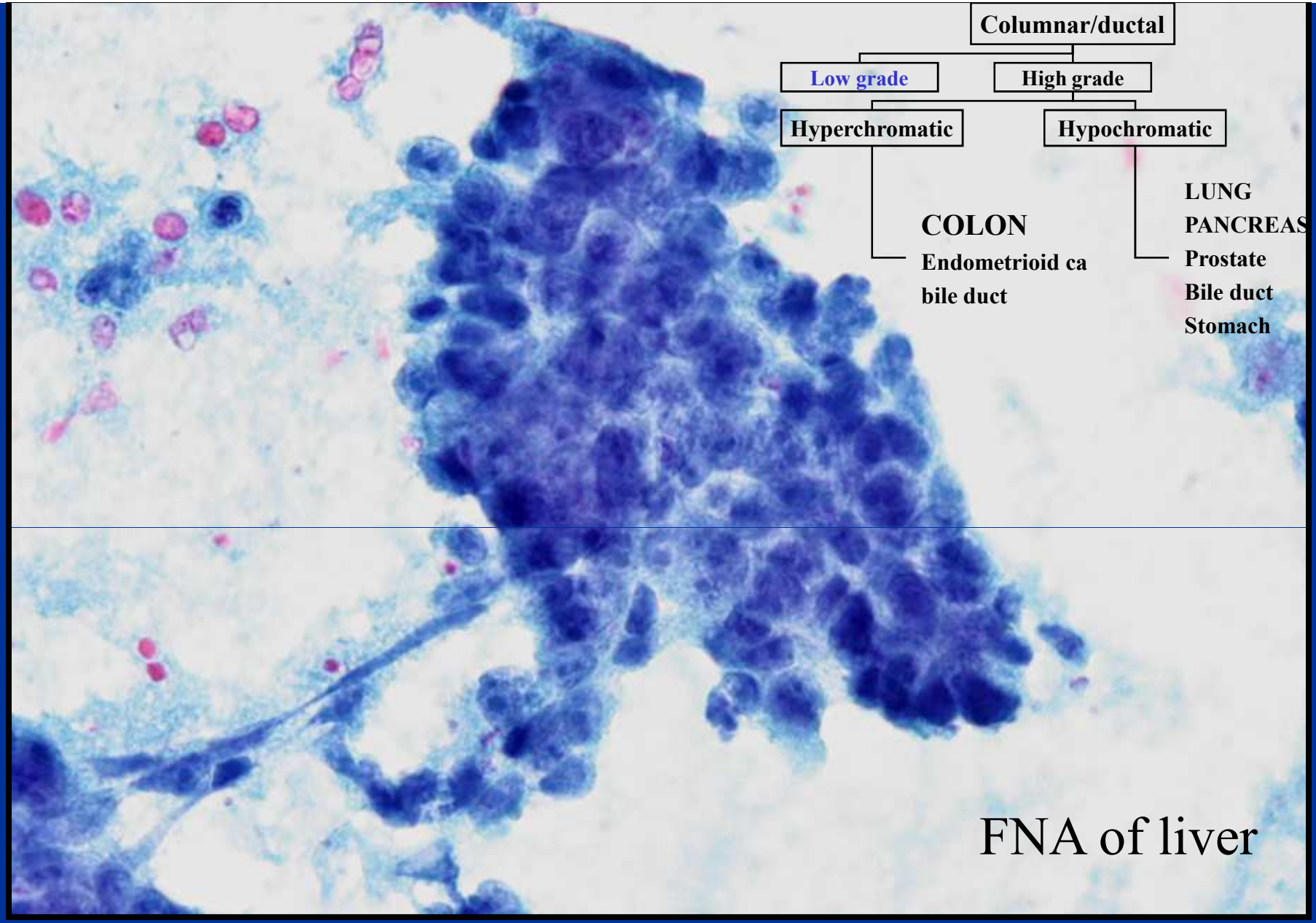
FNA of vertebral body

- High grade, columnar/ductal

Metastatic lung CA to bone



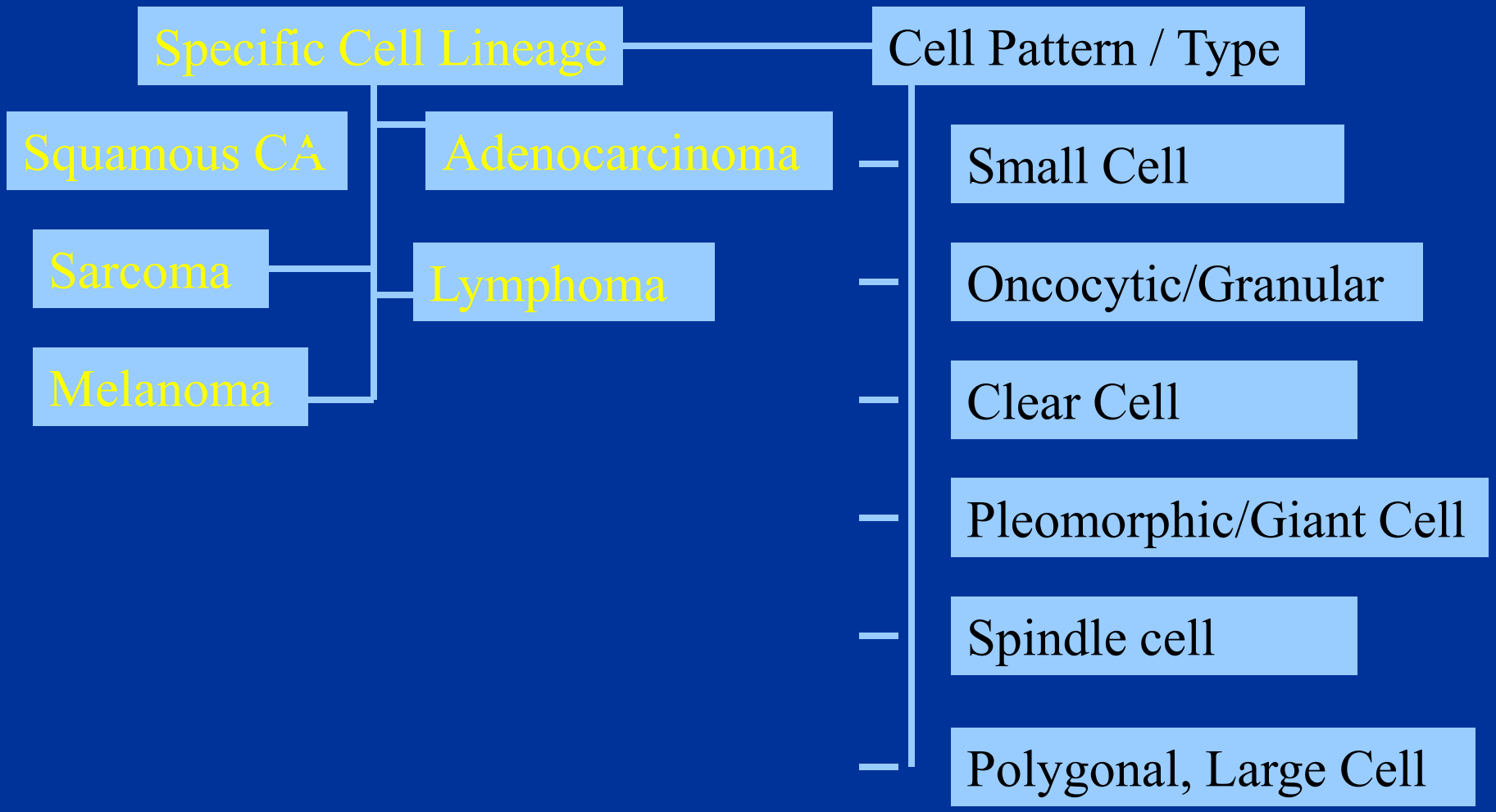
Metastatic pancreatic CA to liver



•High grade, columnar/ductal

Metastatic colon CA to liver

CYTOMORPHOLOGIC PATTERNS OF METASTASIS OF UNKNOWN PRIMARY ORGIN

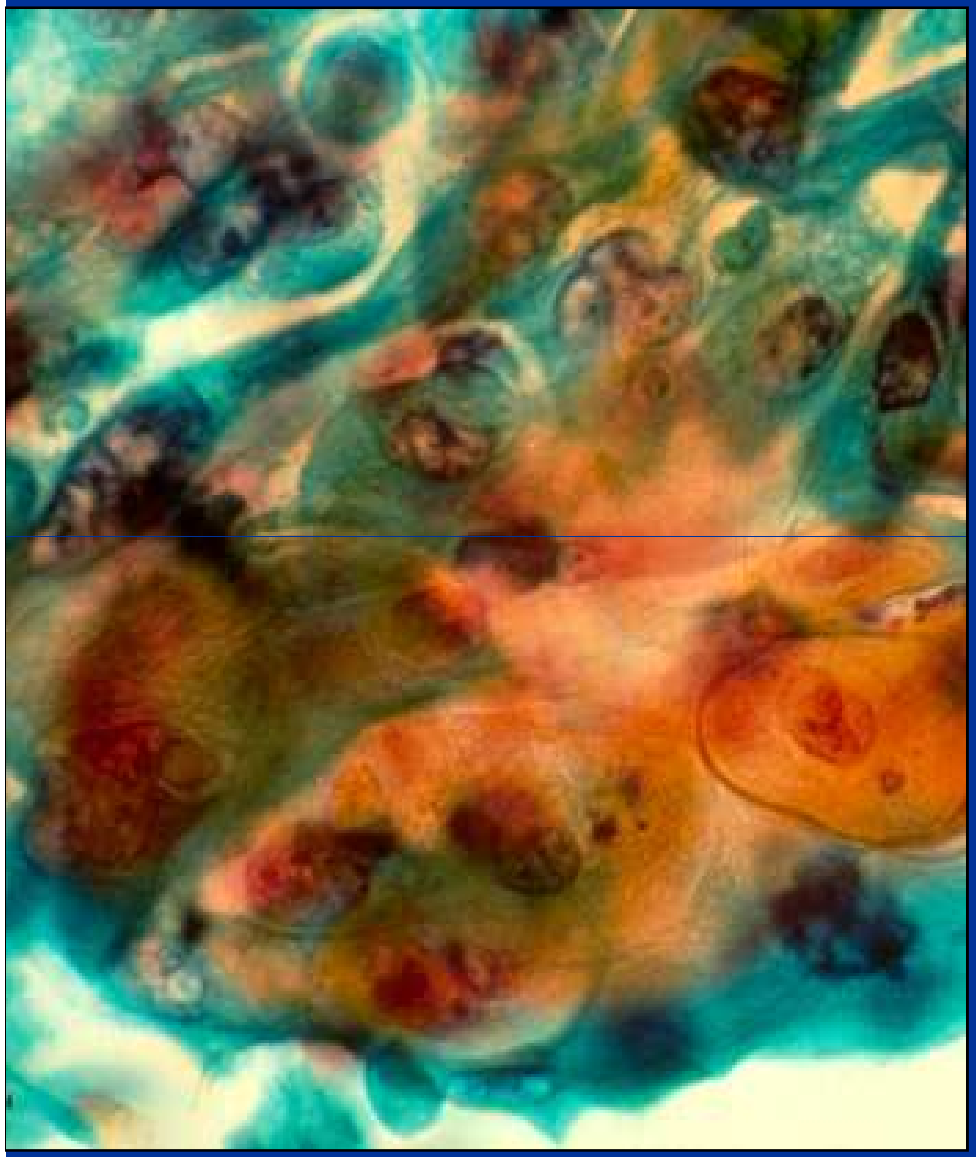


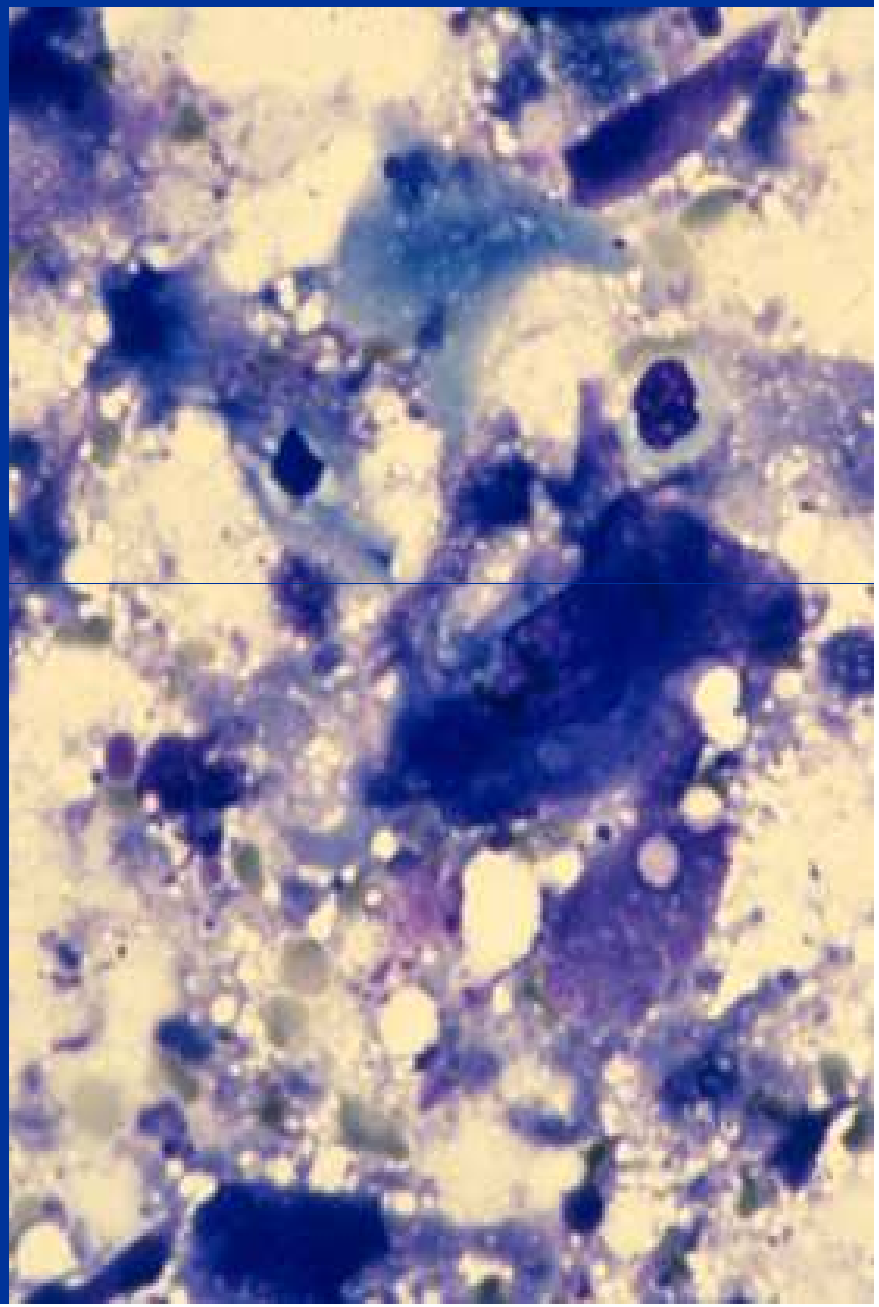
CARCINOMA

- Adenocarcinoma (60%)
- Squamous cell carcinoma (10%)
- Undifferentiated CA/P.D.
- Small cell/NE carcinoma
- Melanoma

Modified from DeMay p493-530

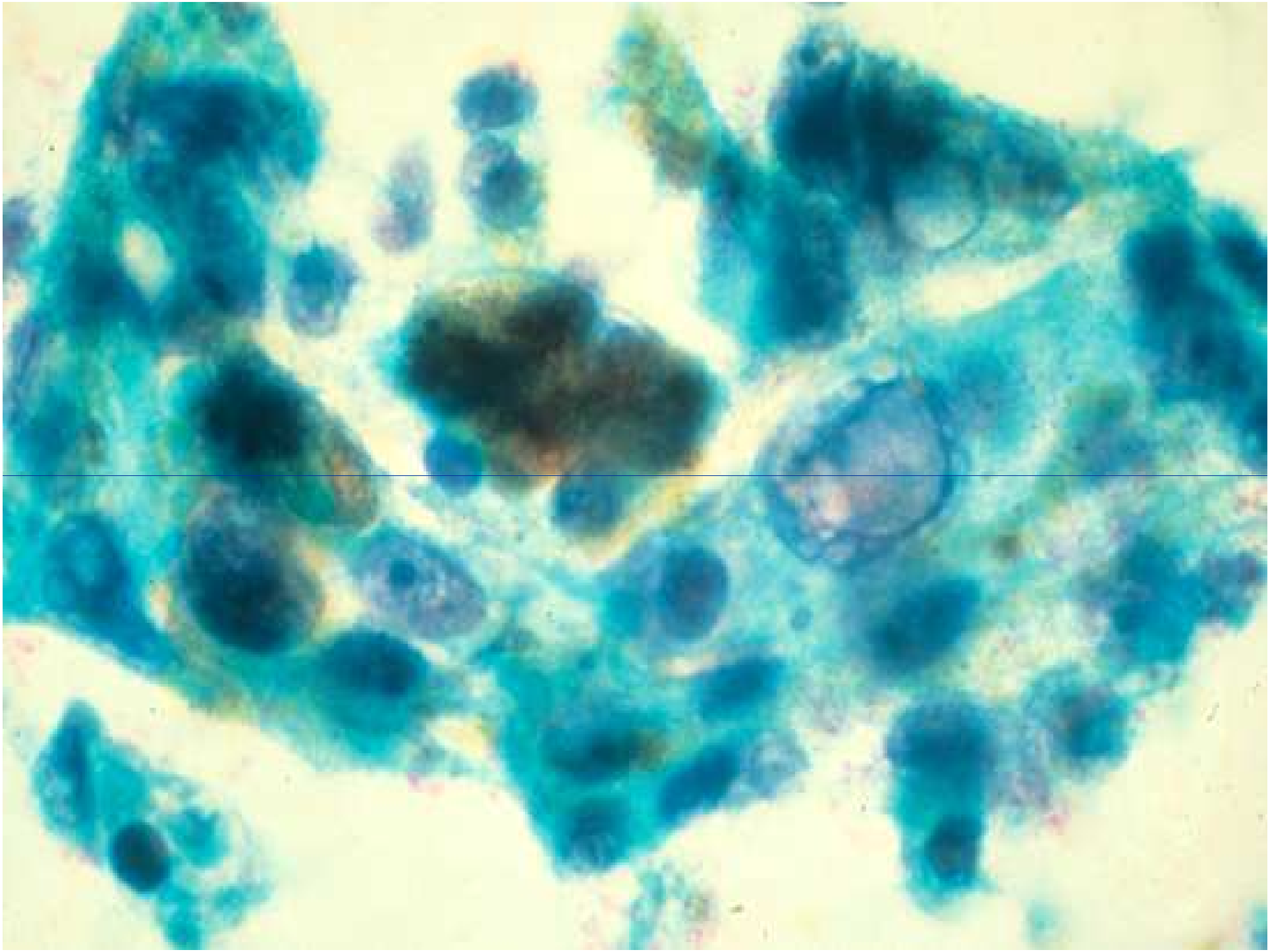
Squamous Cell Carcinoma

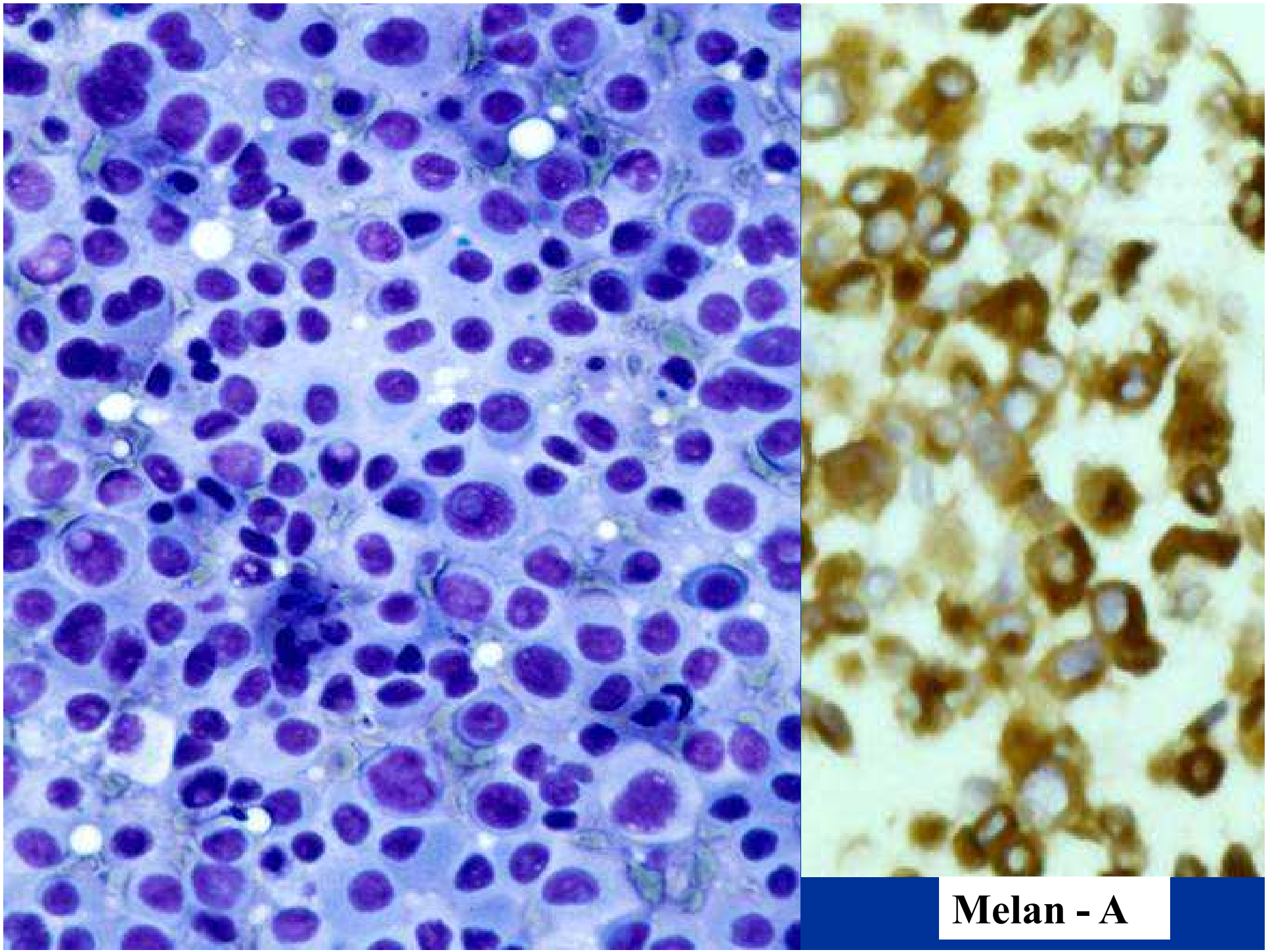




MELANOMA

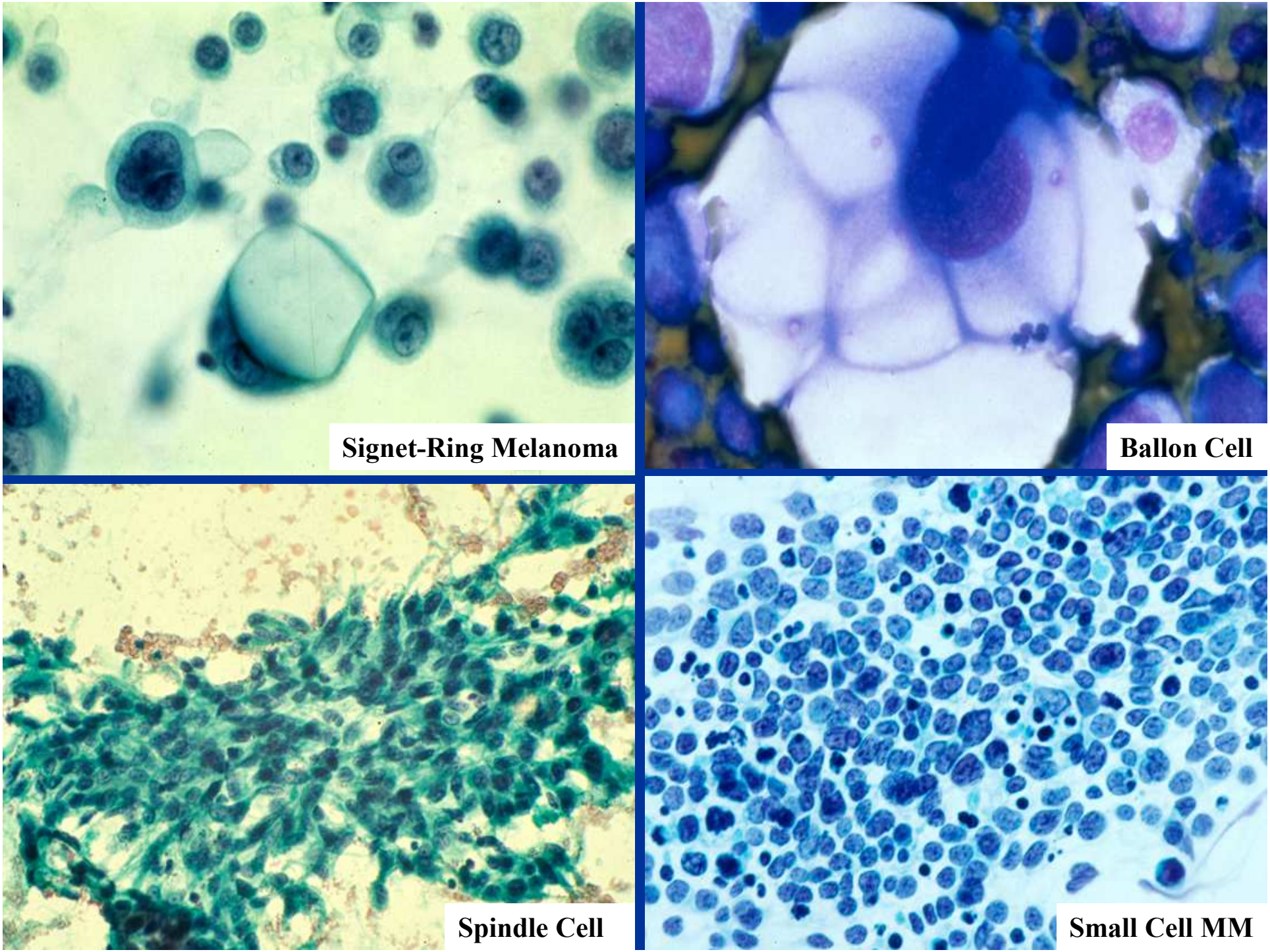
- Metastasis to unusual sites
- Mimics other malignancies
- Primary occult or not apparent by history

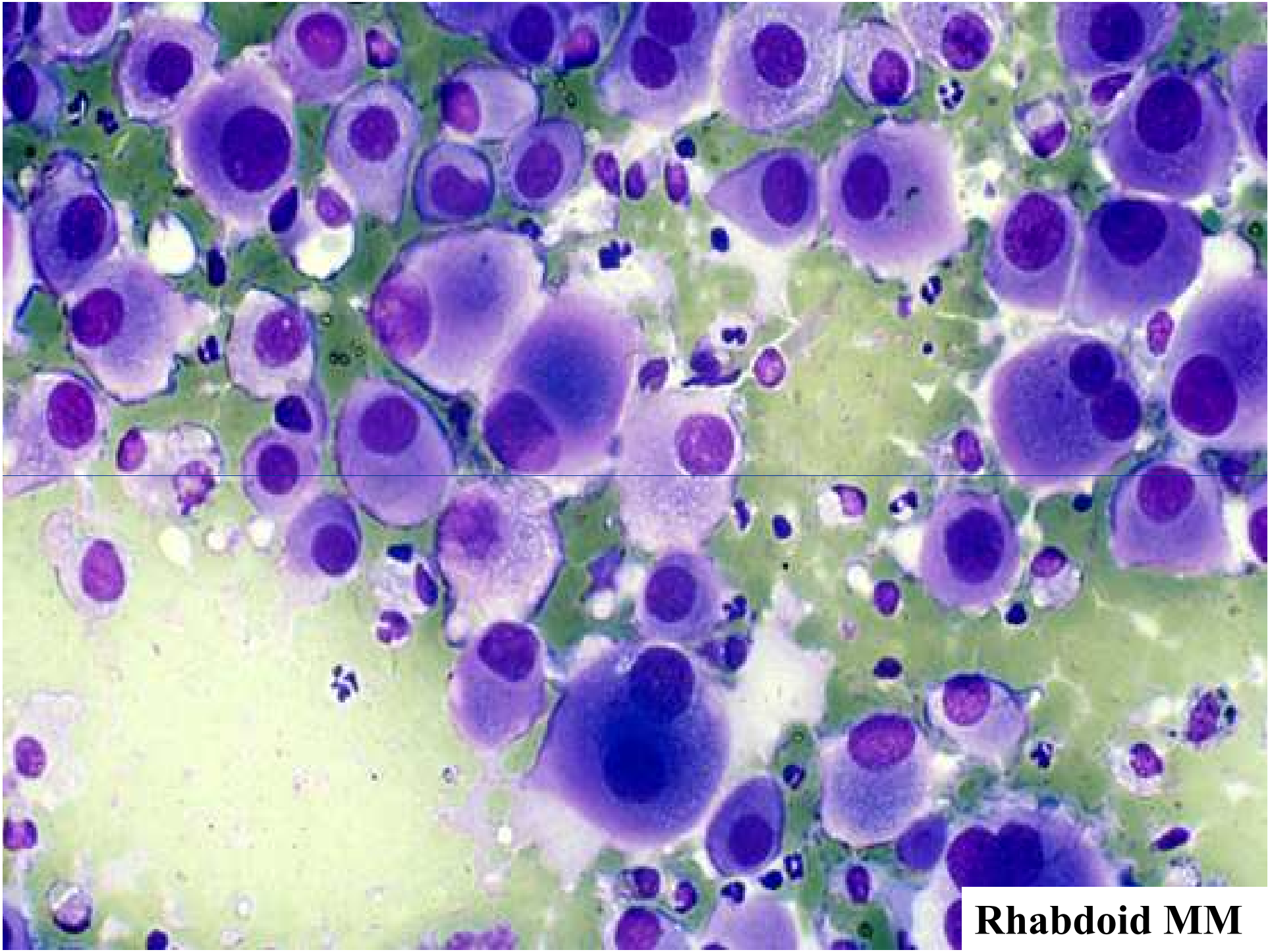



Melan - A

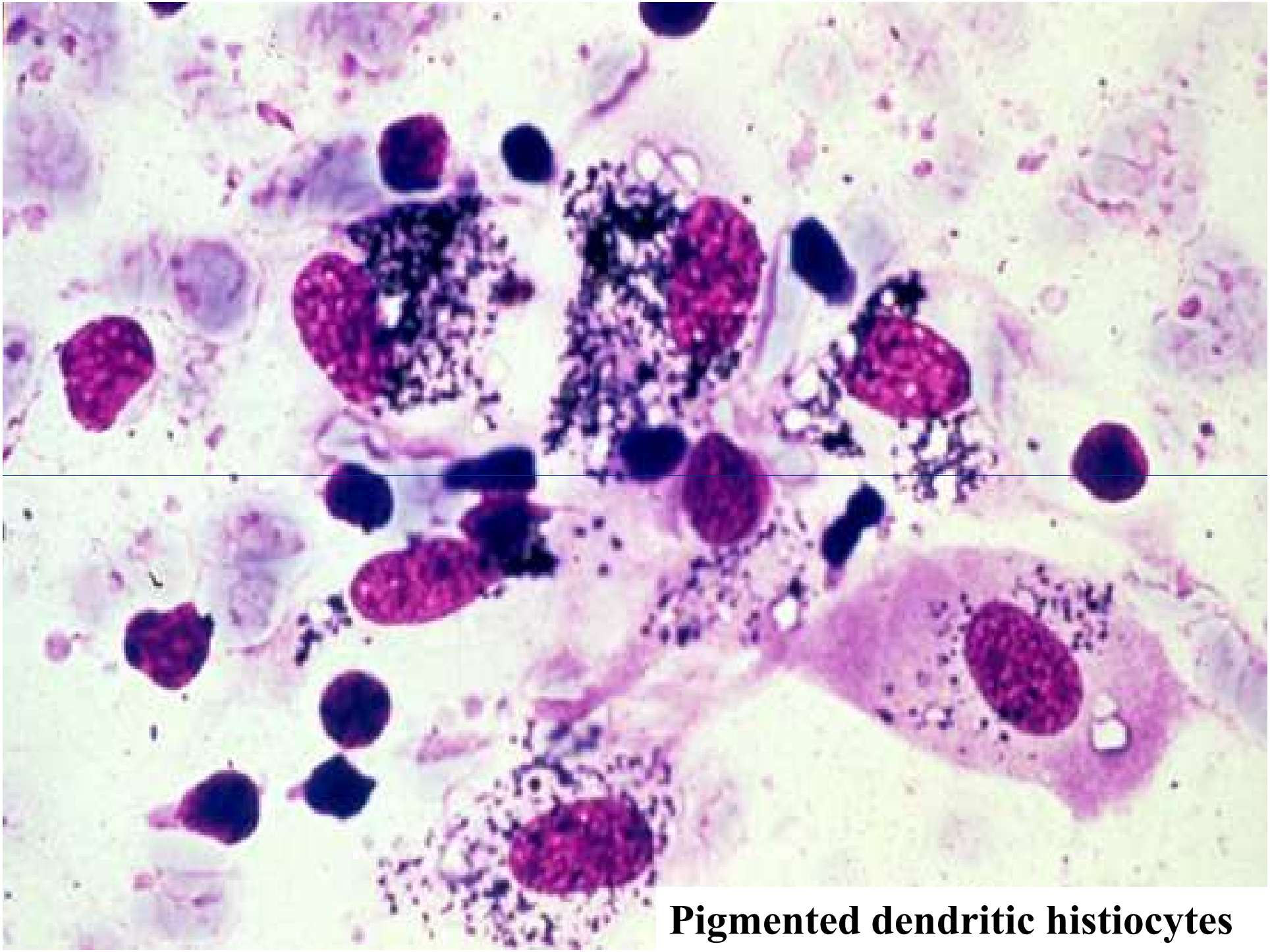
Malignant Melanoma Variants

- Rhabdoid
- Signet-ring
- Spindle
- Myxoid
- Desmoplastic
- Ballon Cell
- Small Cell


Signet-Ring Melanoma
Ballon Cell
Spindle Cell
Small Cell MM



Rhabdoid MM



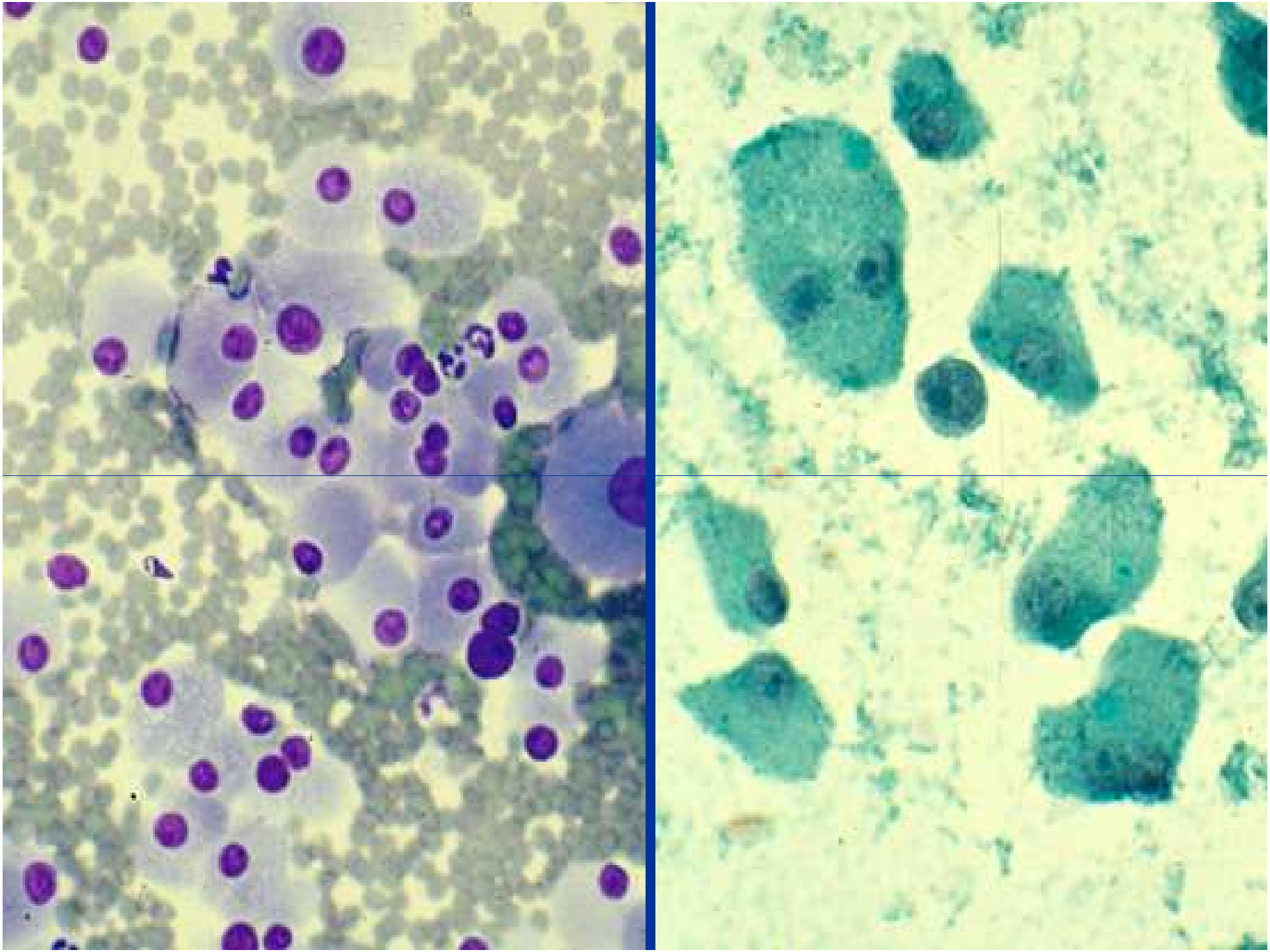
Pigmented dendritic histiocytes

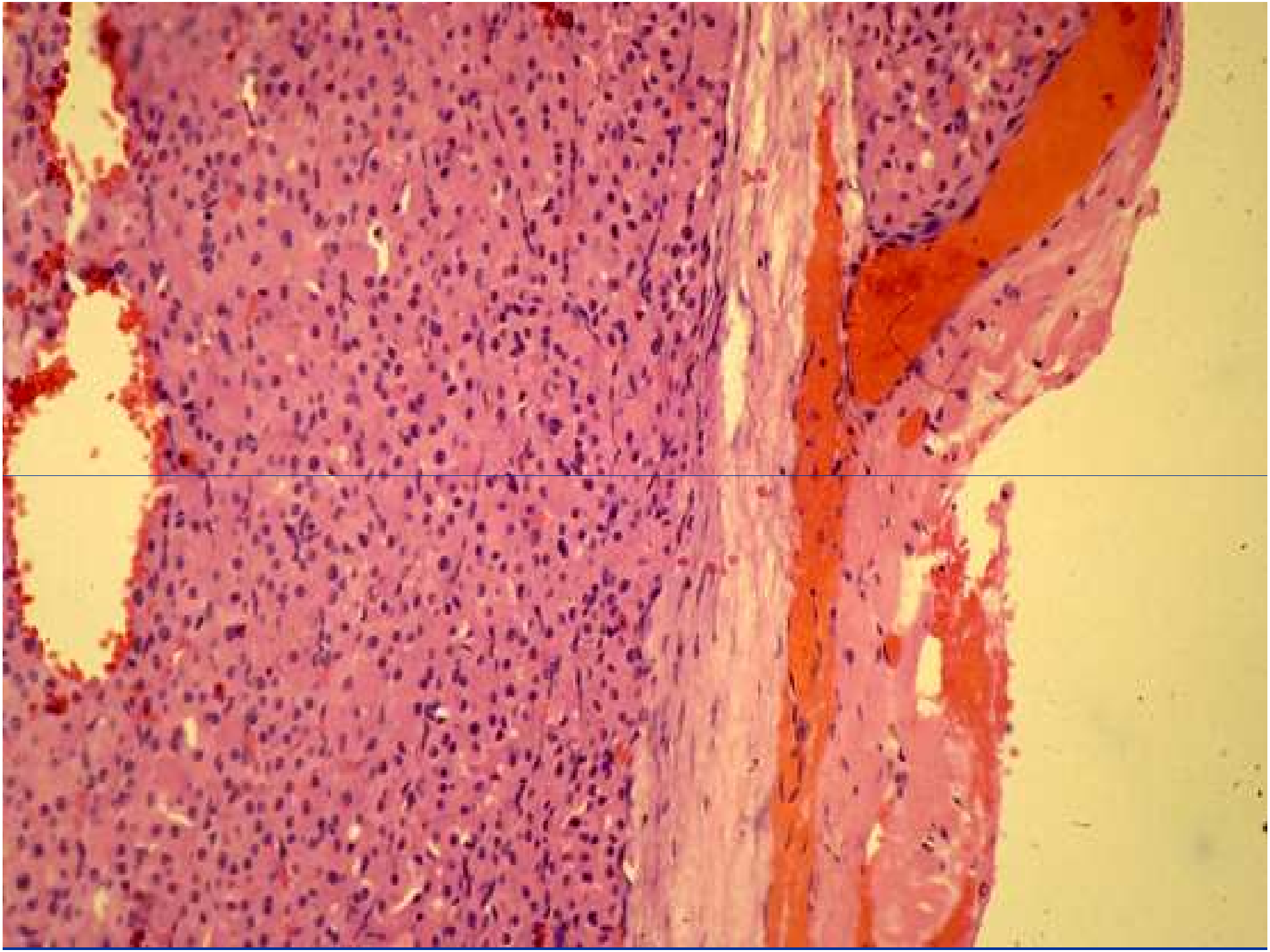
SARCOMA

- Very unusual unknown primary
- Primary site usually obvious
- Diff Dx: Sarcomatoid carcinoma / melanoma
- Spindle, epitheliod, pleomorphic, small cell, myxoid

Case 2

An 81 year old woman was identified as having a right hilar lung mass. FNA biopsy was performed.





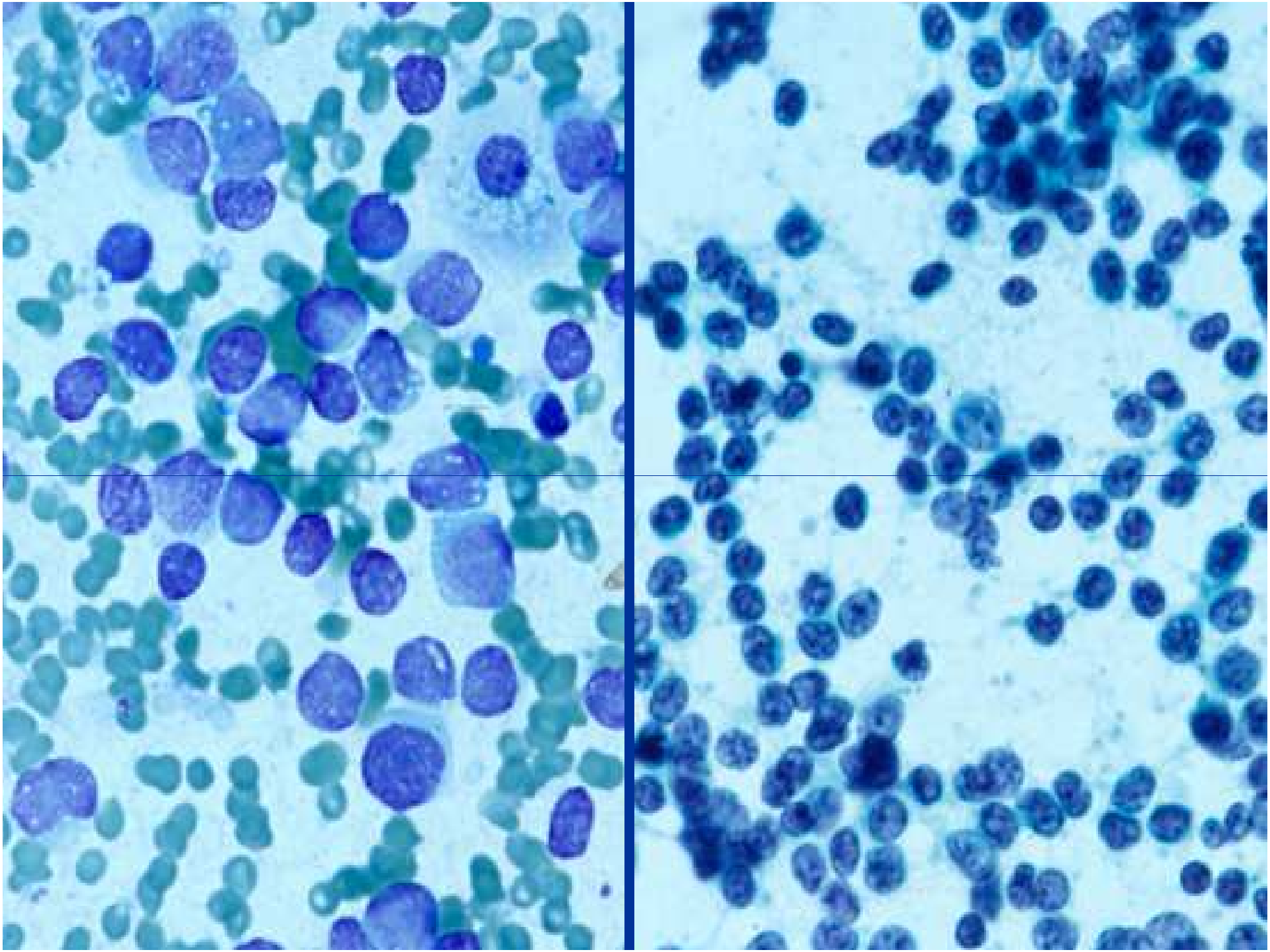
Case 2

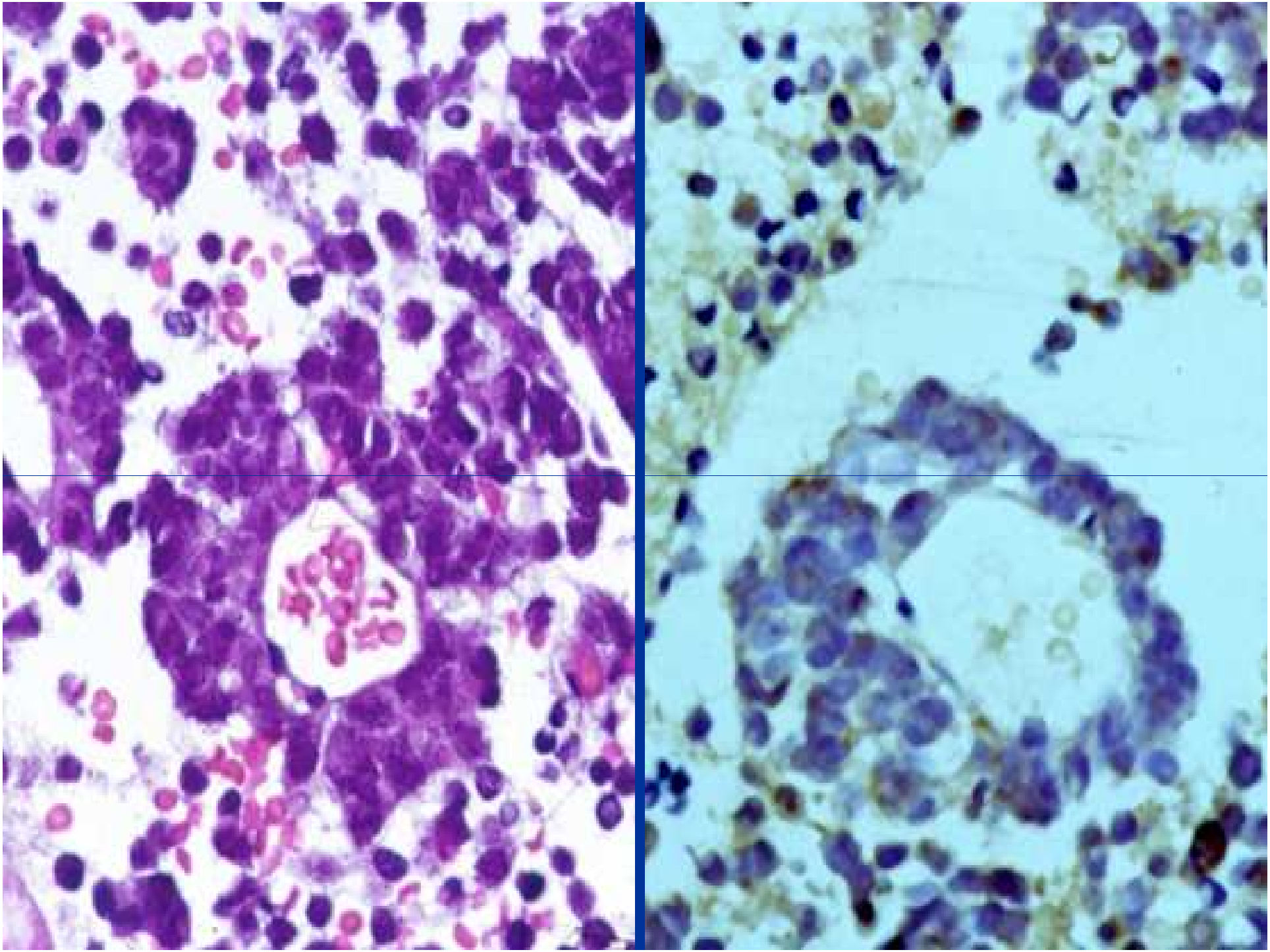
DIAGNOSIS

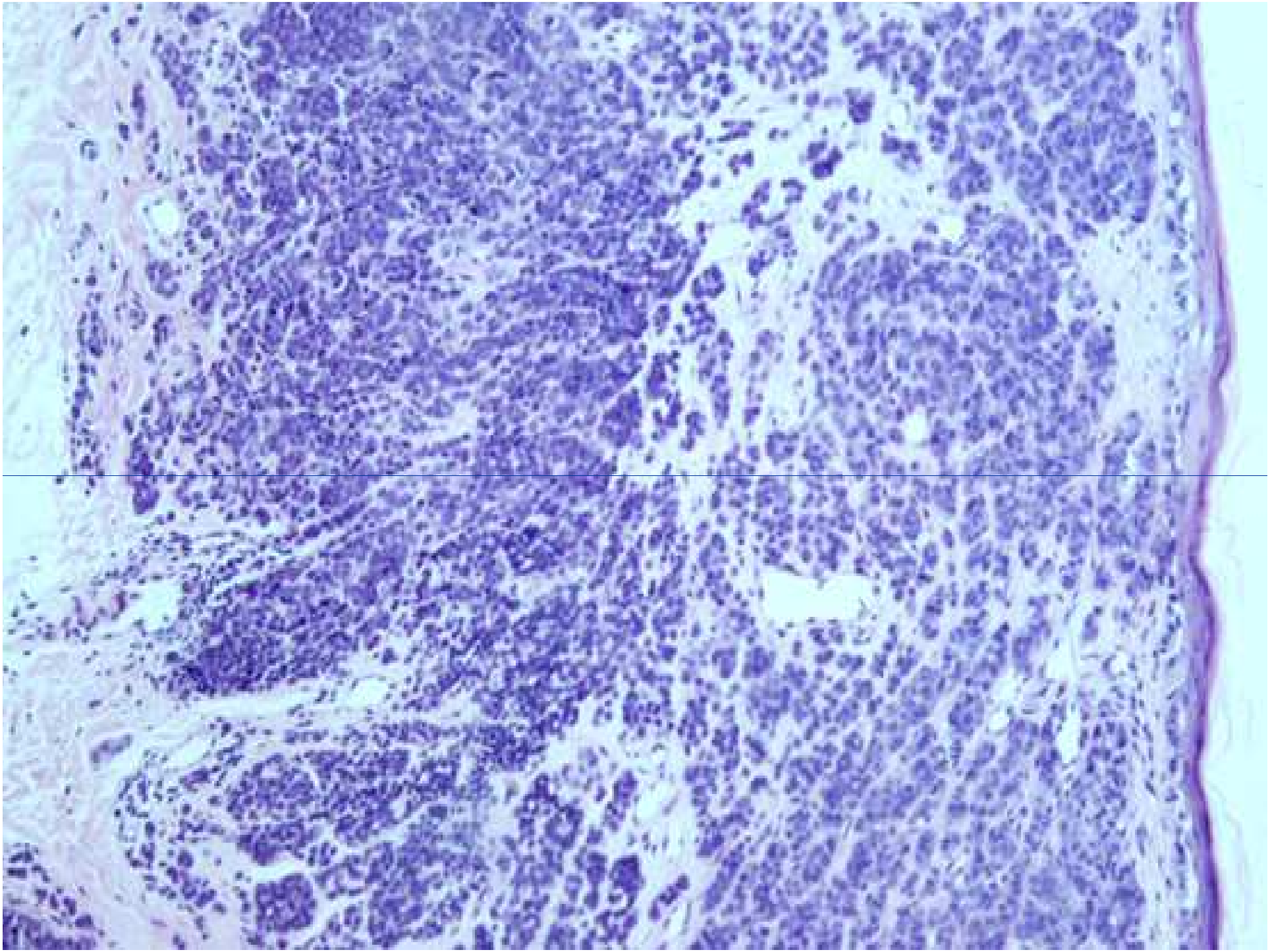
Metastatic Hurthle cell carcinoma of the thyroid

Case 3

A CT guided FNA biopsy of a single mass involving the anterior right lobe of liver was performed in a 72 year old female







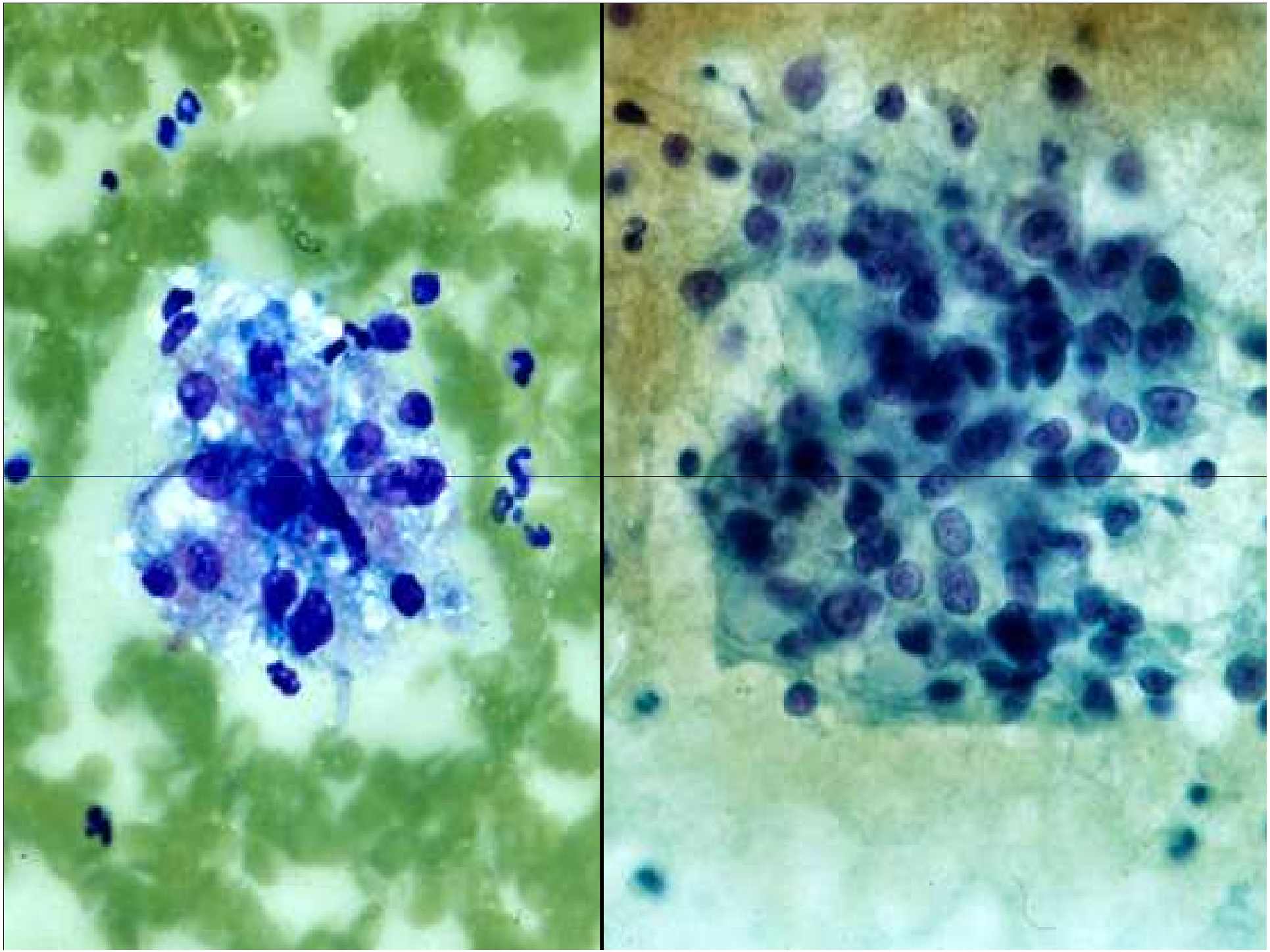
Case 3

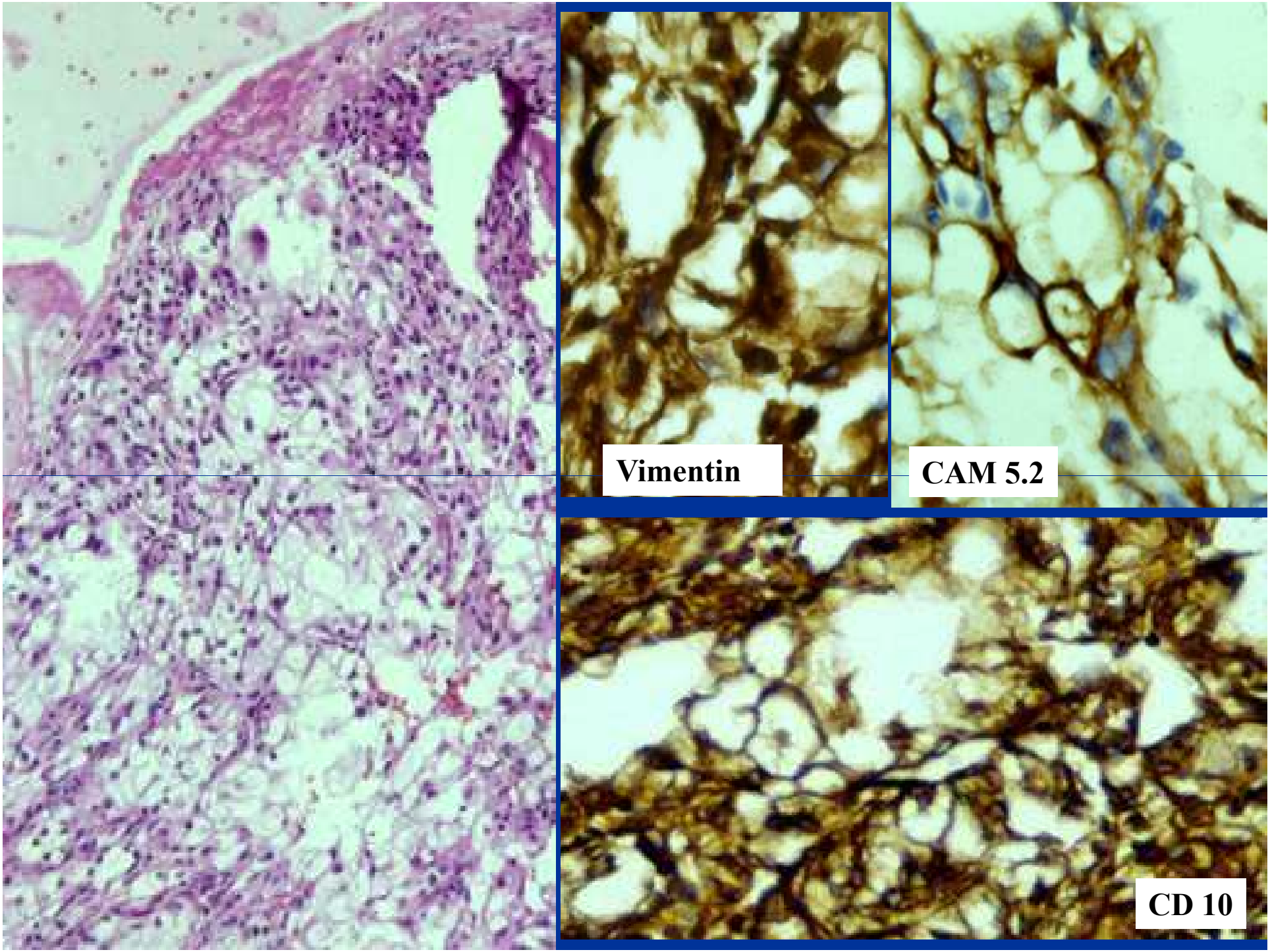
DIAGNOSIS

Metastatic small cell variant of malignant melanoma to the liver

Case 4

53 year old male presented with a 6 cm sacral mass and pain in his legs. A FNA biopsy was performed



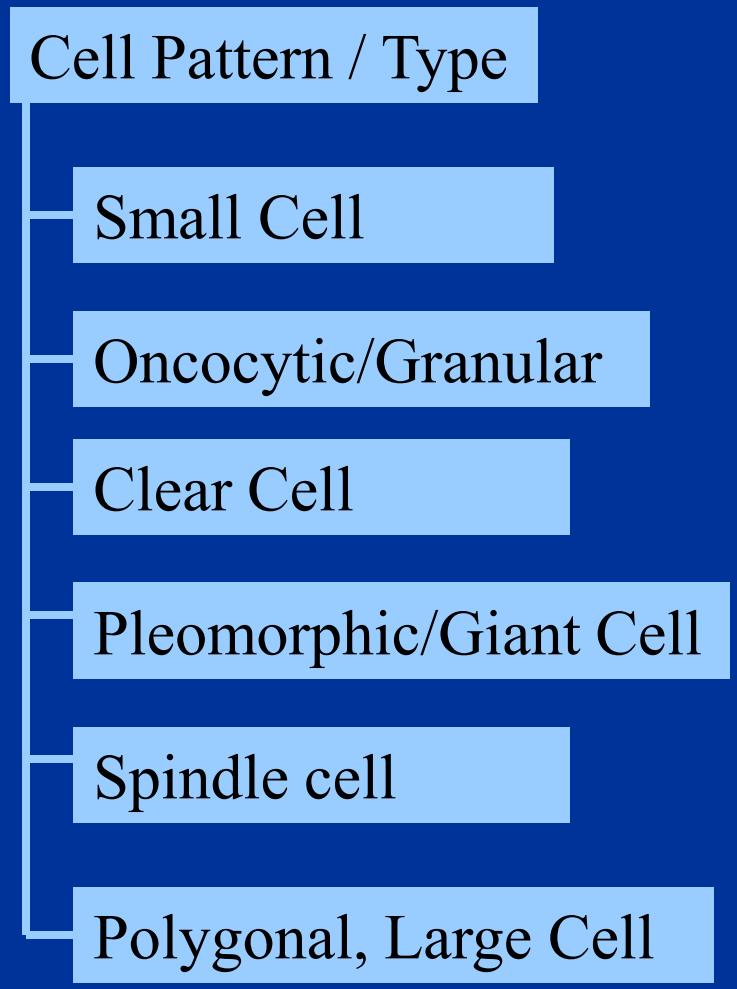

Vimentin
CAM 5.2
CD 10

Case 4

DIAGNOSIS

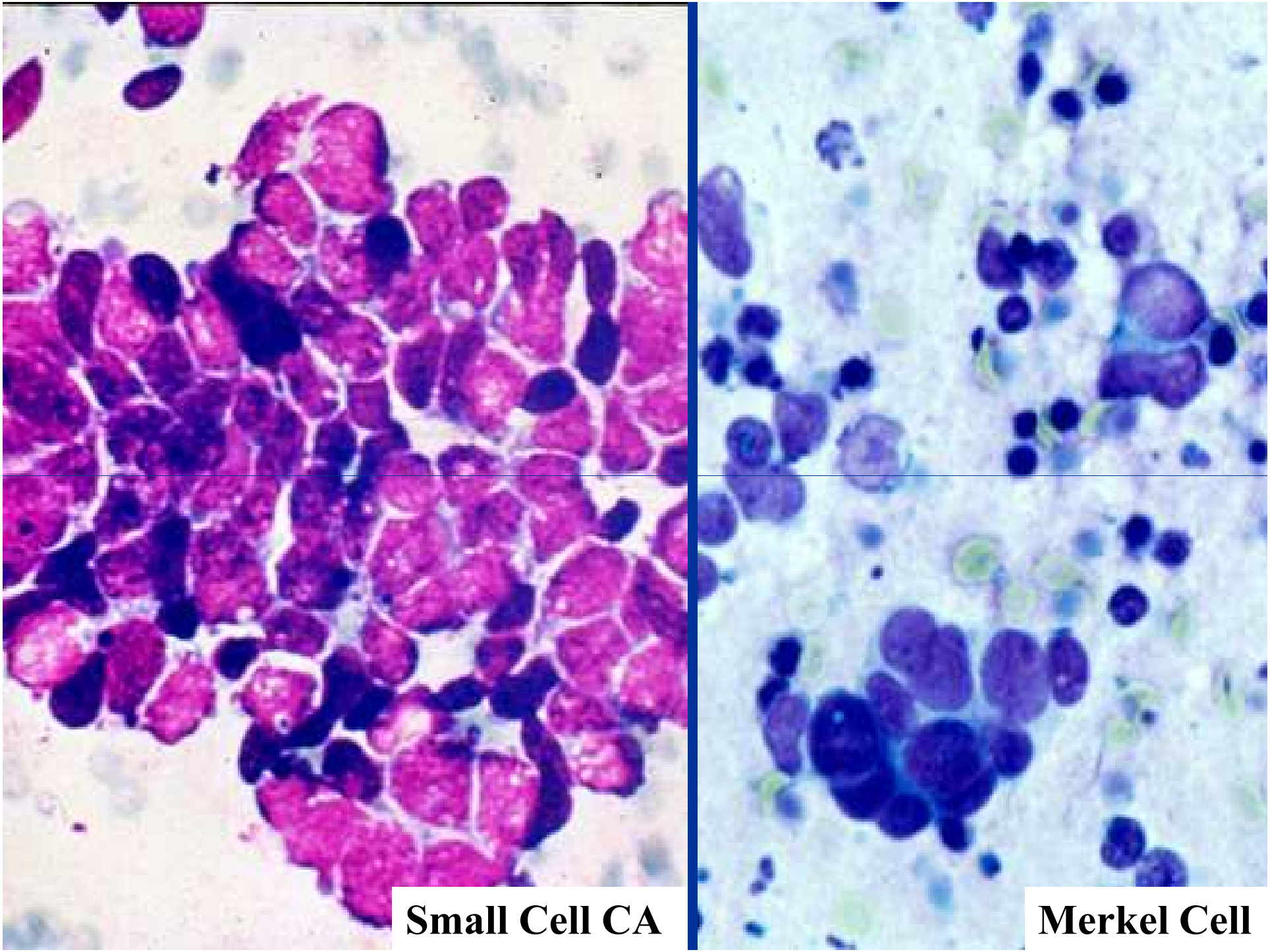
Metastatic conventional clear cell carcinoma of the kidney

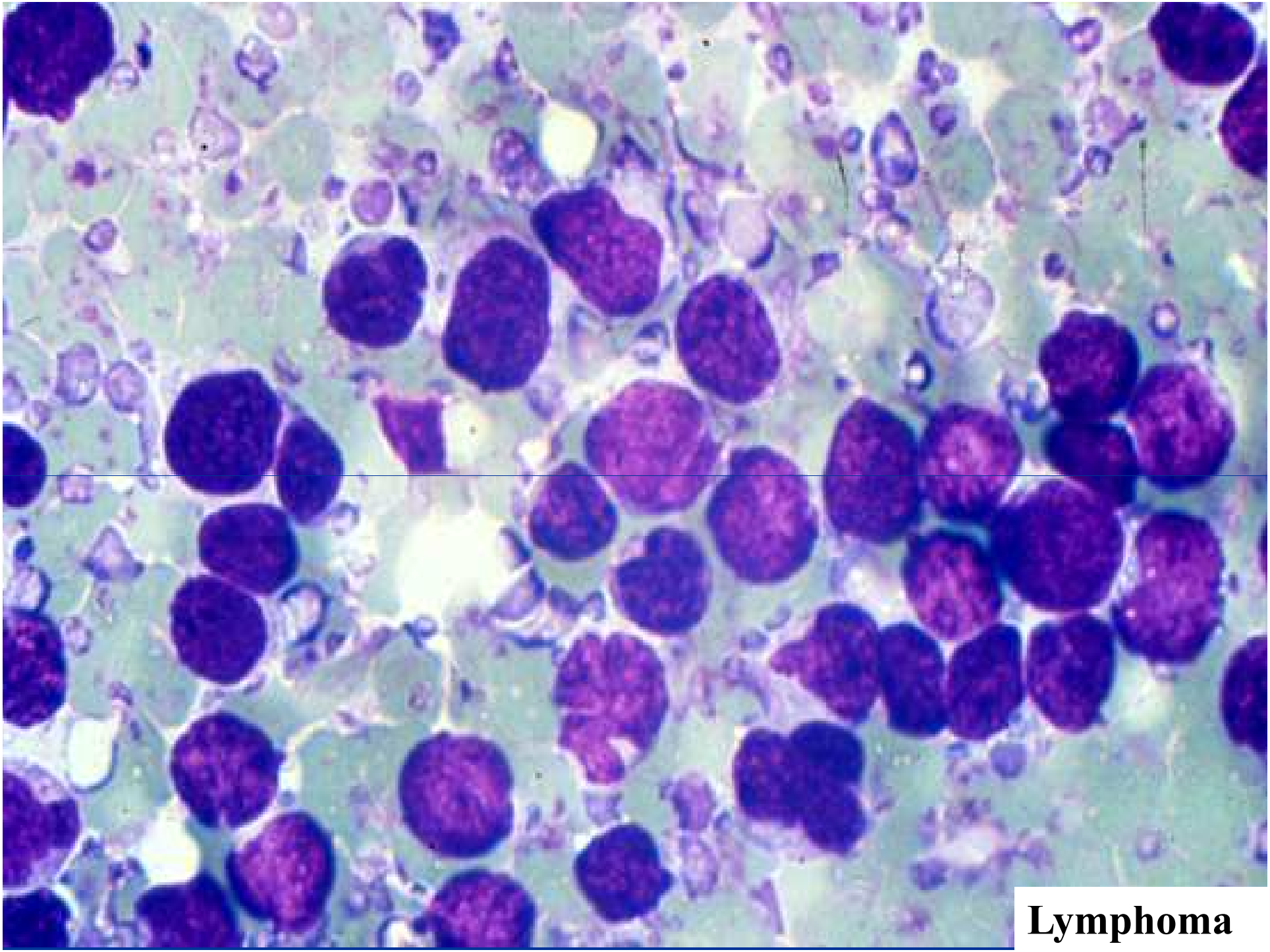
CYTOMORPHOLOGIC PATTERNS OF METASTASIS OF UNKNOWN PRIMARY ORGIN



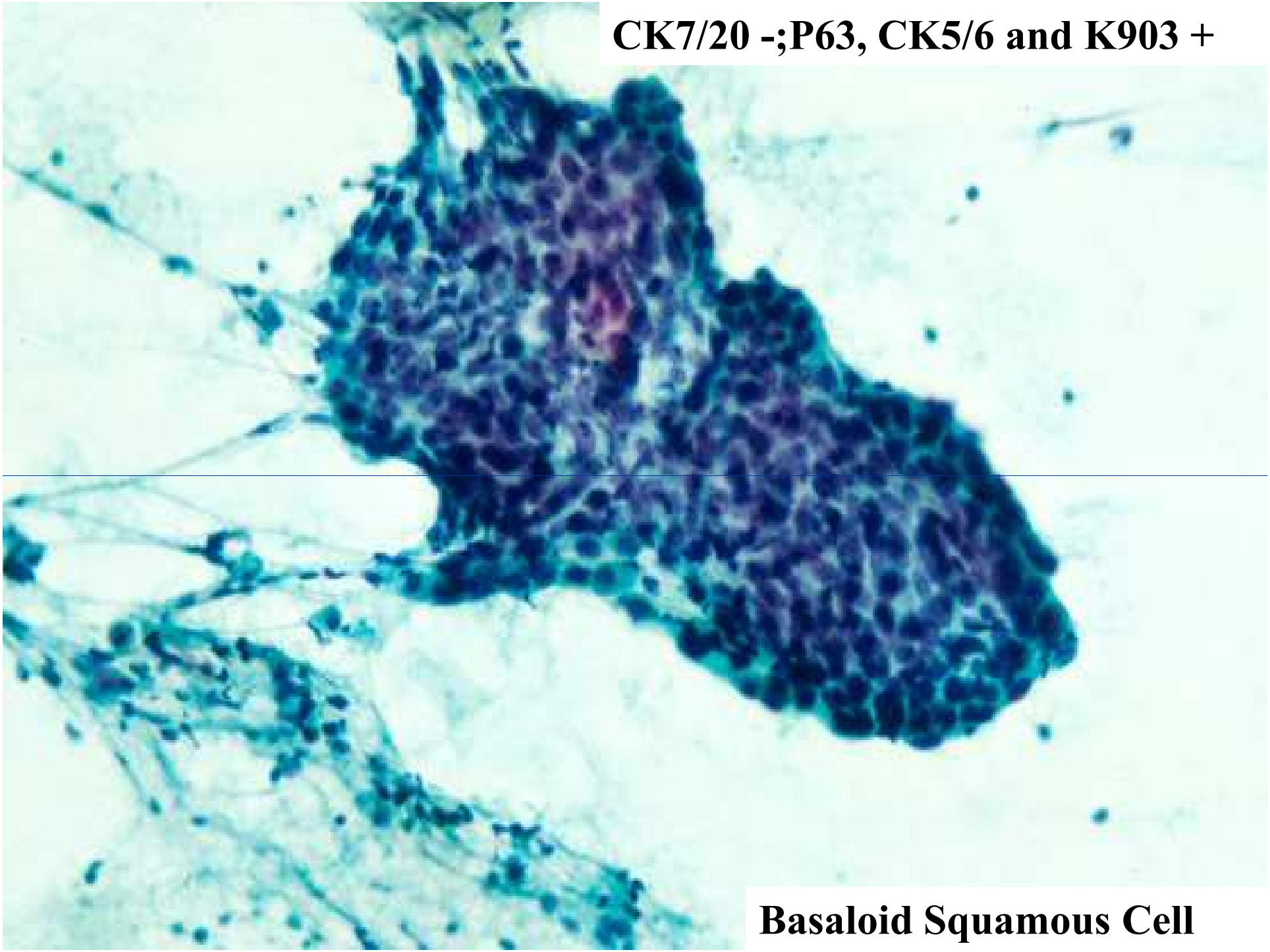
Small Cell Tumors

- Neuroendocrine tumors
  - Carcinoids / Islet cell tumors, ect.
  - Small cell (neuroendocrine) carcinoma
- Poorly differentiated carcinomas
  - Squamous Cell Carcinoma
  - Adenocarcinoma
- Lymphomas
- Small blue cell tumors of childhood
- Some sarcomas (synovial)
- Melanoma variant


Small Cell CA
Merkel Cell



Lymphoma


CK7/20 -;P63, CK5/6 and K903 +
Basaloid Squamous Cell

Pleomorphic / Giant Cells

- Carcinomas

  Lung, Pancreas, Liver, Thyroid, etc.

- Sarcomas

  i.e., Malignant fibrous histiocytoma, etc.

- Germ cell tumors

  Choriocarcinoma

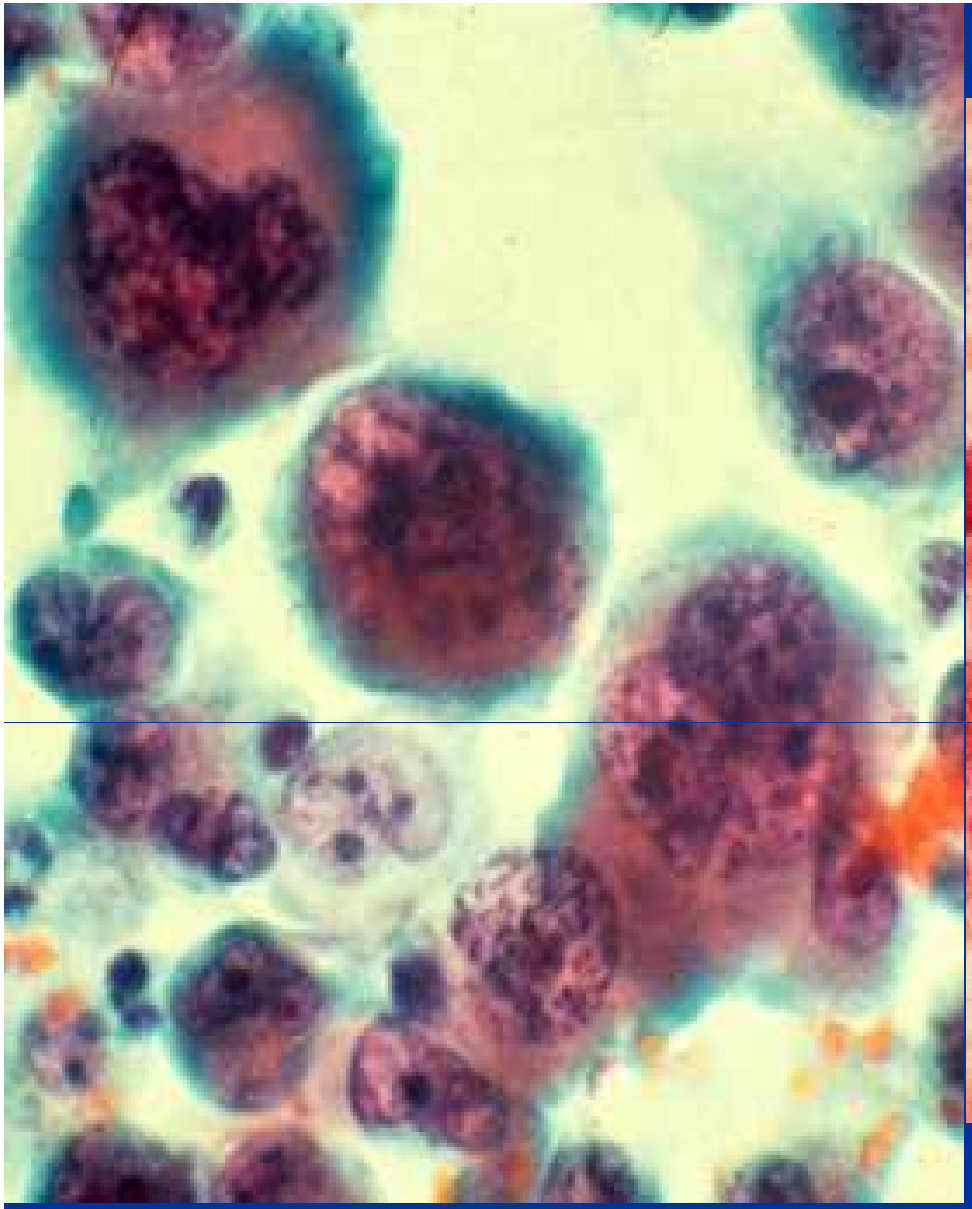
- Neuroendocrine tumors

  Pheochromocytoma

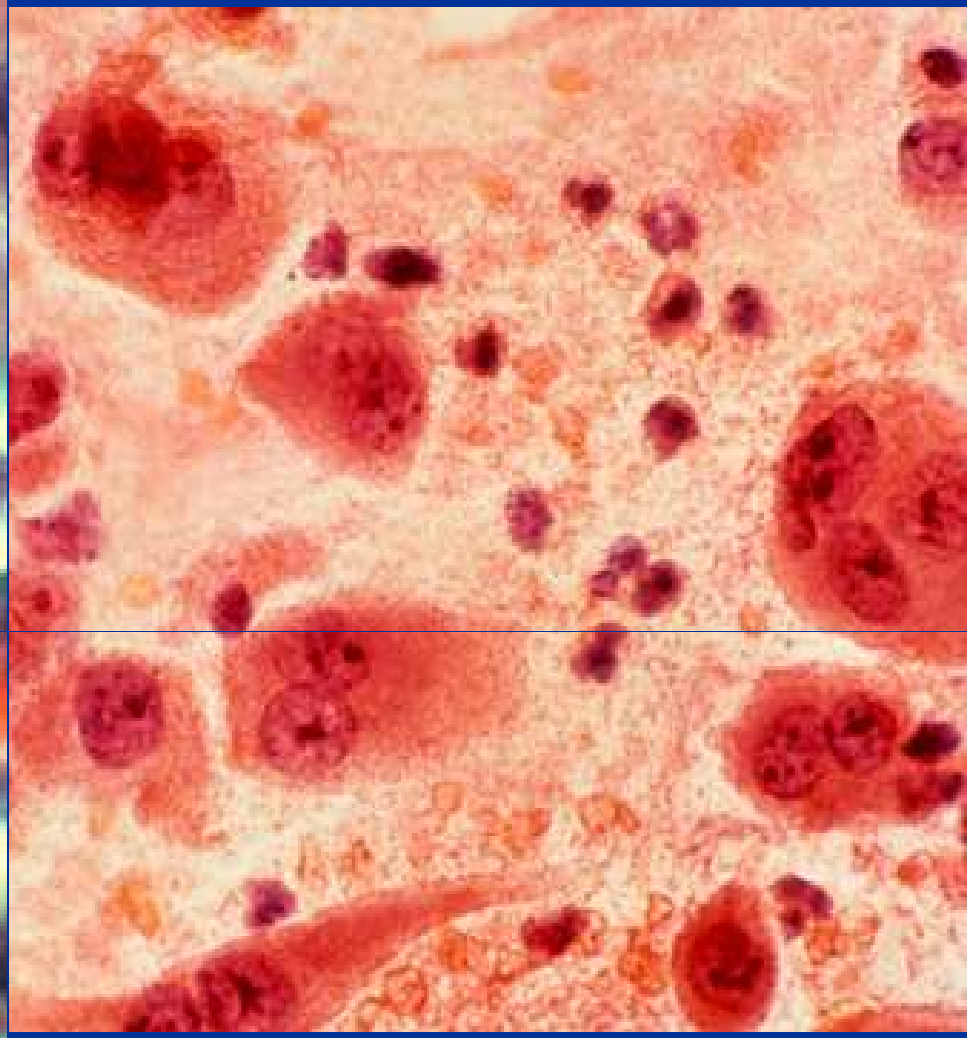
- Lymphoreticular neoplasms

  Anaplastic large cell lymphoma (Ki-1)

- Melanoma



Pleomorphic Large Cell Lung



Pancreas - Pleomorphic Giant Cell CA

Spindle Cells

- Sarcomas

  Fibrosarcoma

- Sarcomatoid Carcinomas

  Renal Cell CA; Spindle Squamous CA

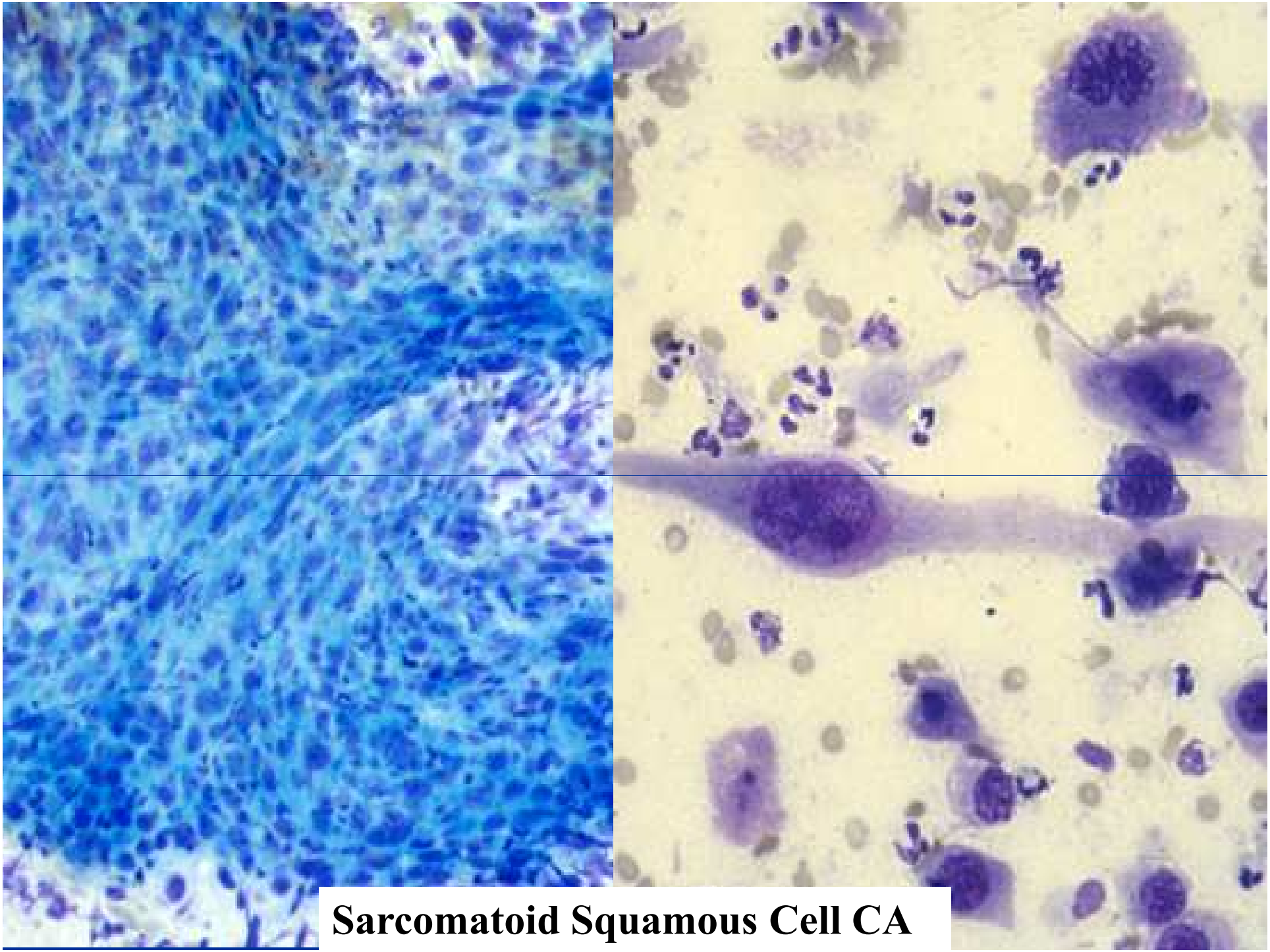
- Pseudosarcomas

  Nodular fasciitis, fibromatosis, repair, etc.

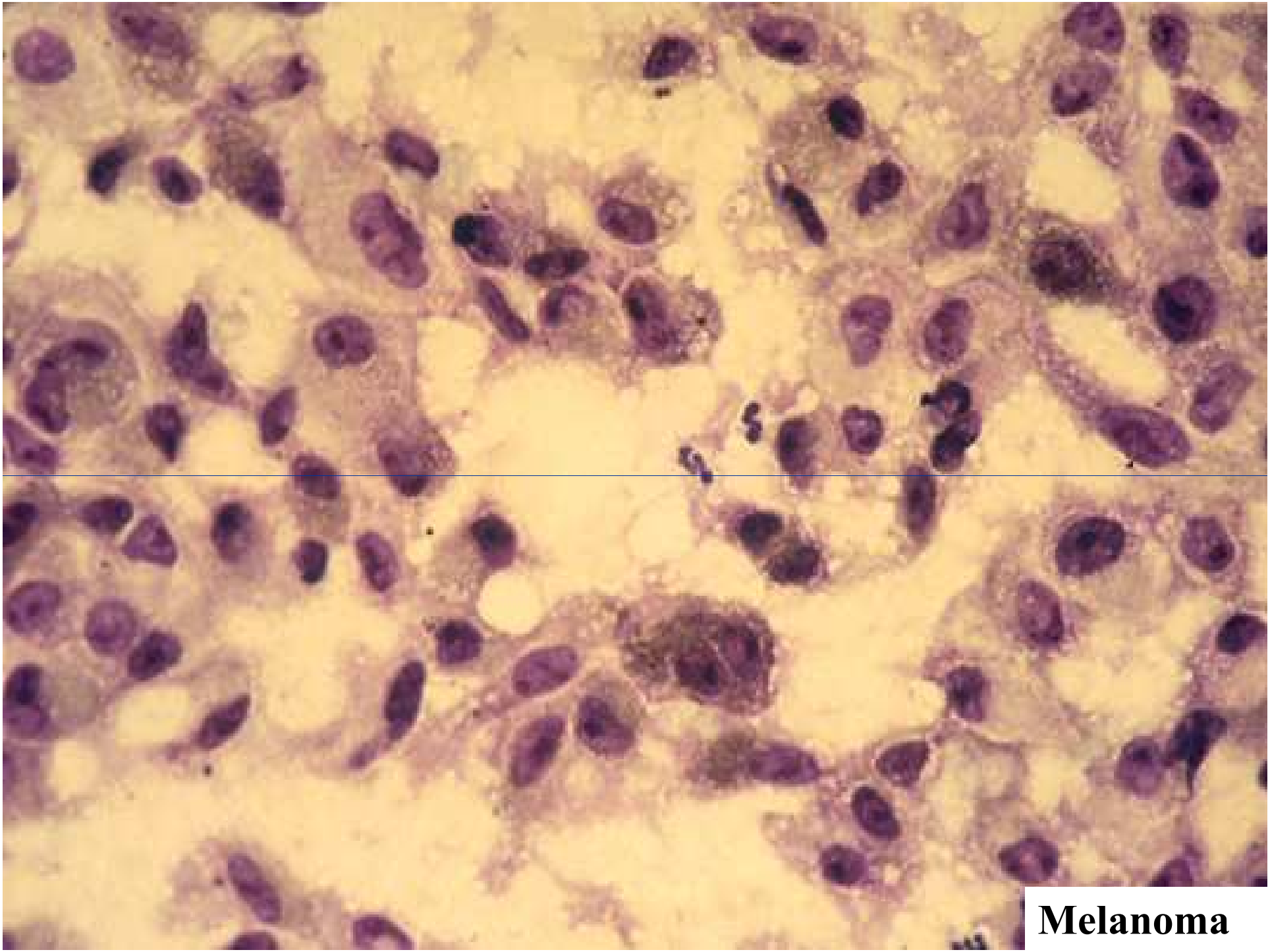
- Neuroendocrine tumors

  Paraganglioma

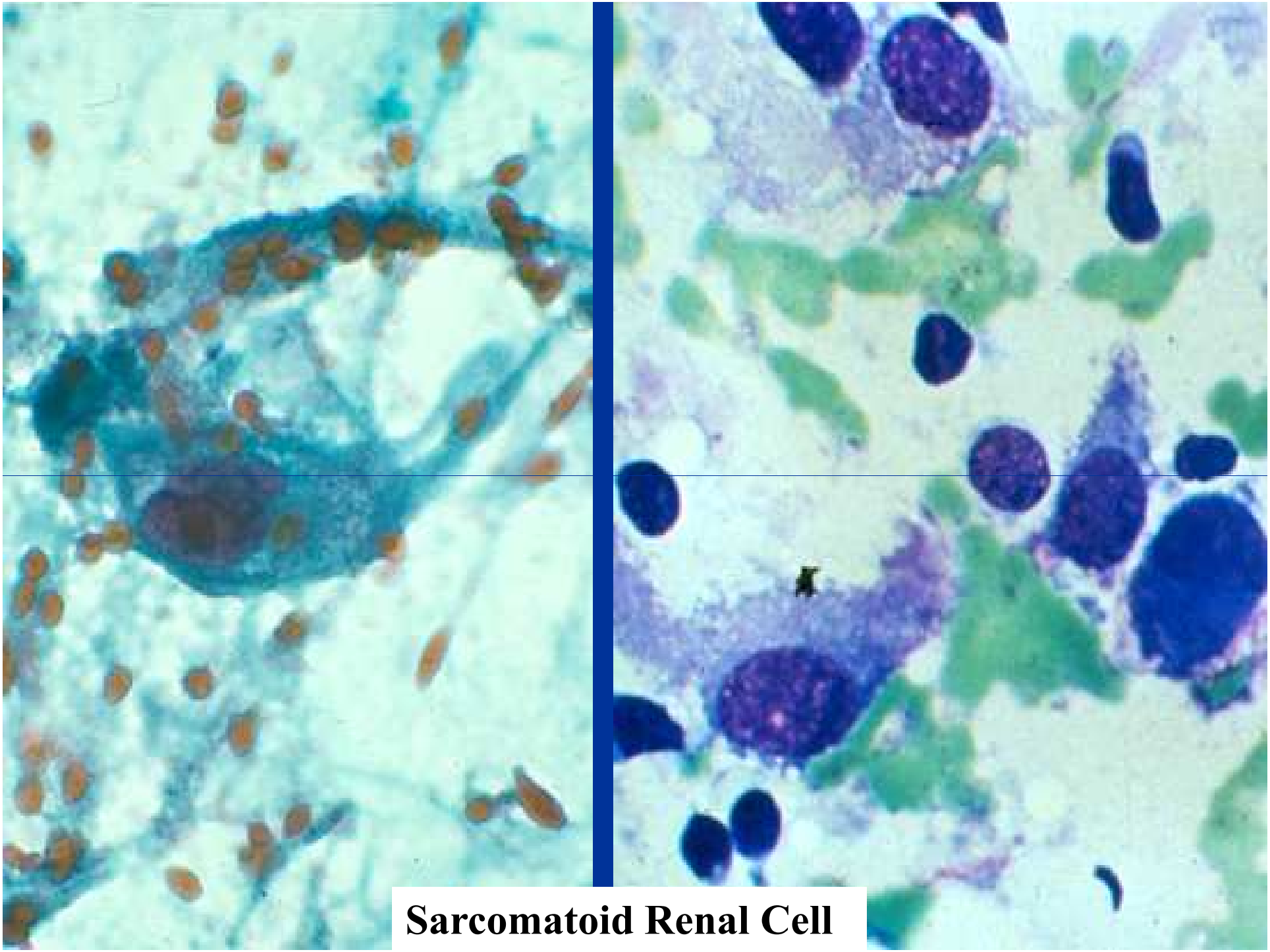
- Melanoma



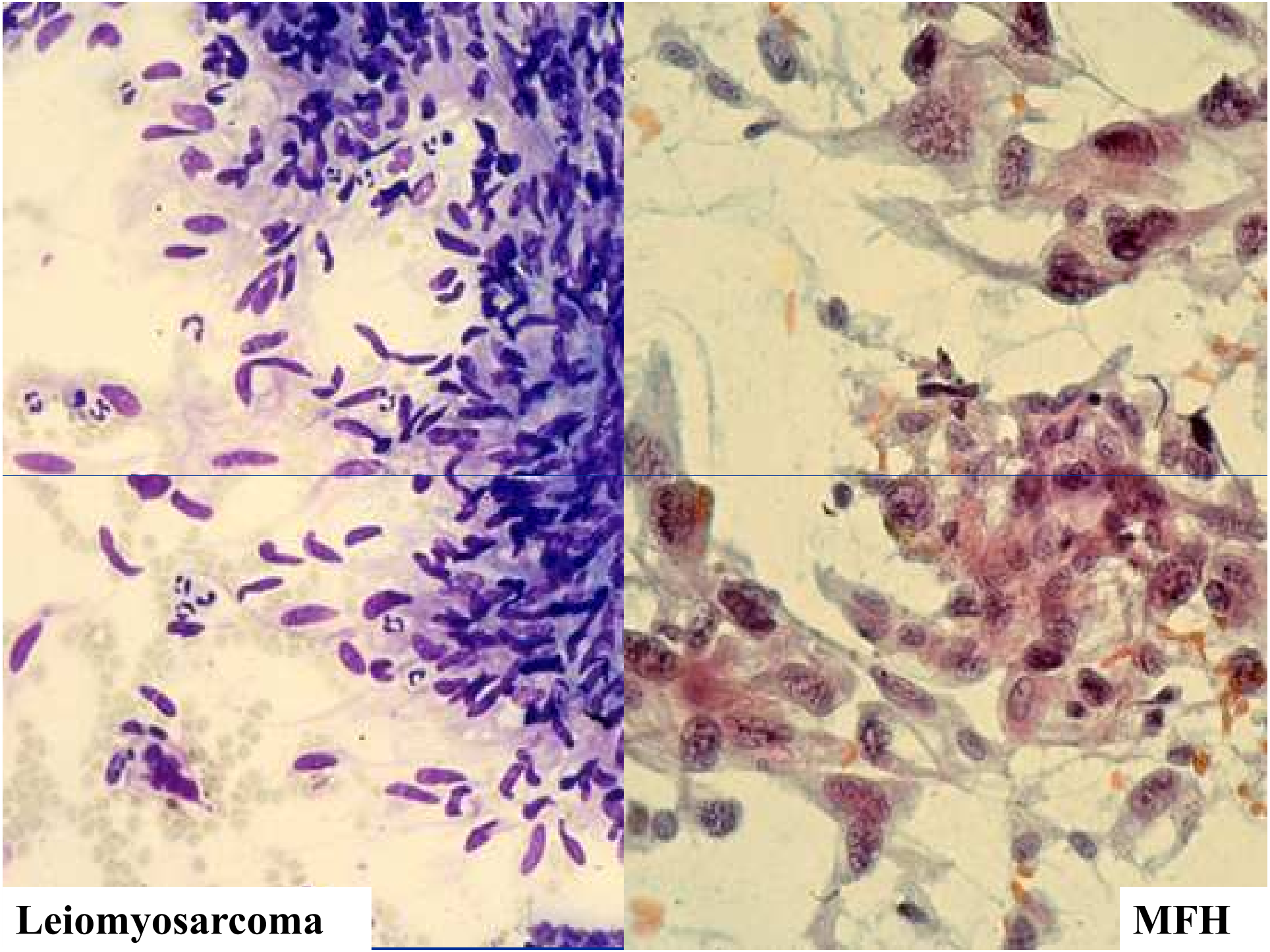
Sarcomatoid Squamous Cell CA



Melanoma



Sarcomatoid Renal Cell



Leiomyosarcoma

MFH

Granular Cell Neoplasms

- Carcinomas (Adenomas)

  Kidney, Liver, Salivary Gland, Glassy Cell (cervix)

- Oncocytic / Hurthle Neoplasms

  Kidney, Thyroid, etc.

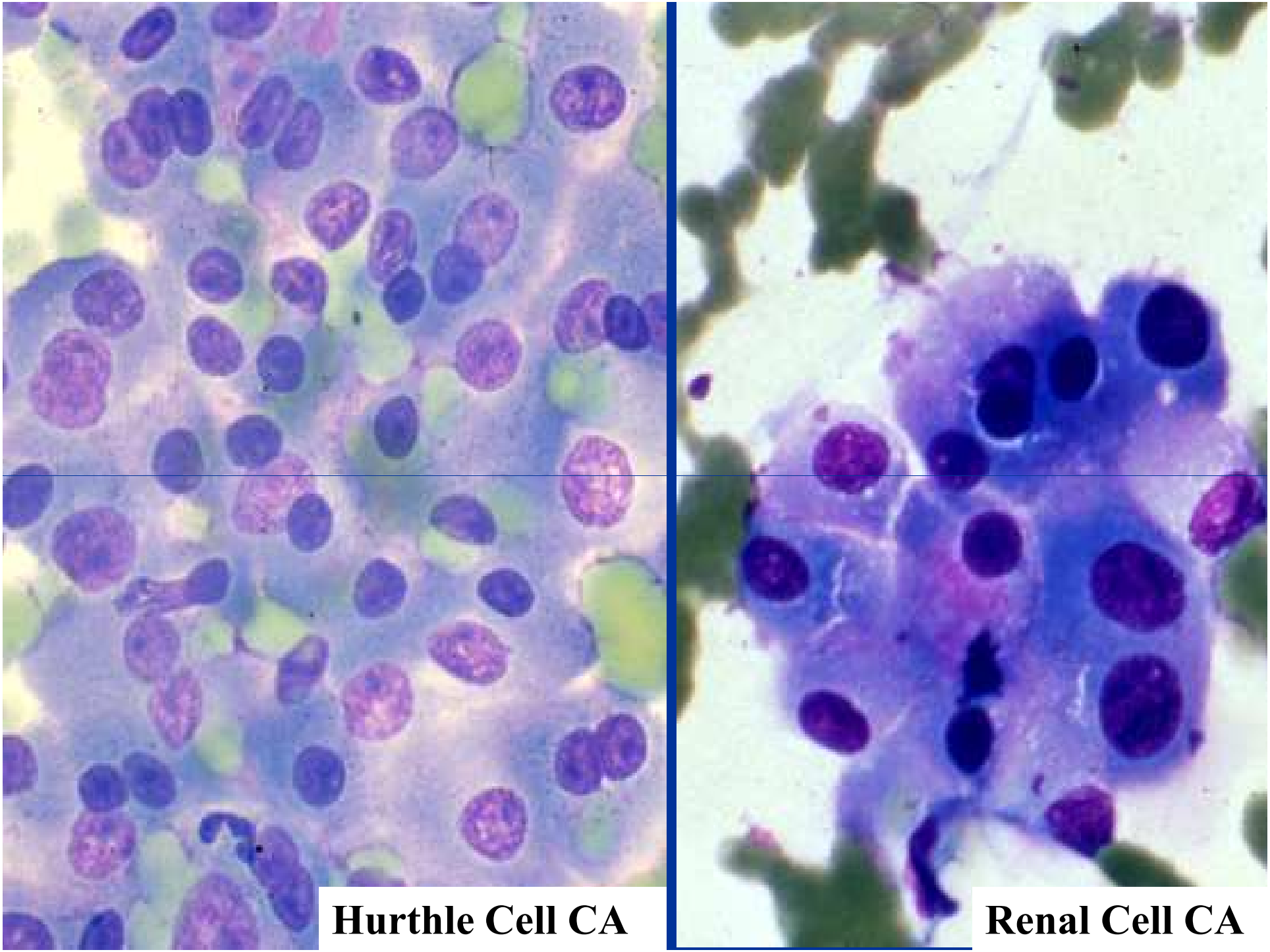
- Apocrine - Breast, Sweat Gland
- Neuroendocrine Tumors - Carcinoid, Paraganglioma
- Soft Tissue Tumors - Granular Cell Tumor

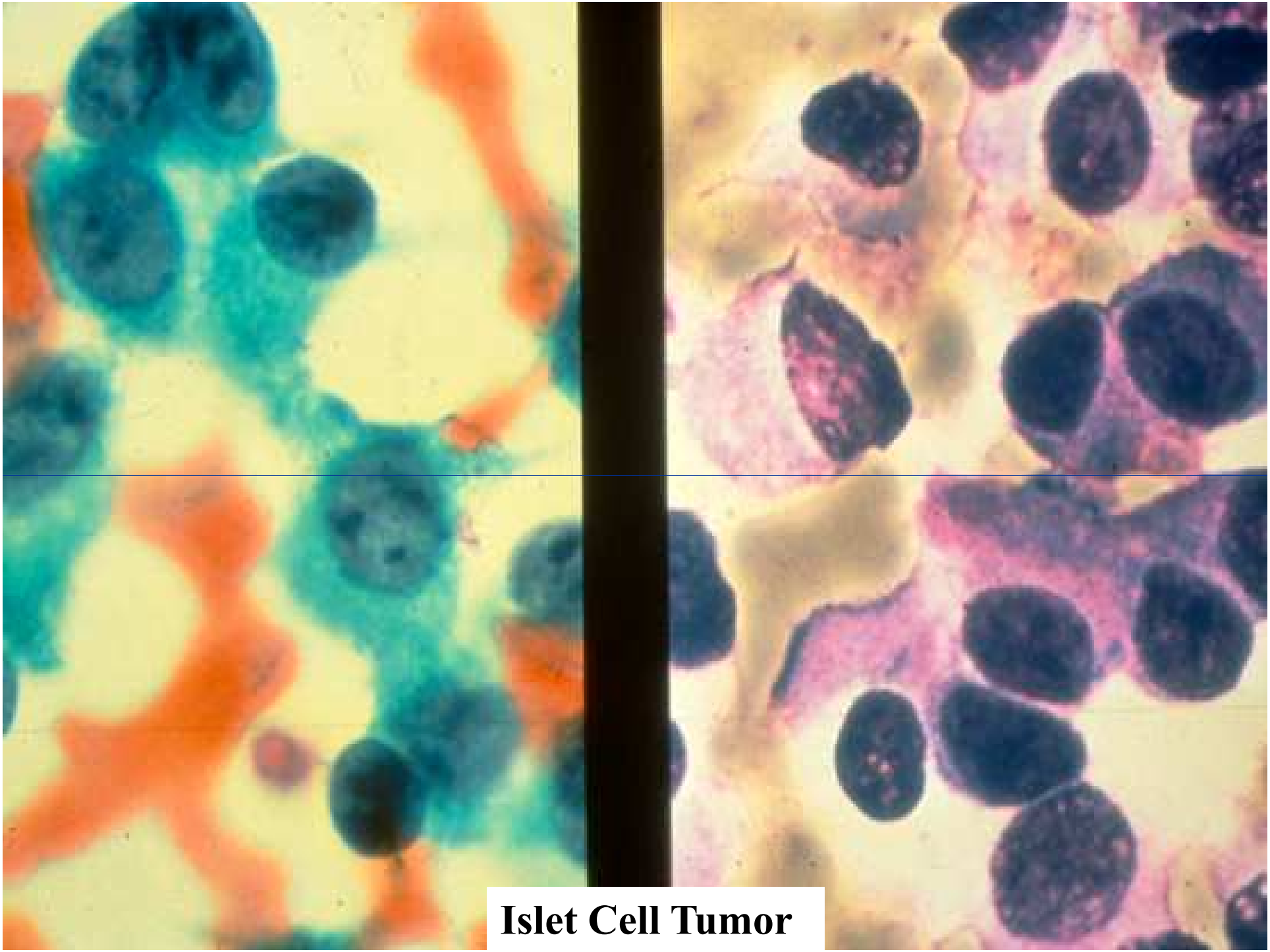
  Others: Muscle, Alveolar Soft Parts Sarcoma

- Melanoma
- Hilar / Leydig Cell Tumor

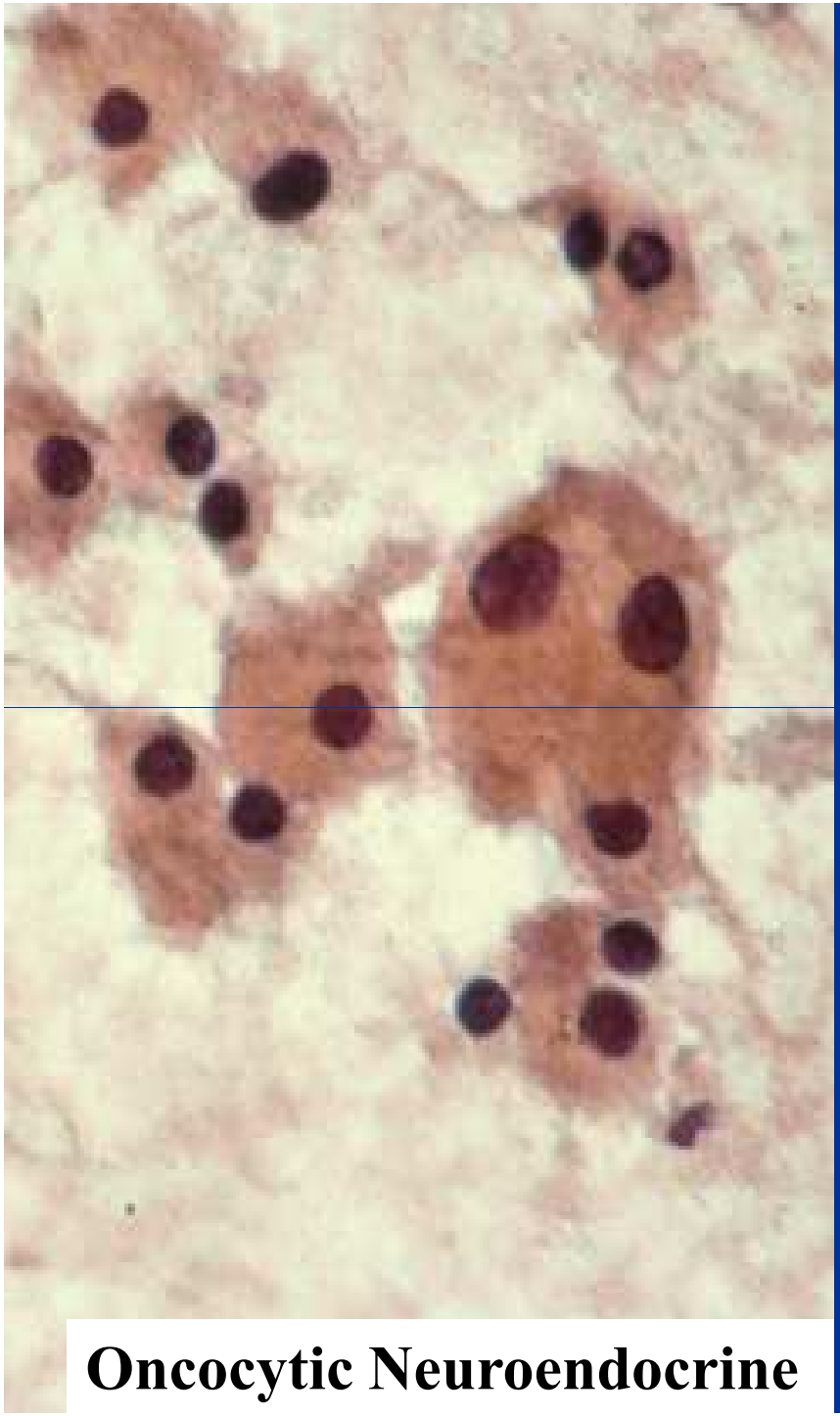
DDX: Nonspecific degeneration

Modified from DeMay

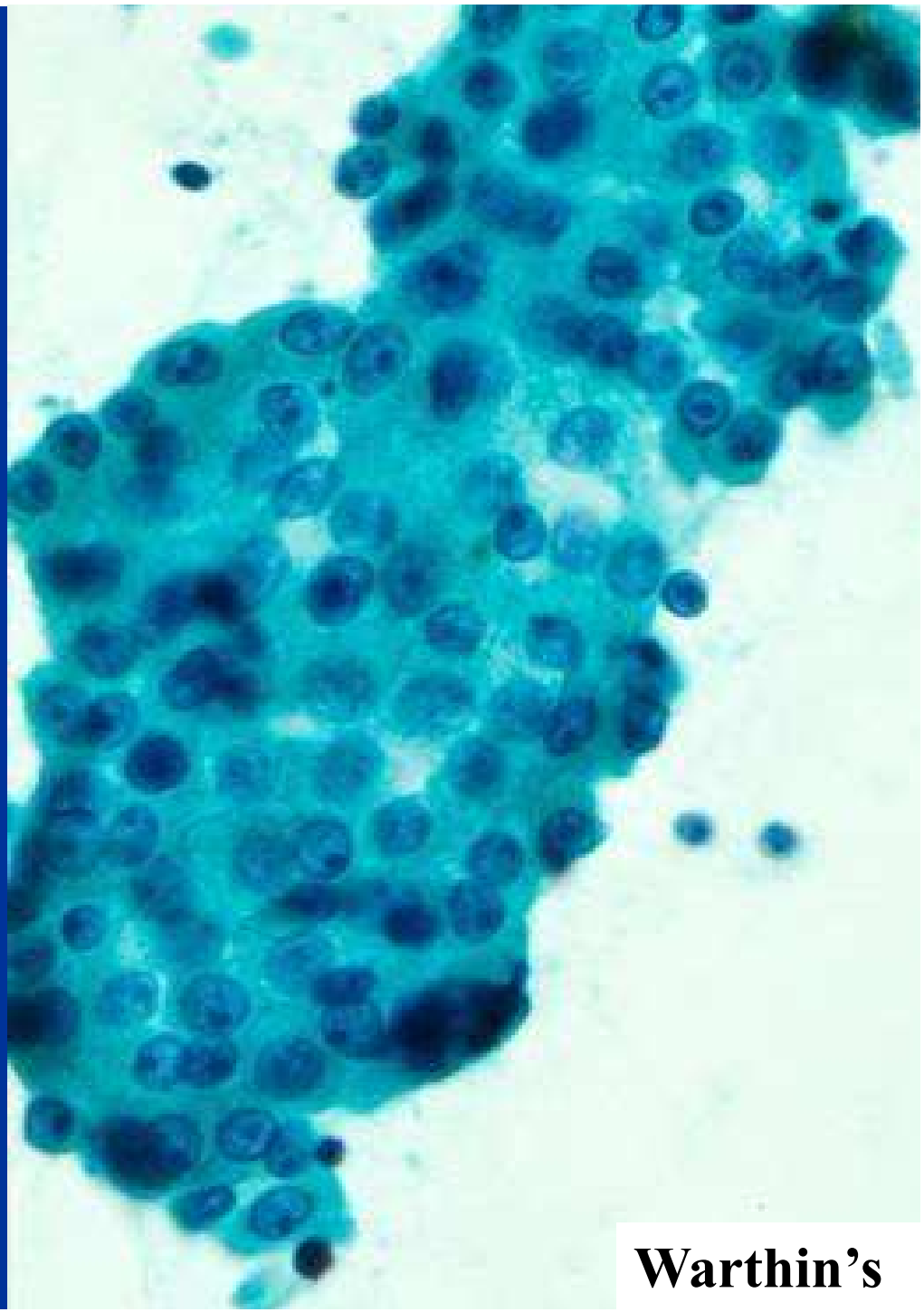

Hurthle Cell CA
Renal Cell CA



Islet Cell Tumor



Oncocytic Neuroendocrine



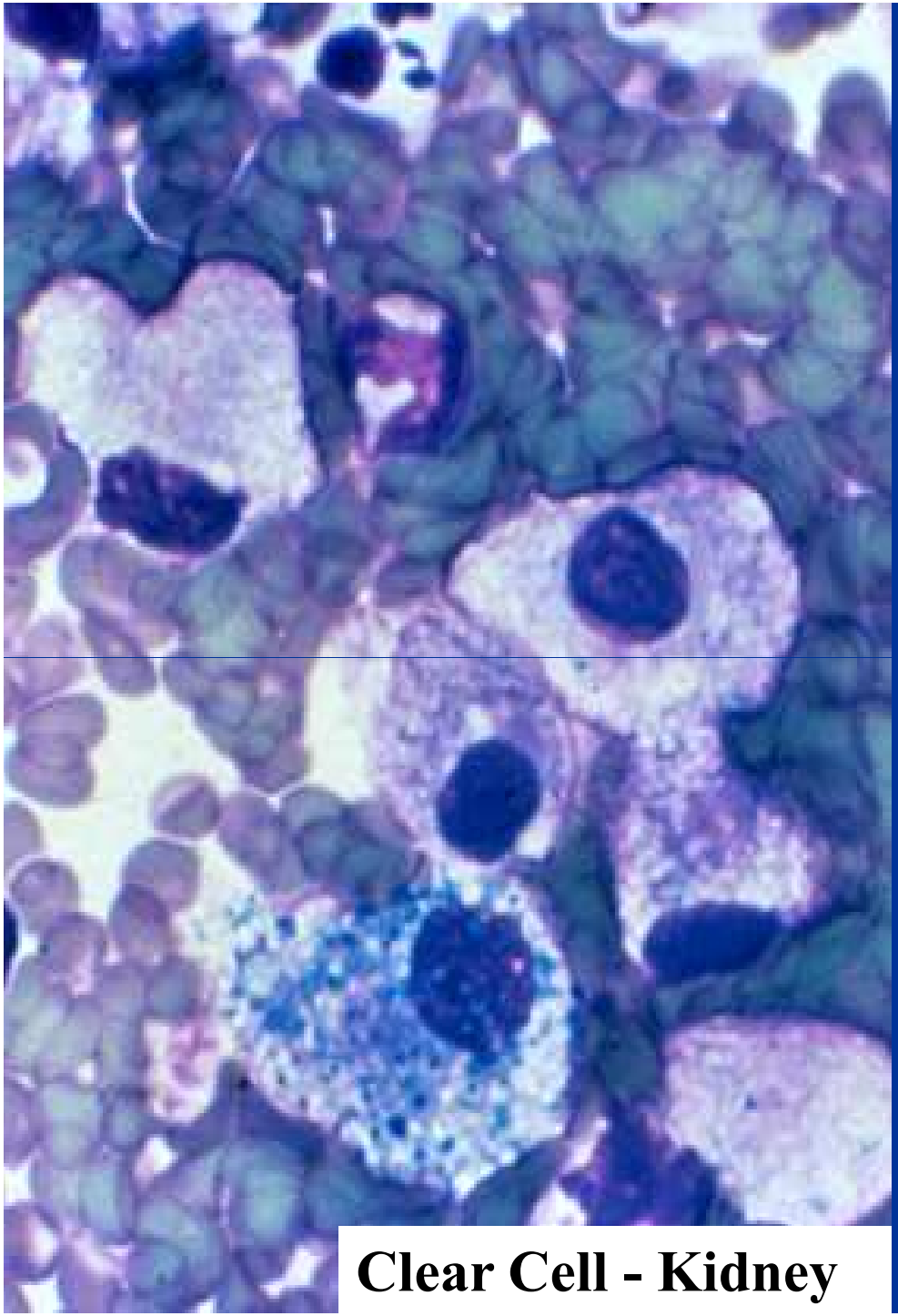
Warthin's

Clear cell Tumors

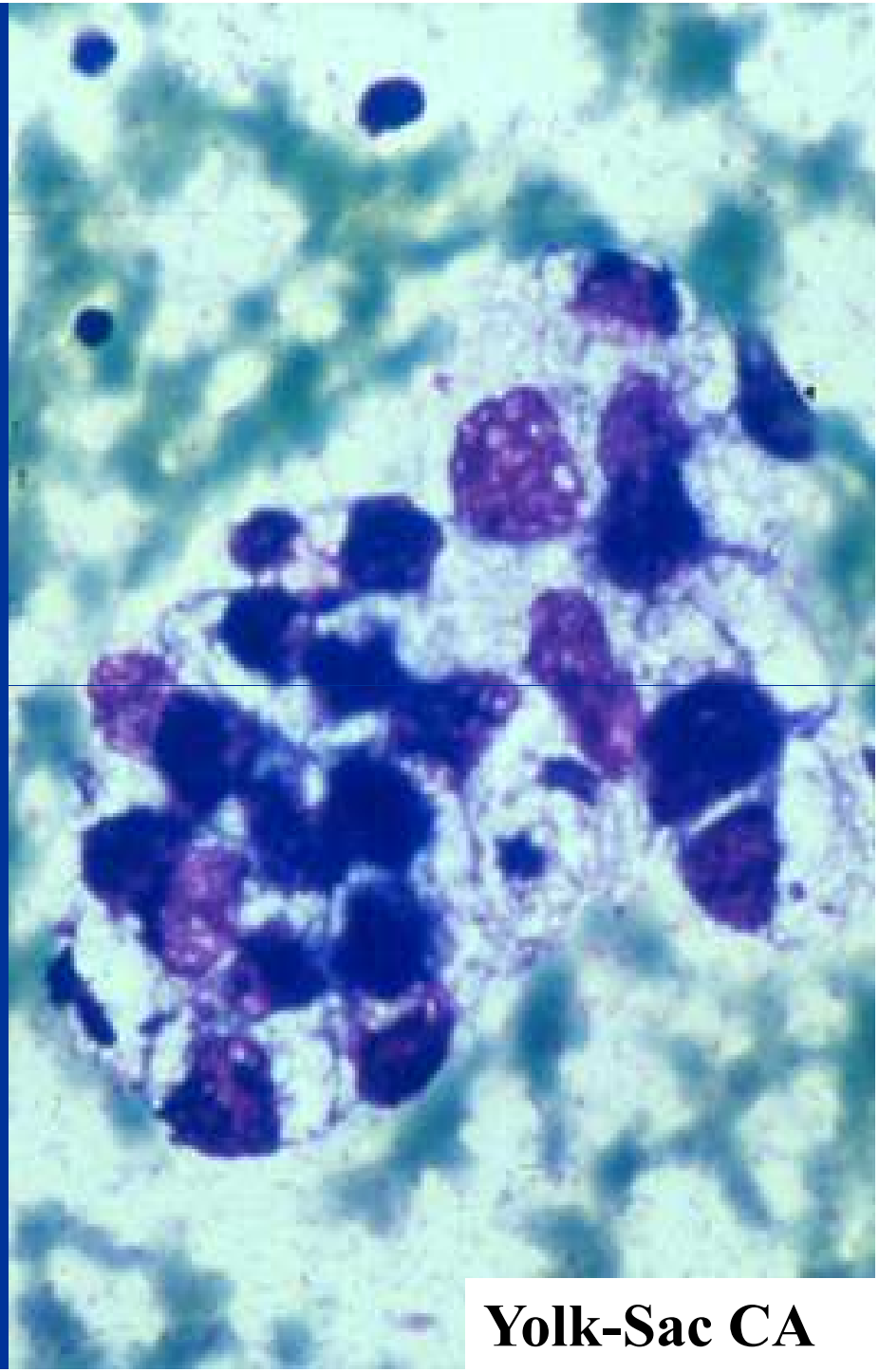
- Carcinomas

  KIDNEY, also Ovary, Liver, Adrenal, Salivary Gland, lung GYN, Thyroid

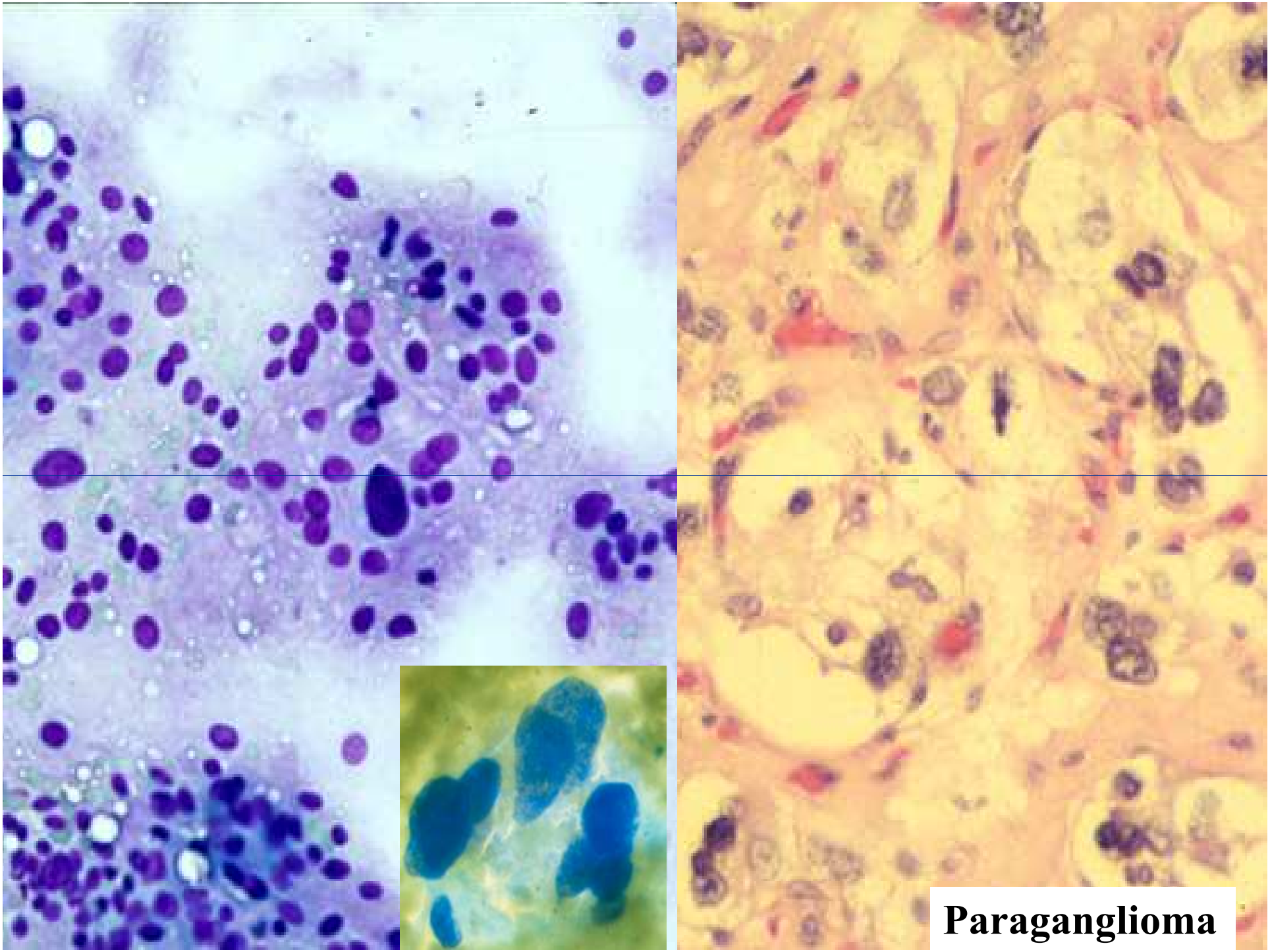
- Oncocytic neoplasms
- Acinic / Acinar Tumors
- Neuroendocrine Tumors (i.e., paragaglioma)
- Soft Tissue Tumors (i.e., clear cell sarcoma)
- Lymphoma - very rare
- Germ Cell Tumors
- Melanoma (ballon cells)



Clear Cell - Kidney



Yolk-Sac CA


Paraganglioma

Intranuclear Cytoplasmic Inclusions

- Thyroid

  Papillary CA, others

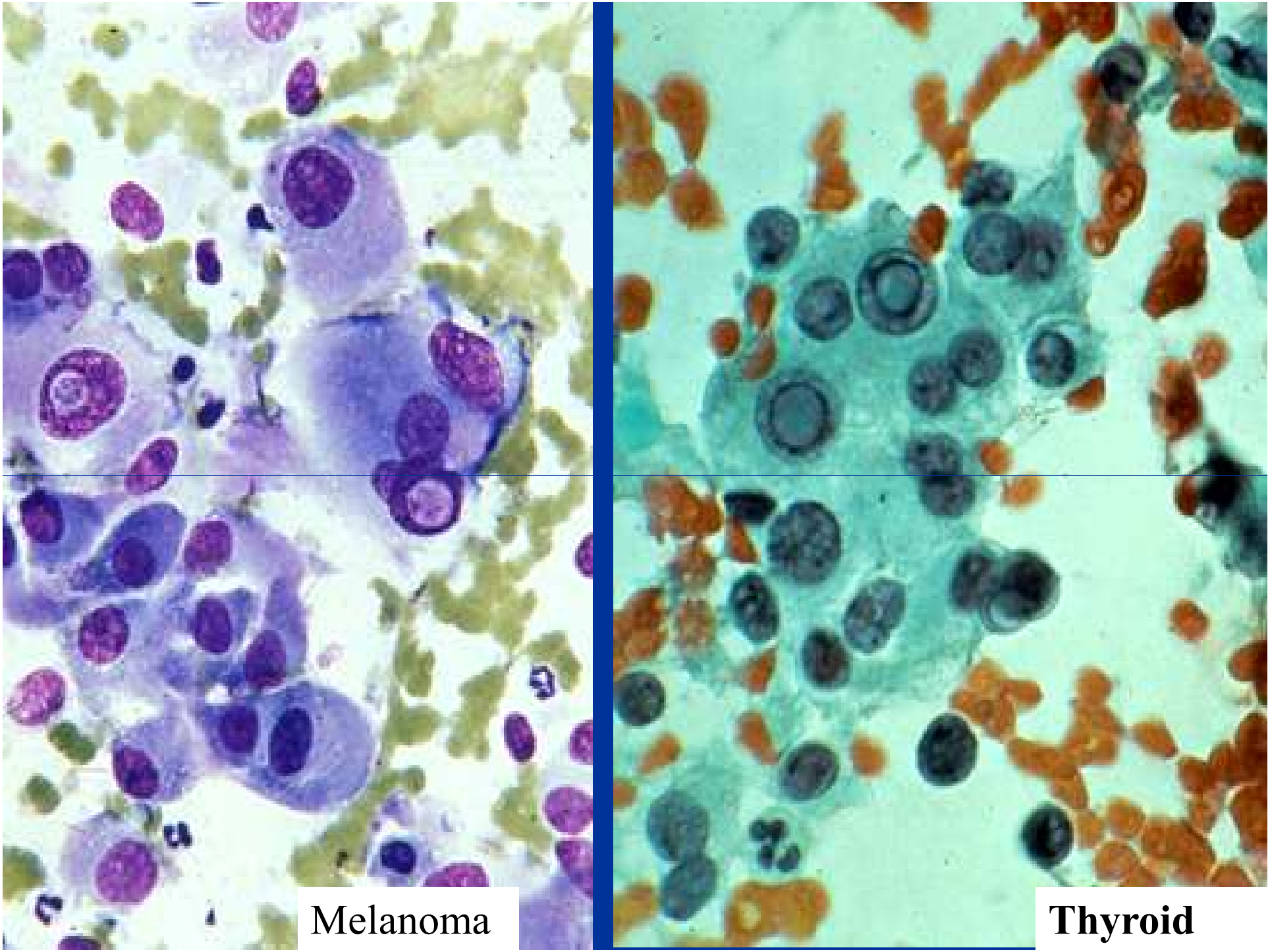
- Lung

  Bronchioloalveolar CA

- Liver

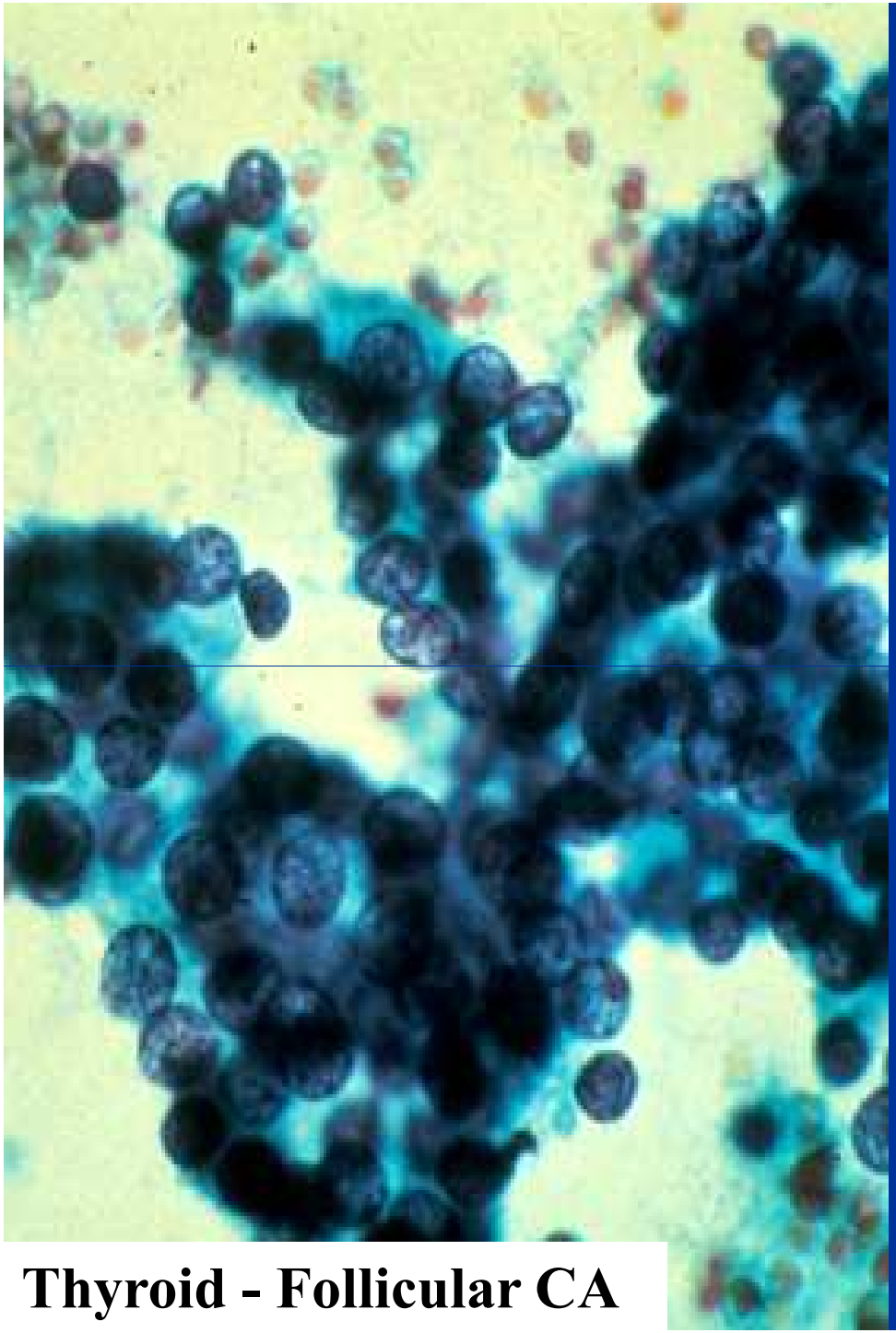
  Favors HCC

- Melanoma
- Many others

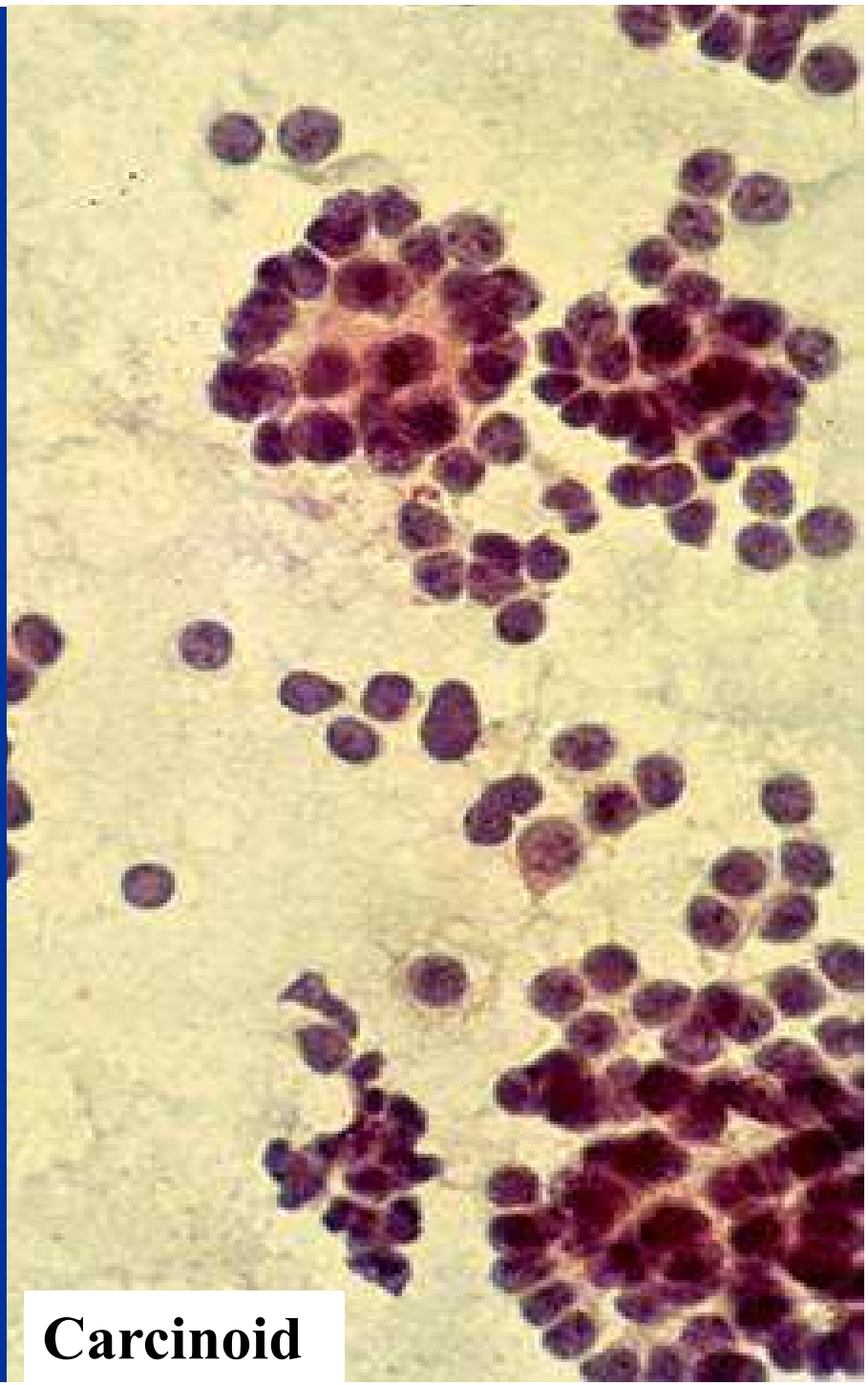

Melanoma
Thyroid

Microacinar Complexes

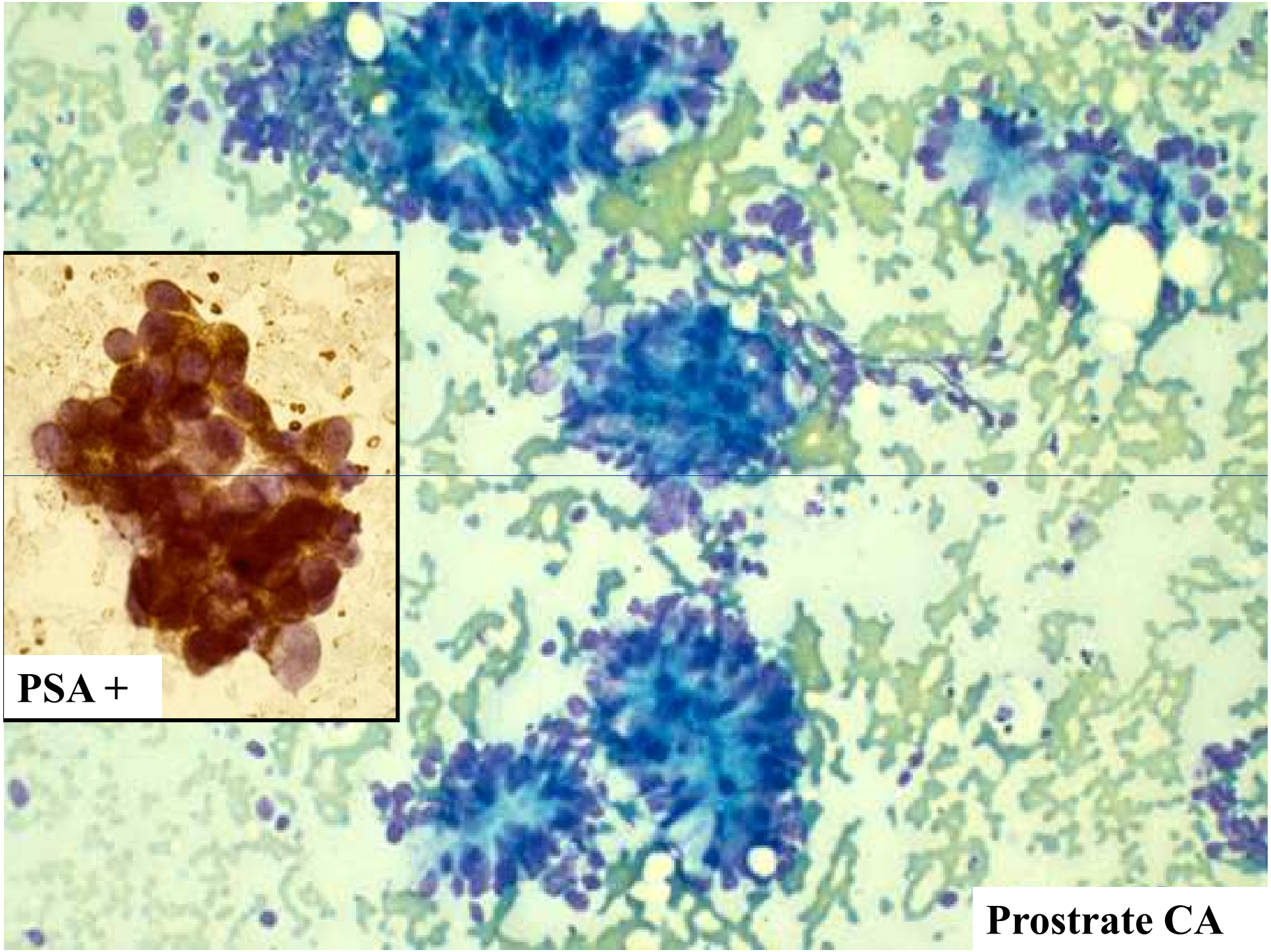
- Prostate
- Thyroid
- Carcinoid / Islet (Rosettes)
- Others - Granulosa cell tumor, other SRCT of childhood



Thyroid - Follicular CA



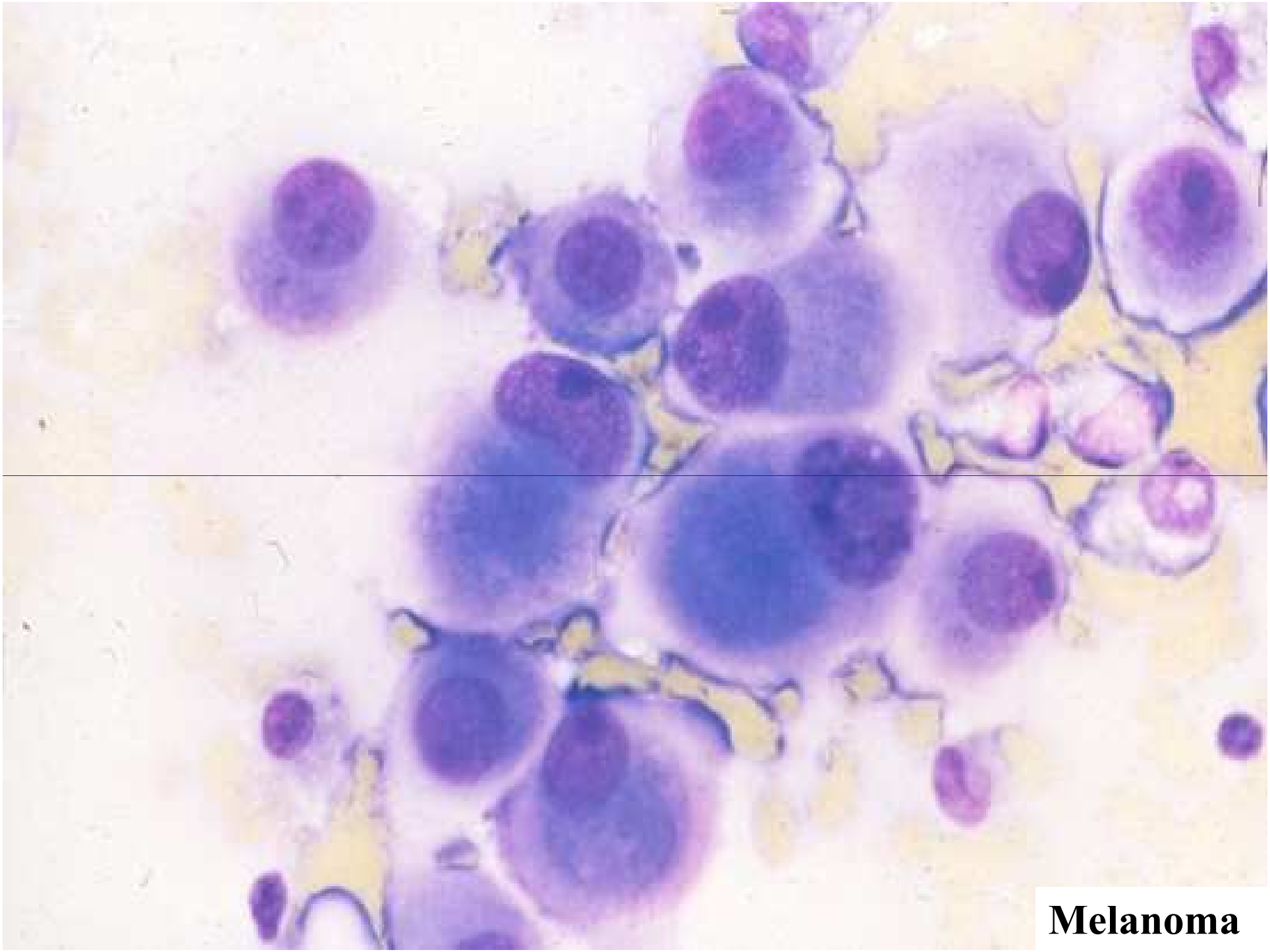
Carcinoid

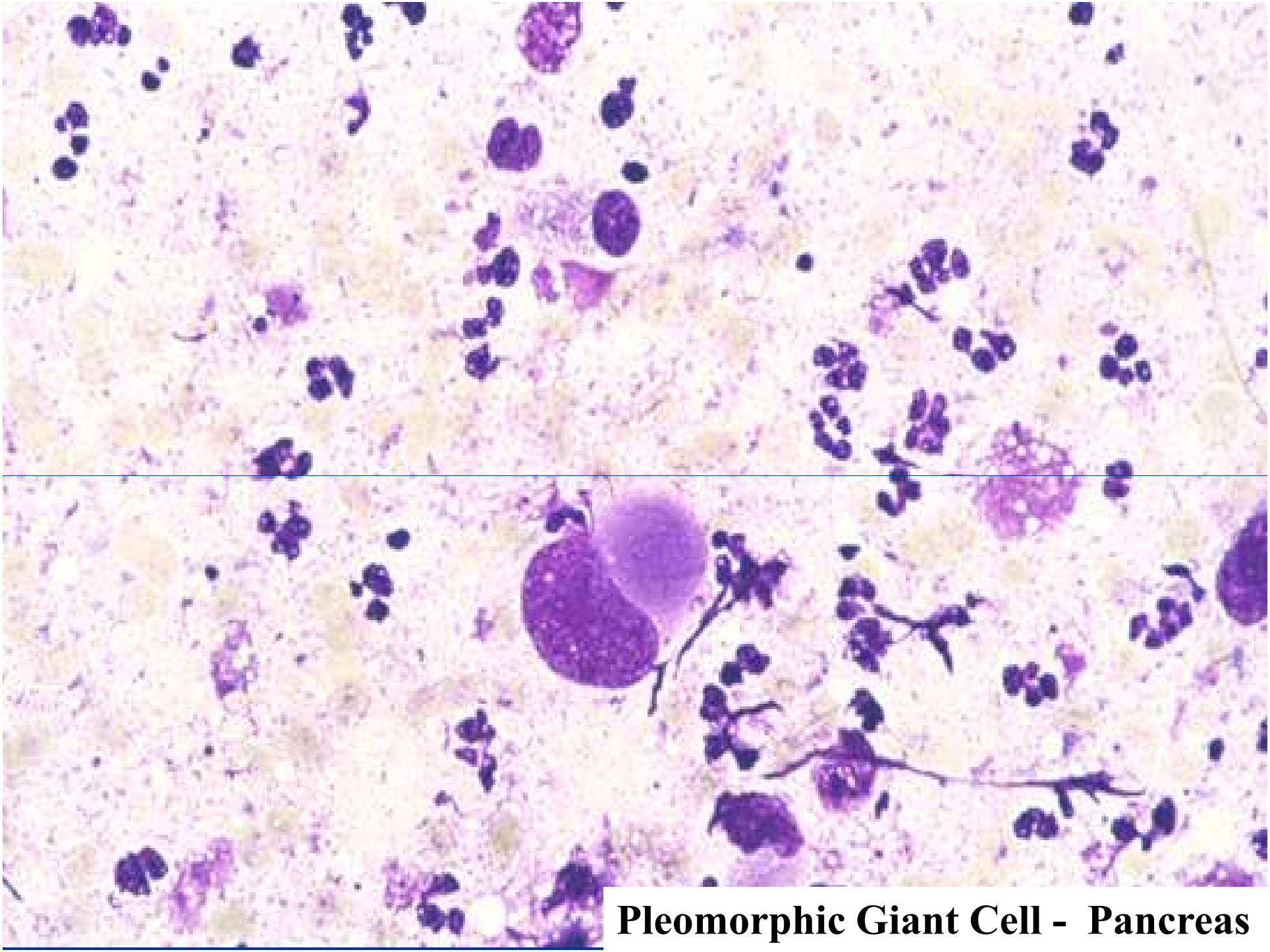

PSA +
Prostrate CA

Hyaline Globules

- Carcinoma (Rhabdoid)

  Wide variety, often PD malignancies
- Sarcomas
- Lymphoma
- Melanoma (Rhabdoid)
- Hepatocellular, renal, ovary


Melanoma



Pleomorphic Giant Cell - Pancreas

Single Cell

Adeno CA

BREAST

Pancreas

Stomach

Prostate

Other Tumors

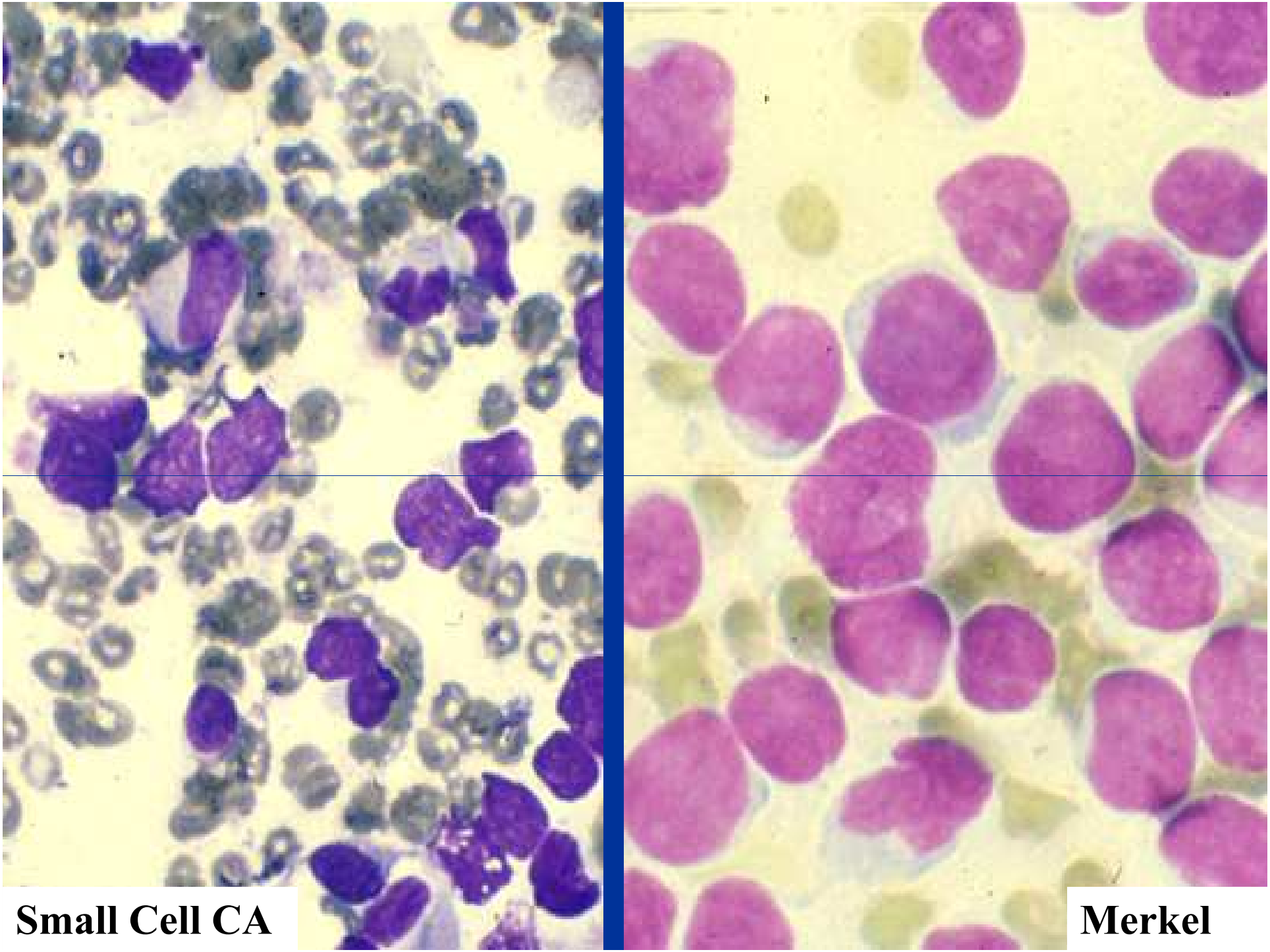
Small Cell CA

Mesothelioma

Carcinoids

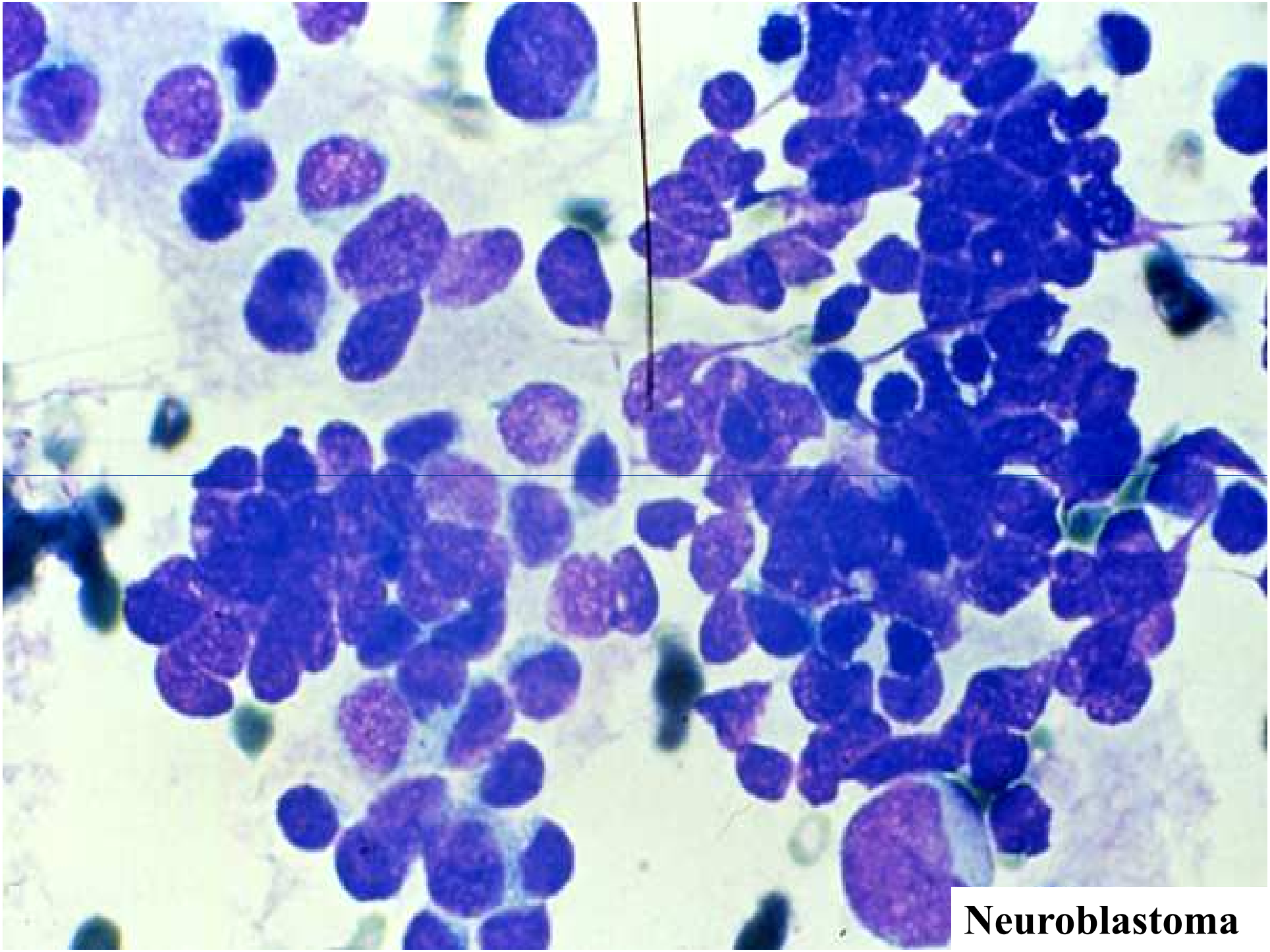
Melanoma

Hematopoeitic

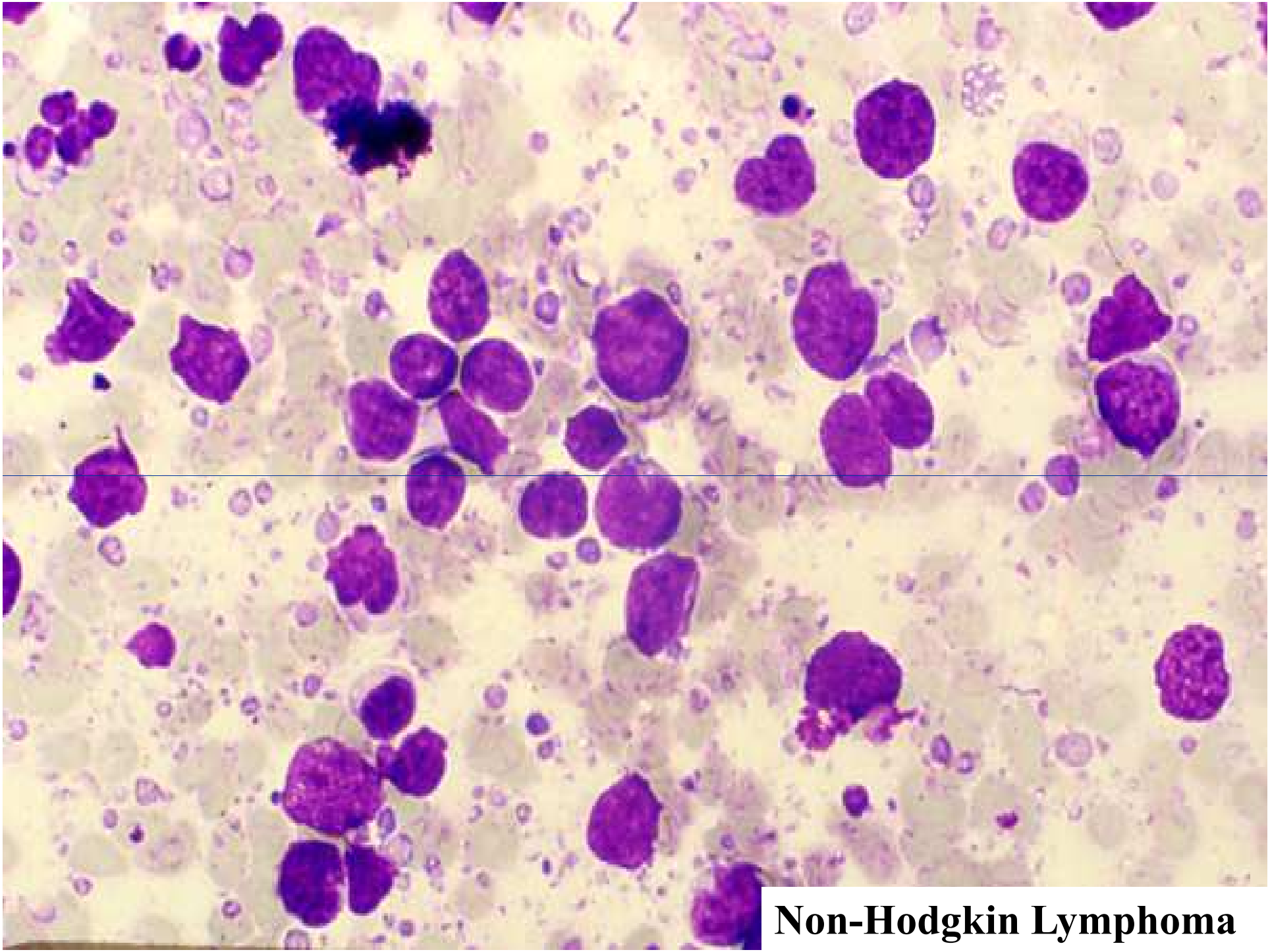


Small Cell CA

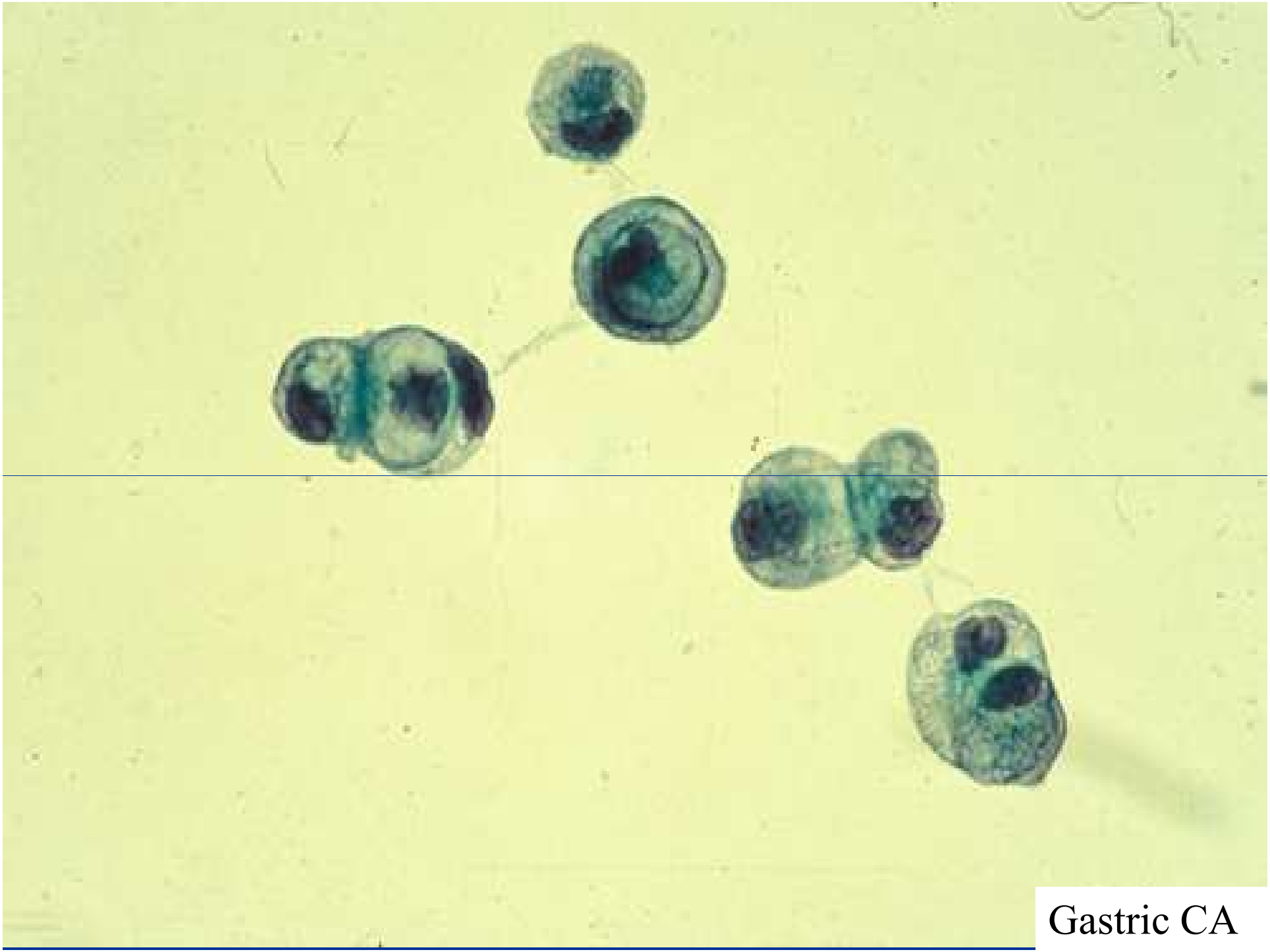
Merkel



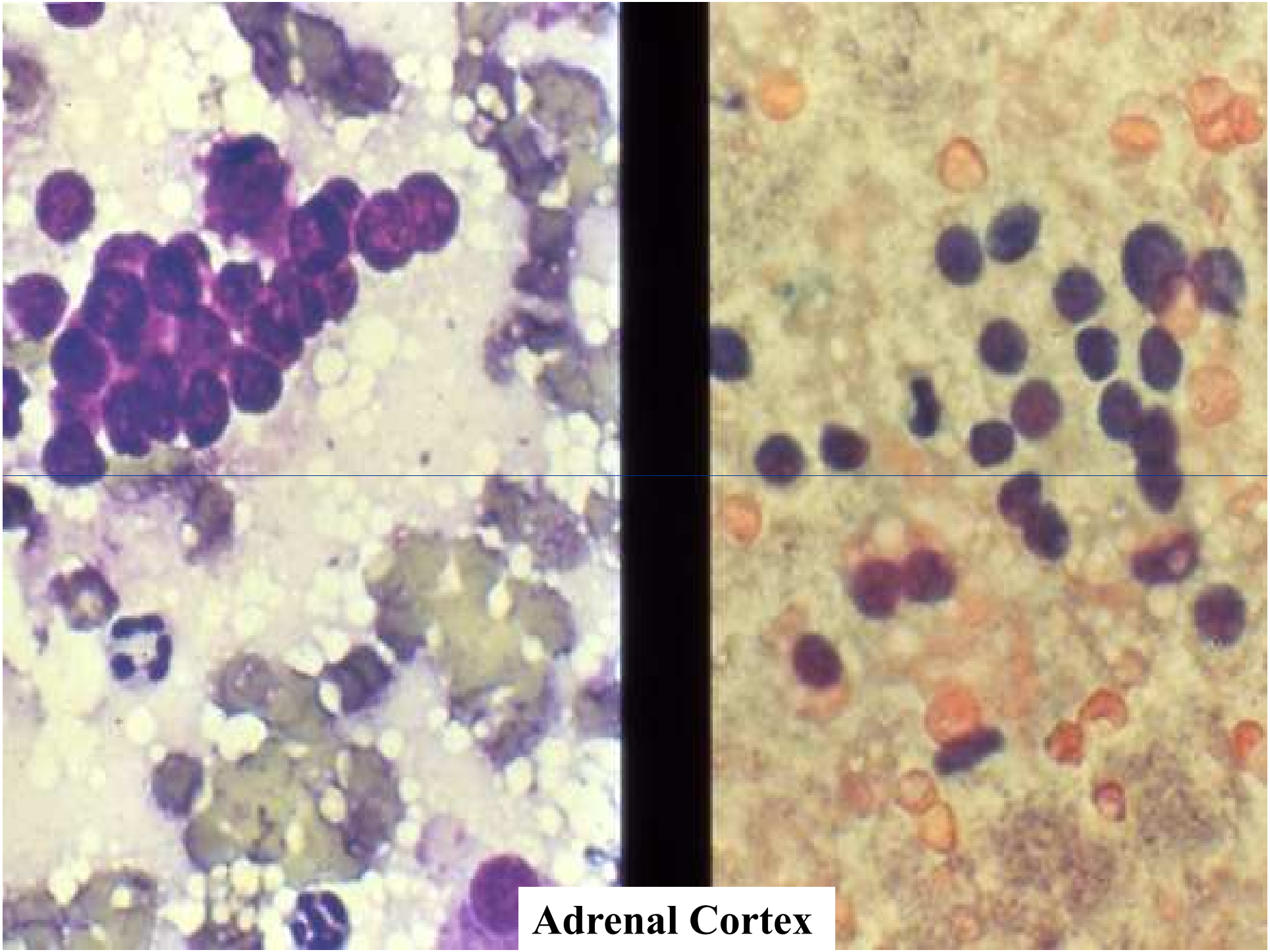
Neuroblastoma



Non-Hodgkin Lymphoma



Gastric CA


Adrenal Cortex

Papillary Neoplasms

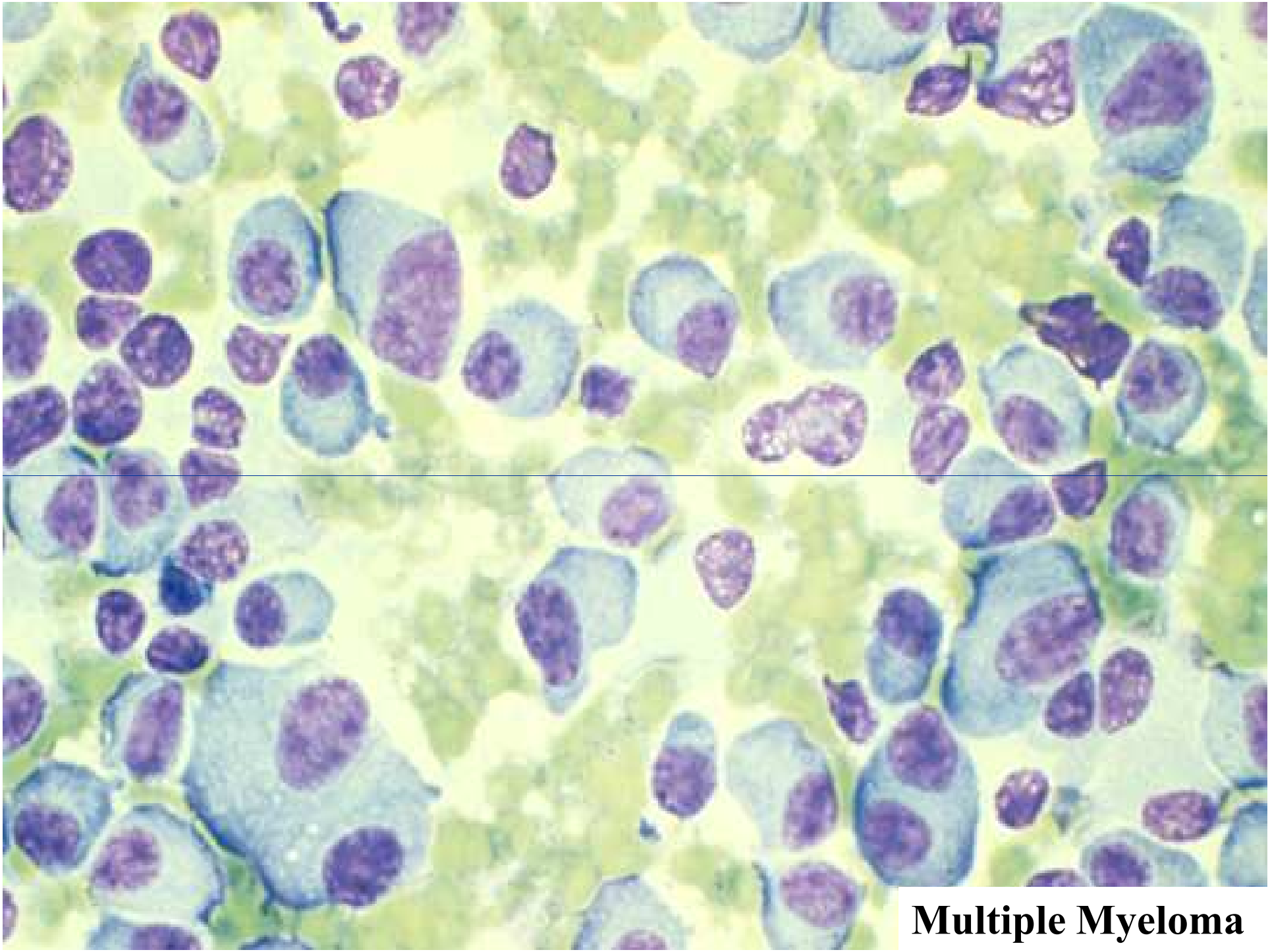
- Ovary
- GI Tract, Pancreas
- Lung (Bronchioloalveolar)
- Thyroid
- Renal
- Others

Papillary RC

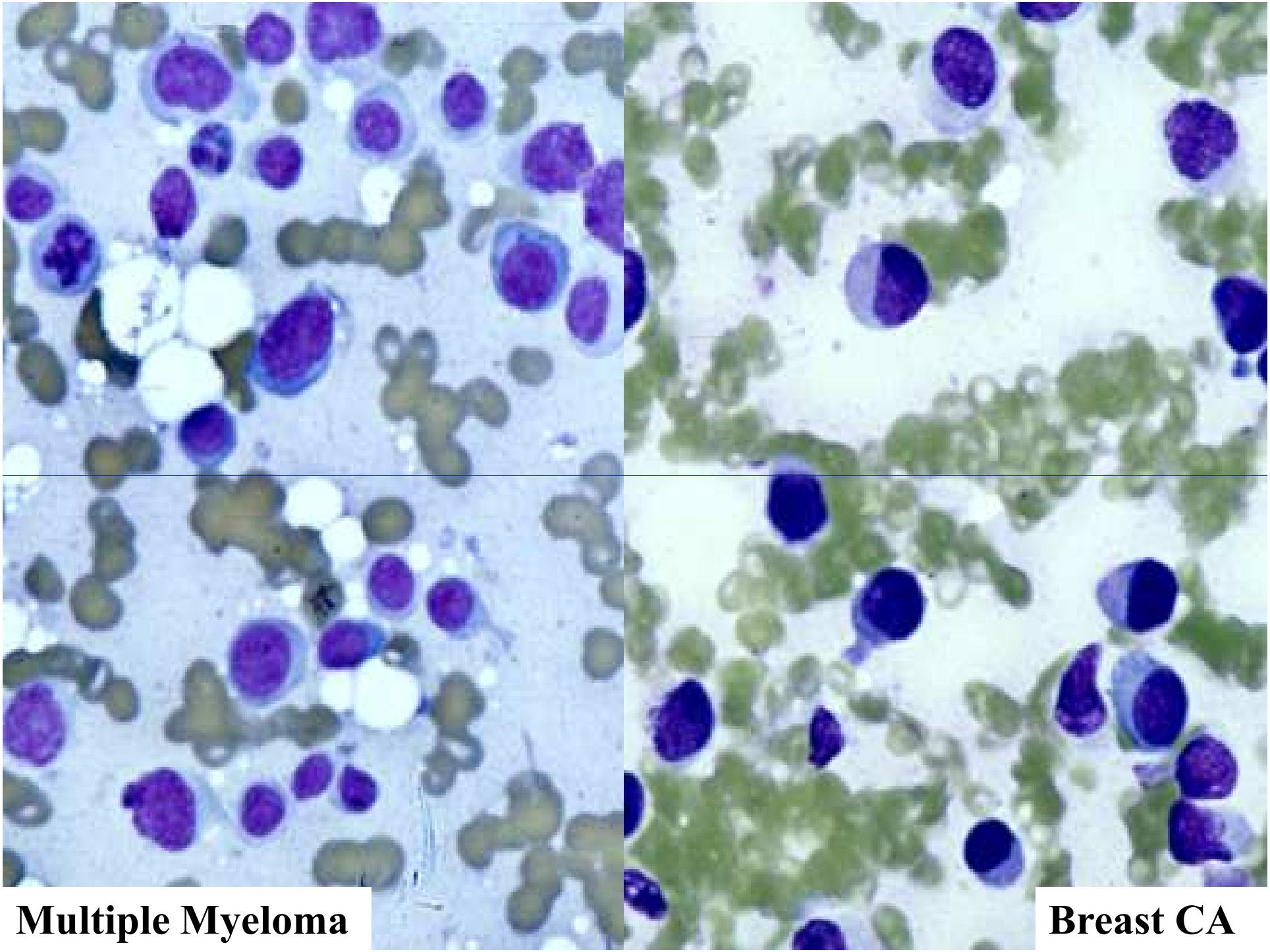

Papillary TC

Plasmacytoid Cells

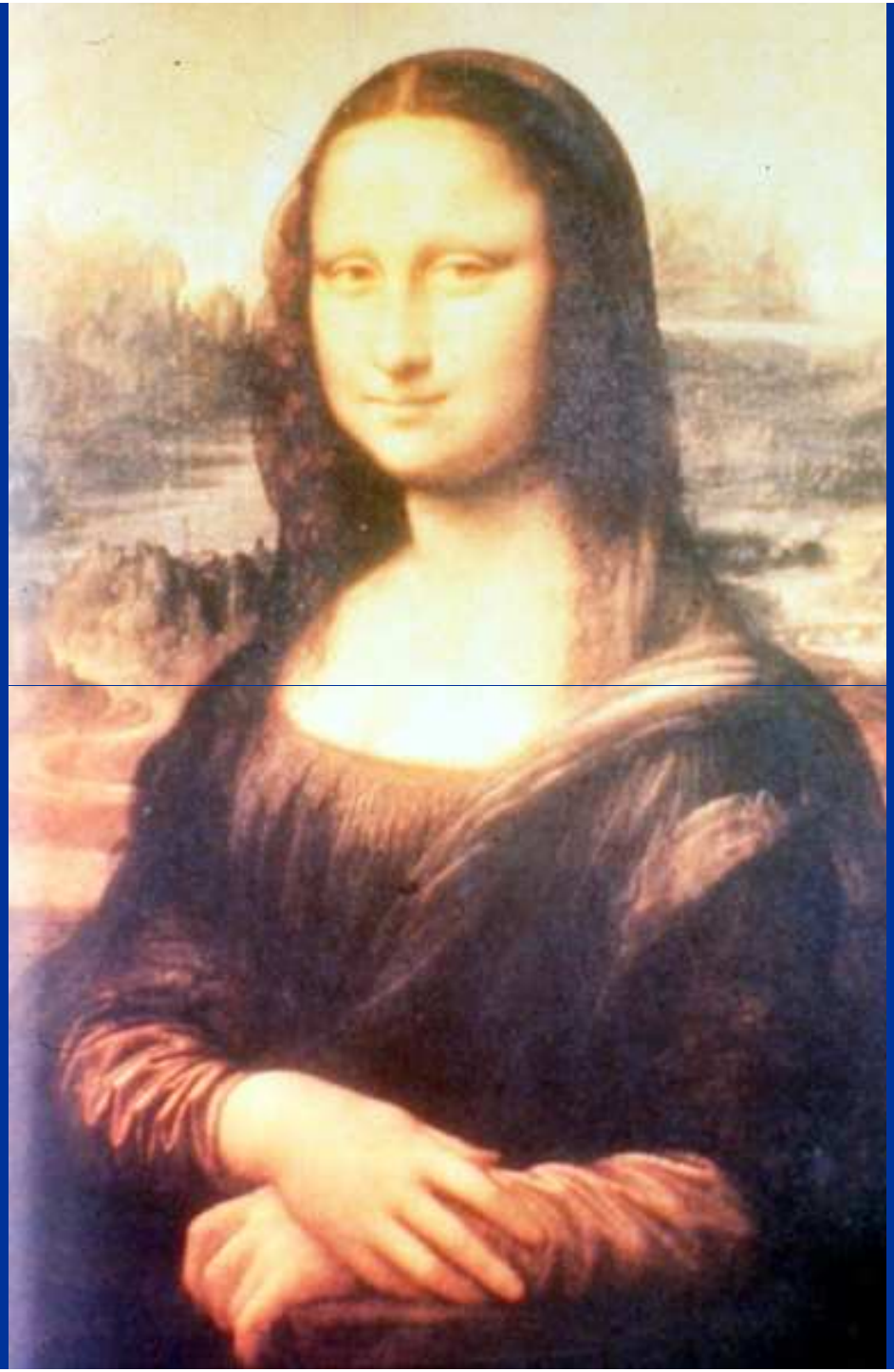
- Plasma Cells
- Carcinoid / Islet
- Melanoma
- Breast CA
- Pleomorphic adenoma



Multiple Myeloma



Multiple Myeloma **Breast CA**

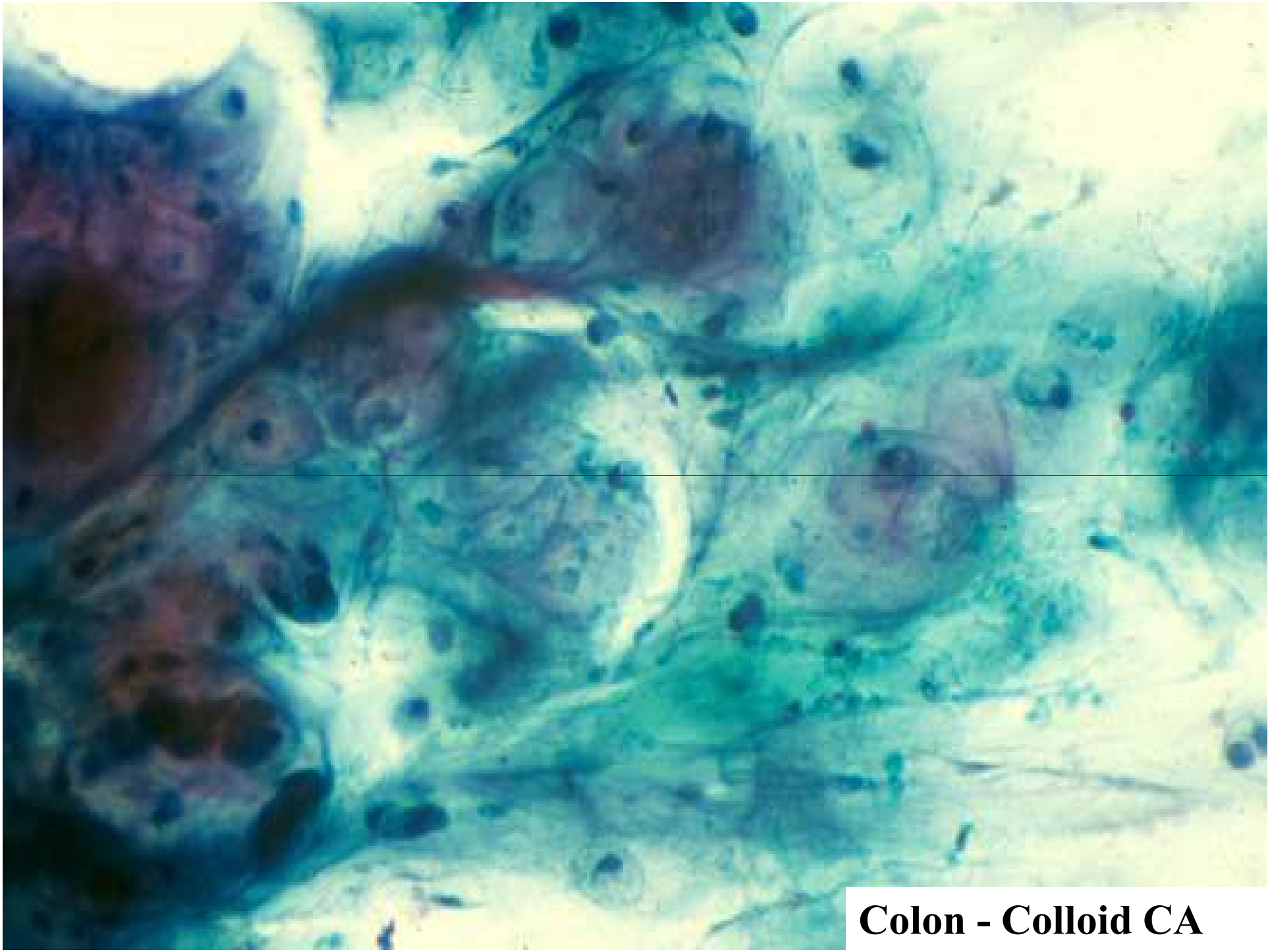



Price $3.00
THE
NEW YORKER
Feb. 8, 1999

Colloid (Mucinous) Neoplasms

- Colloid Carcinomas

  GI tract, Breast, Ovary, Pancreas
- Pseudomyxoma peritonei (appendix)
- Myxoid sarcomas
- Melanoma (Rare)



Colon - Colloid CA

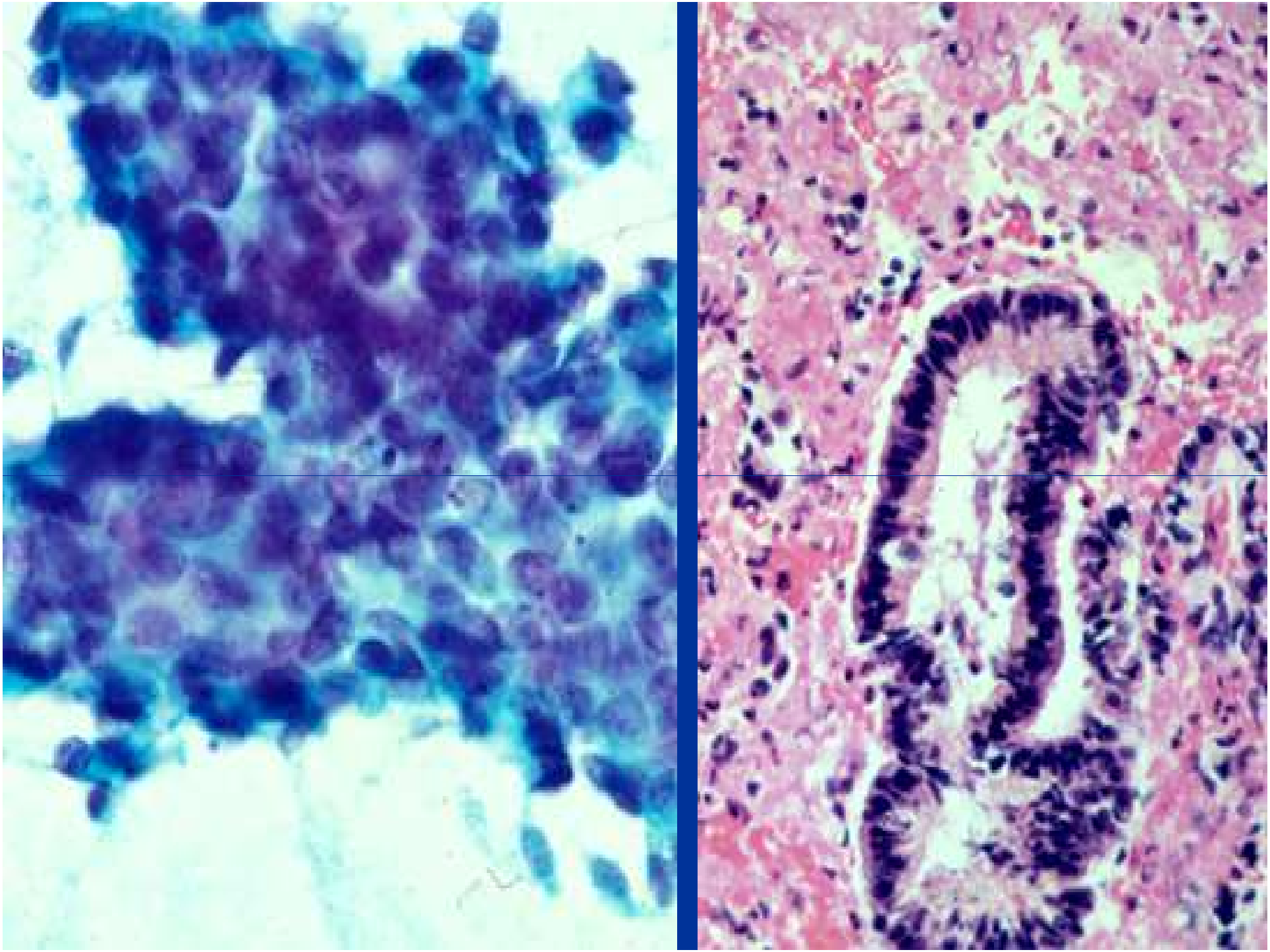
Mucin Positivity *excludes:*

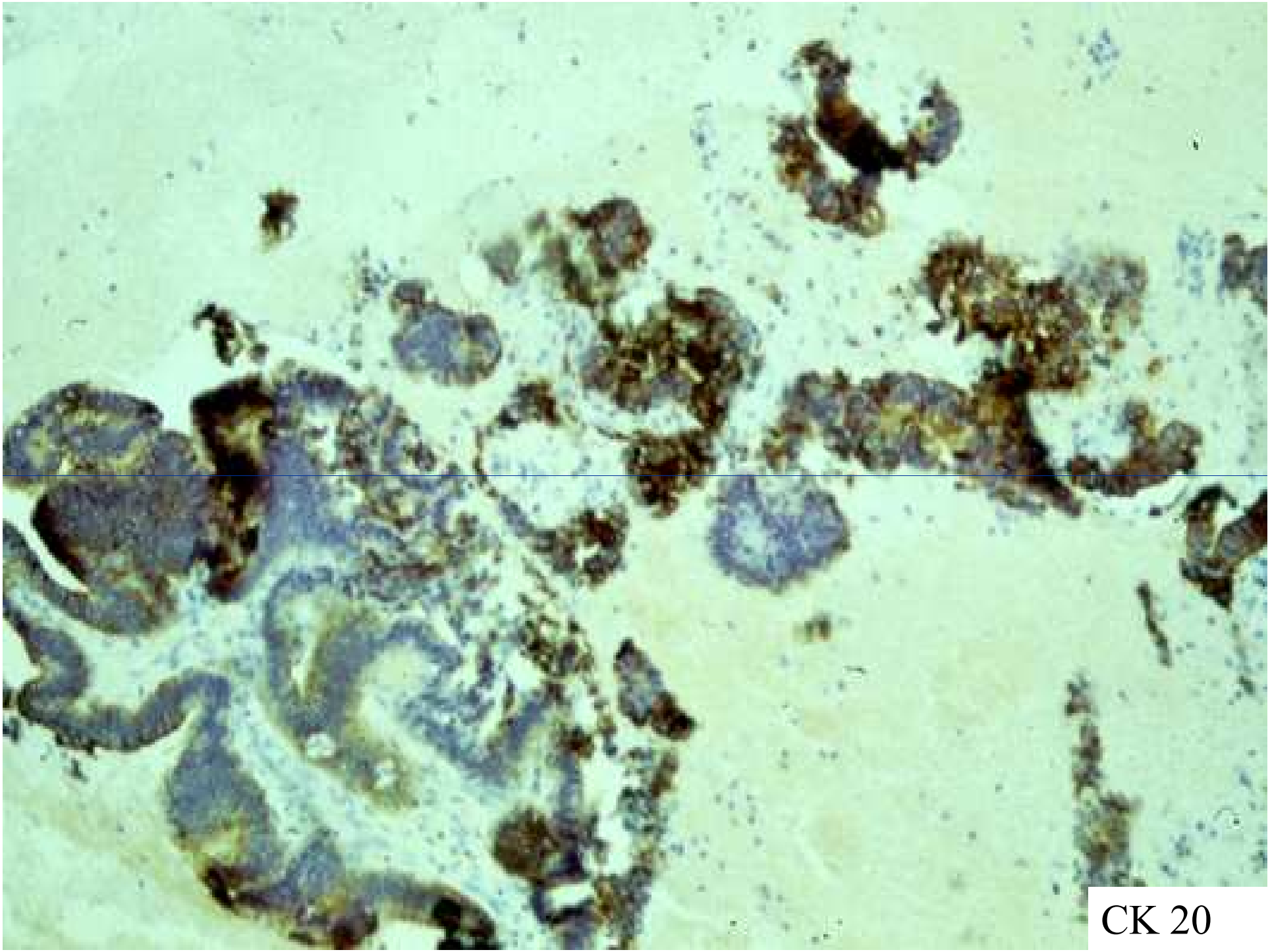
- LYMPHOMA / LEUKEMIA
- SARCOMA (except chordoma)
- MELANOMA

Modified from DeMay

Case 5

72 year old male presented with a single lung mass. FNA biopsy was performed





CK 20

Case 5

DIAGNOSIS

Metastatic colon cancer to the lung

Which Cytokeratin to use?

Complex keratin (K903, 34BE12) - Basal cell and squamous cell

CK 5/6 - Squamous cell, mesothelium, urothelium

CK 7/20 - Adeno CA of unknown primary

IHC MARKERS FOR INTESTINAL CA

- CK 7/20
- Villin - Colorectal, pancreas. Occasionally in non - GI i.e. endometrial, RCC (brush border staining)
- CDX2 - Intestinal tumors, also bladder adeno, ovarian mucinous

Strong uniform CDX-2 +/with or without villin

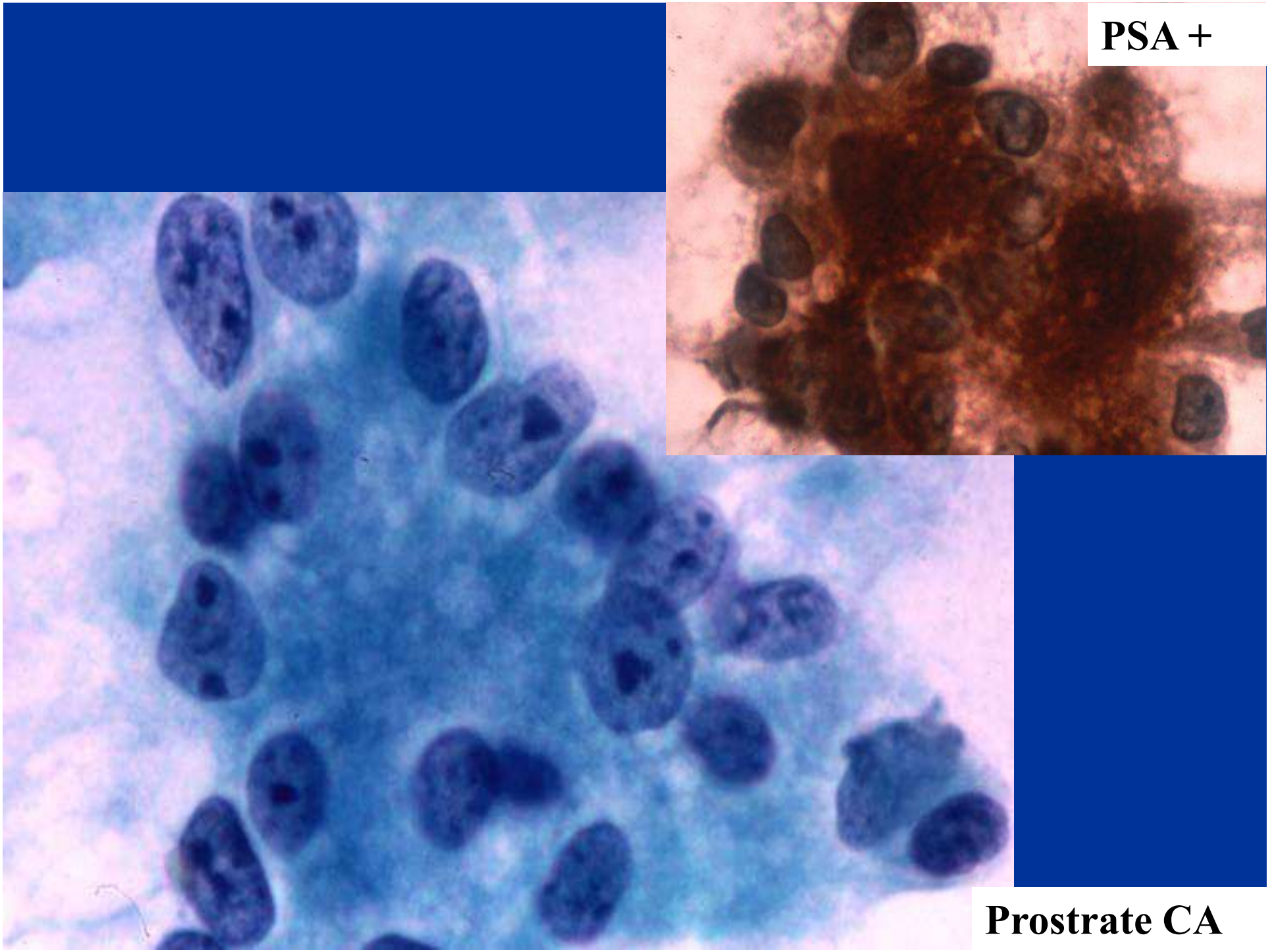
- favors colorectal

Organ-specific and Organ-associated Markers

Antibodies to:	Identifying:	Also identifies:
Prostatic specific antigen (PSA)	Prostrate Carcinoma	-----
Prostatic acid phosphatase (PAP)	Prostrate Carcinoma	Neuroendocrine carcinomas
Gross cystic disease fluid protein -15	Breast Carcinoma	Salivary gland, sweat gland tumors
Thyroglobulin	Thyroid carcinoma	-----
Thyroid transcription factor-1 (TTF-1)	Thyroid and Lung carcinomas	Rare other carcinomas
Uroplakin	Urothelial carcinomas	-----
Inhibin	Adrenal	Sex cord / stromal, granular cell
Hep PAR-1	Liver	
LCA, B&T	Lymphoid	

Modified from Pathol case Review 4(6), p254, 1999

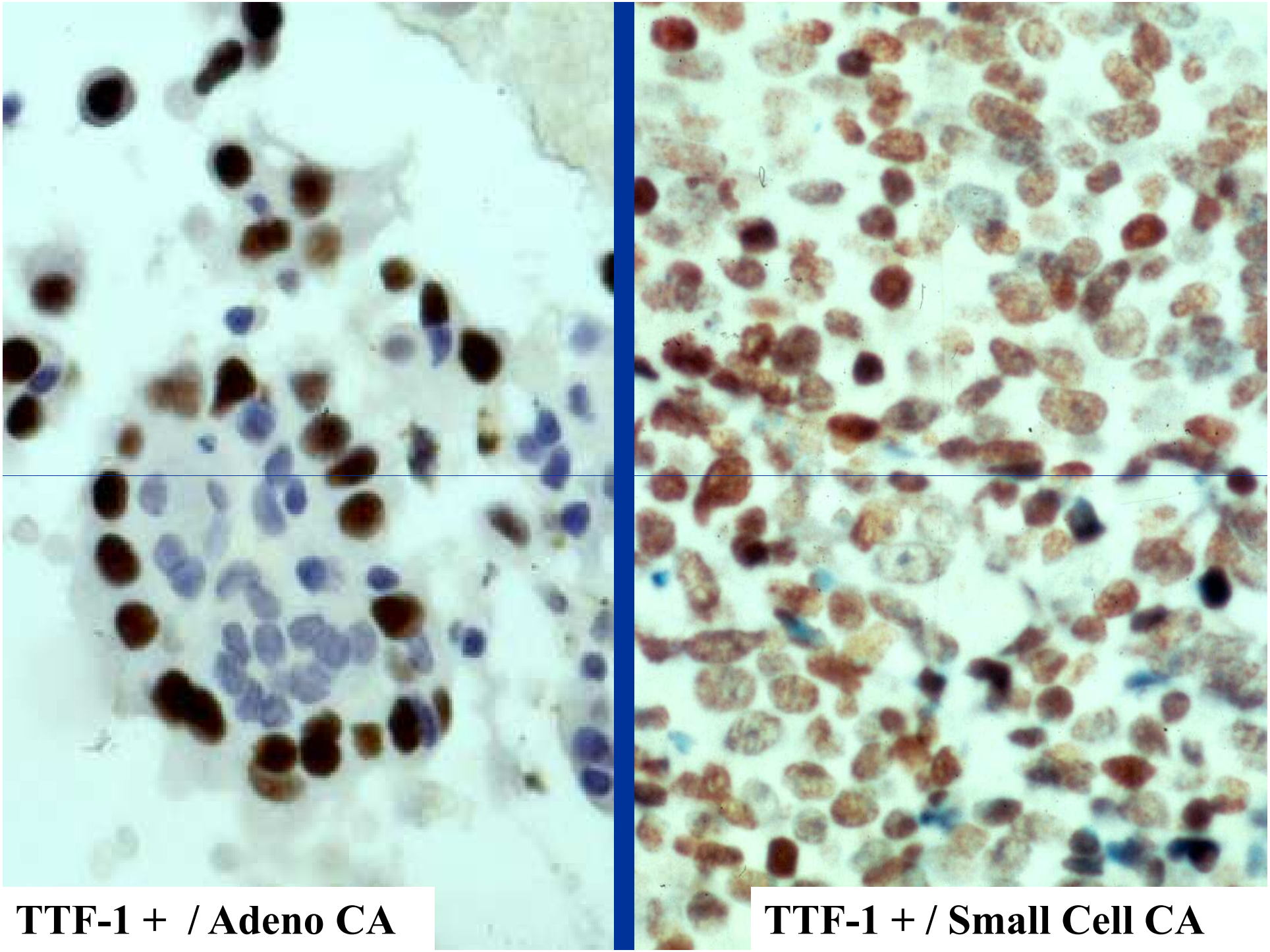
Pathol case Review 4(6), p150, 2001


PSA +
Prostrate CA

IMMUNOHISTOCHEMICAL DETECTION OF TTF-1 IN LUNG TUMORS

Adenocarcinoma	72.5%
Squamous carcinoma	10%
Large cell carcinoma	25.8%
Large cell neuoendocrine carcinoma	75.0%
Typical carcinoid	30.5%
Atypical carcinoid	100%
Small cell carcinoma	94.1%
Alveolar adenoma	100%

Ordonez, N., *Adv Anat Path* 7:124, 2000



TTF-1 + / Adeno CA

TTF-1 + / Small Cell CA

NUCLEAR TRANSCRIPTION FACTOR ANTIBODIES

- MyoD1 and Myogenin - Skeletal Muscle
- TTF-1 - Lung and Thyroid
- CDX2 – Intestinal
- Microphthalmia transcription factor (MITF)
  - Melanoma
- WT1- Serous CA, Mesothelial
- Pax8/Pax2- Mullerian, Thyroid

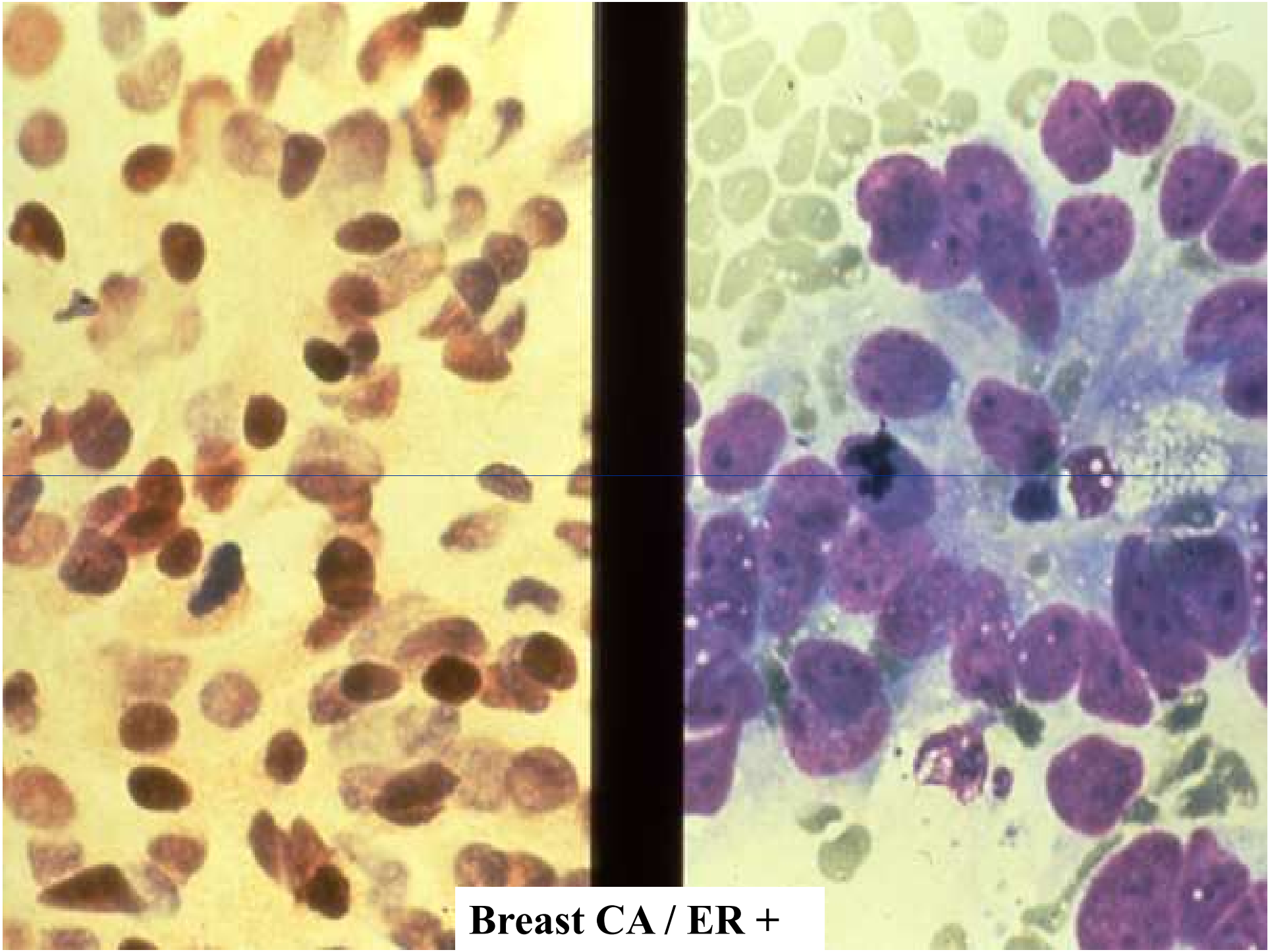
Advantages - All or none positive; no false positive, cytoplasmic positive due to biotin, etc.; not related to differentiation

Hormone Receptor Expressions in Carcinomas

ER and/or PR Positive Carcinomas (Subset)	ER and/or PR Negative Carcinomas
Breast, Ovarian, Endometrial	Lung non-small cell (antibody dependent)
Cervical	Colorectal
Skin sweat gland	Hepatocellular
Thyroid	
Neuroendocrine (e.g., carcinoid	

ER = estrogen receptors; PR = progesterone receptors

Pathol Case Review 4(6), p254, 1999



Breast CA / ER +

IHC Panel for the Workup of METS X known Primary

- Cytokeratins: CAM 5.2, CK7, CK20, PAN CK, AE1/3, CK 5/6
- EMA, CEA
- S-100, HMB-45, etc.
- LCA, etc.
- Specific-PSA, Thyroglobulin, TTF-1, GCDFP-15, inhibin, Hep par 1, CDX-2
- NE markers-NSE, Synatophysin, CD56, Chromogranin, MAP-2, etc.
- Germ Cell-CK, PLAP, Oct 3/4, CD30, C-kit
- Hormonal (ER/PR)

IHC WORKUP OF UNDIFFERENTIATED/POORLY DIFFERENTIATED MALIGNANCY

	AE-1/3	CD – 45	S-100	PLAP	*Additional markers*
Carcinoma	+	-	+ -	-	**Differential keratins, EMA**
Melanoma	-	-	+	-	**HMB 45, Melan A**
Lymphoma	-	+	-	-	**CD 20, CD 3, CD 30 etc**
Germ cell tumor	- +	-	-	+	**EMA, OCT-4, CD-30**

Clinical Patterns of Metastasis

FNA Workup of MUP
A Clinico-pathologic approach

1. Cytomorphologic features
2. Ancillary studies: IHC
3. Clinical patterns of metastases
   - Common metastatic sites
   - Uncommon metastatic sites

Metastatic Malignancies

- Determination of primary site is facilitated by familiarity with cytologic features of the malignancy and selected use of ICC
- Still, a primary site may not be determined because of non-specific cytologic & IHC features, or an atypical pattern of dissemination

Patterns of Metastases

- Usual patterns of METS to common sites : lung, lymph nodes, liver
- Cancer may occasionally metastasize to unusual sites: breast, spleen, pancreas
- This unpredictable pattern of METS may pose diagnostic problems for clinicians and pathologists → misdiagnosis as a primary neoplasm
- Familiarity with variable patterns of metastasis → a more specific diagnosis

Initial Sites of Metastasis

- Parallel natural drainage pathways of primary malignancy, i.e. related to anatomic location of tumor
- Lymphatic: regional lymph nodes
  - head & neck, cervix, melanoma
- Vascular: venous pathways
  - head & neck, bone, kidney→ lung
  - pancreas, stomach, colon → liver
  - prostate → axial skeleton via paravertebral veins

Common Sites of Metastasis

- Most common sites of metastasis:
  - Lymph nodes
  - lung
  - large bones
  - liver
- Most common primary sites of MUP:
  - Lung
  - Pancreas
  - Colon
  - Liver
  - stomach

Reyes 1998, FNA of 116 MUP

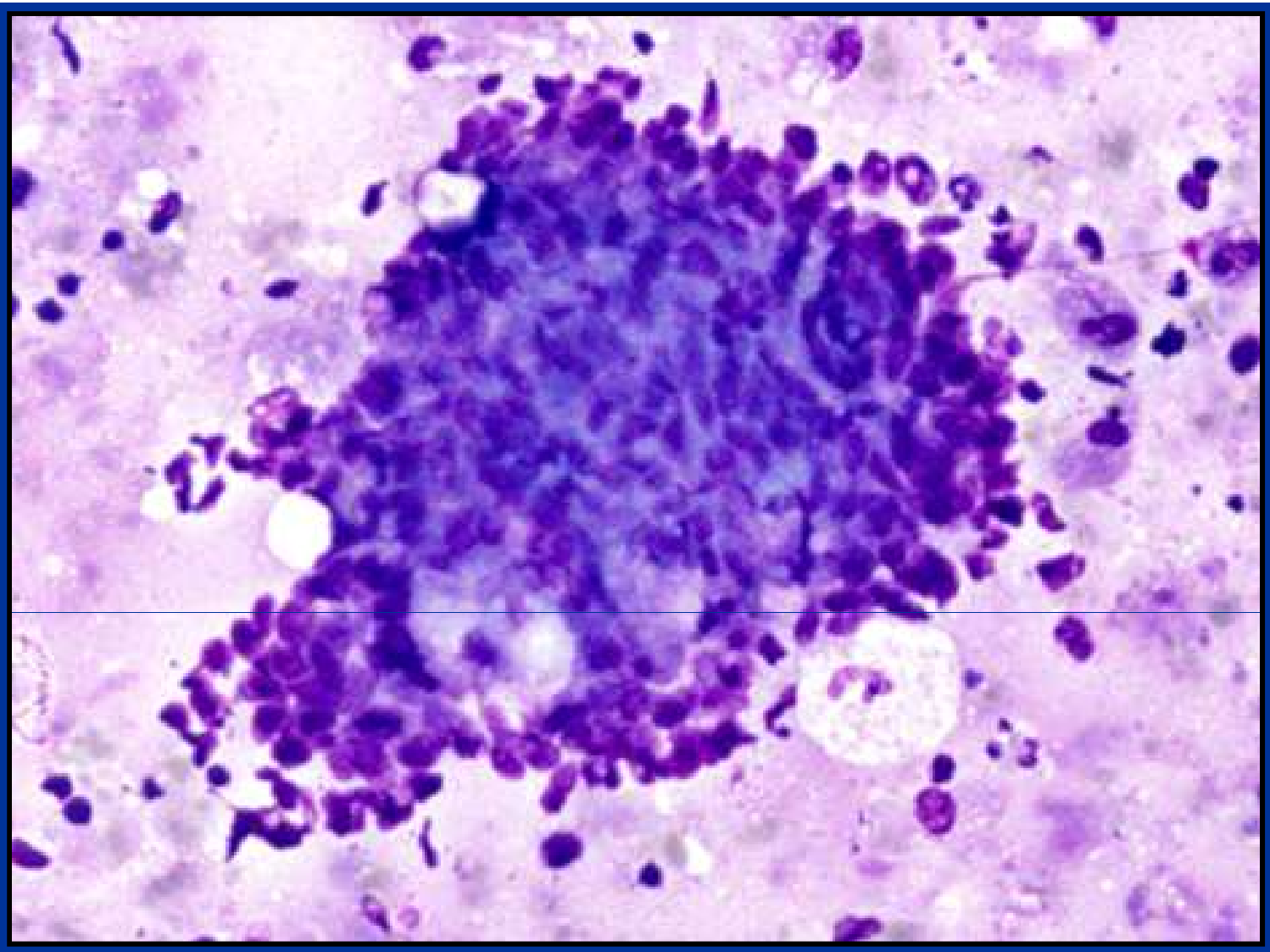
- Most common sites of metastasis
  - Lymph nodes
  - liver
- Most common primary sources
  - Lung
  - Prostate
  - Kidney
  - colon

Lymph Nodes

- Most common site for metastasis
- Diagnostic accuracy for metastatic carcinoma is 82-99%
- Knowledge of exact location of involved lymph node is of prime importance

Lymph Node Metastasis

Lymph nodes	**Common/Probable primary site or malignancy**
Cervical	Head and neck, lung, melanoma, breast
Right supraclavicular	Lung, breast, lymphoma
Left supraclavicular	Lung, breast, cervix, prostate, lymphoma
Axillary	Breast, lung, arm, regional trunk, GI tract
Inguinal	Melanoma, trunk, leg, vulva, prostate, anorectal, bladder



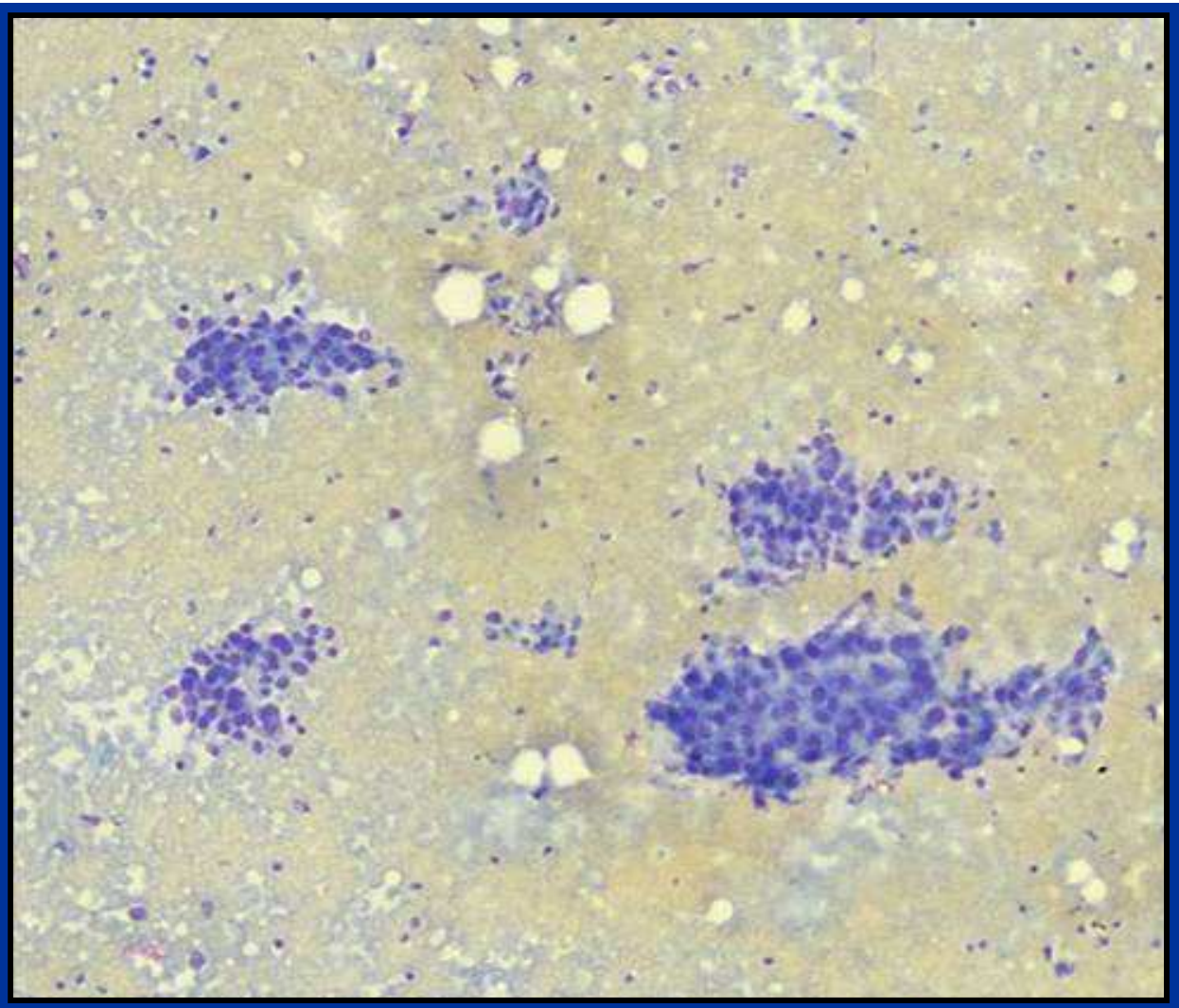
- Metastatic basaloid squamous cell carcinoma to upper cervical lymph node
- Hypopharyngeal primary was found

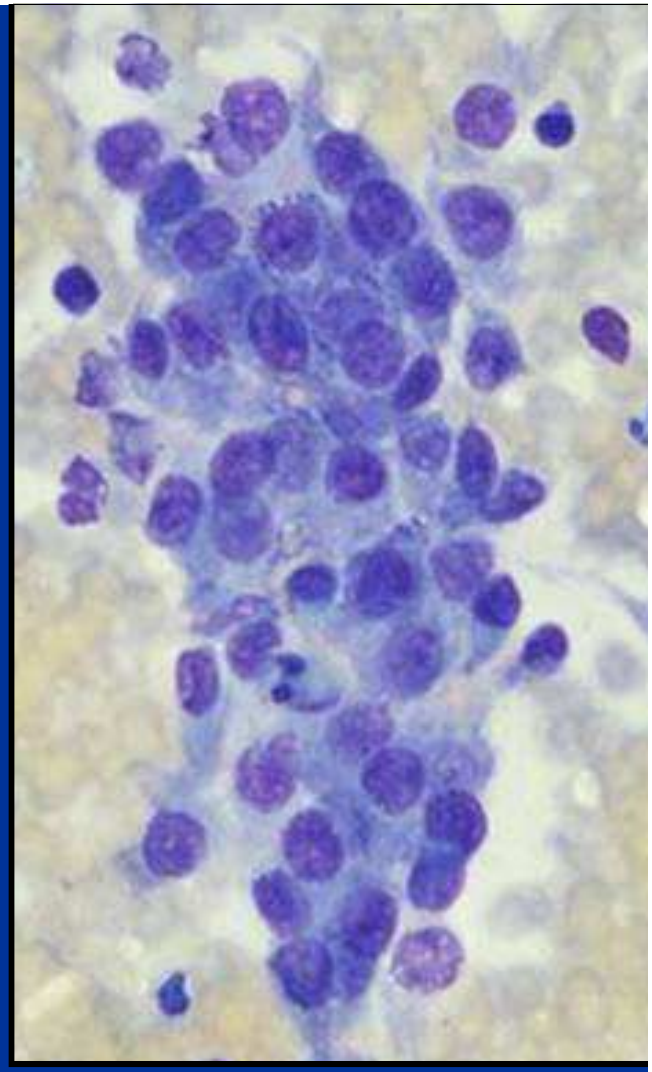
METS to Cervical Lymph Nodes

- Head & neck squamous CA , melanoma : most common
- Adenocarcinoma
  - Primaries arising in supra-clavicular organs
    - Thyroid
    - Salivary glands
  - Primaries arising in infra-clavicular organs
    - Lung
    - GI tract
    - Breast
    - Ovary
    - Prostate

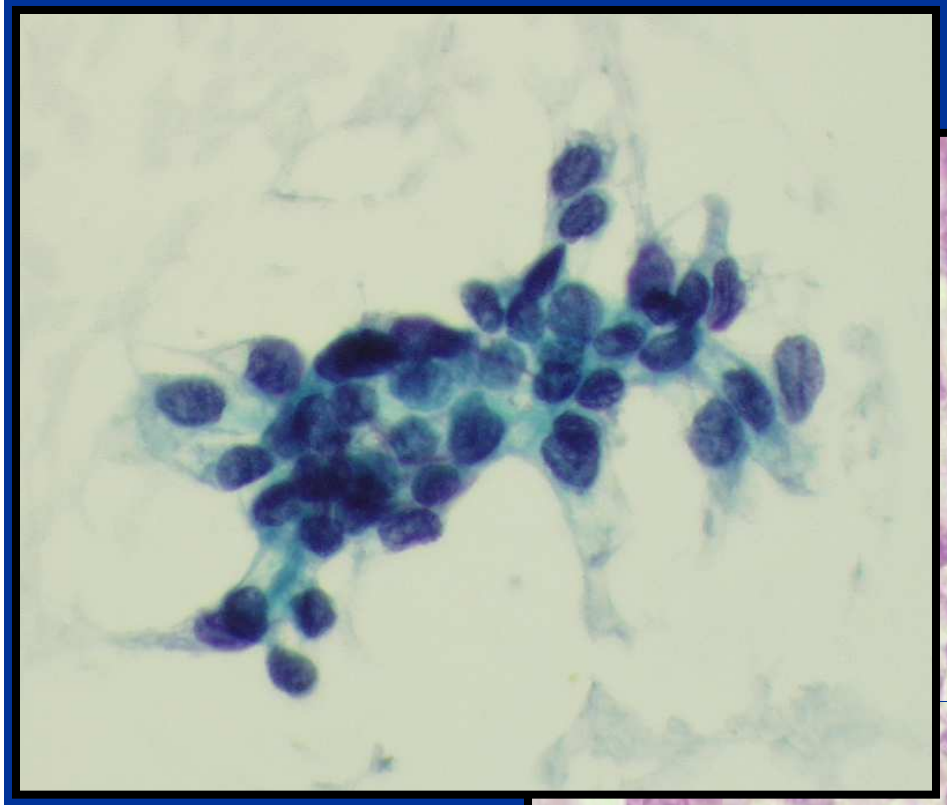
Supraclavicular Lymph Nodes

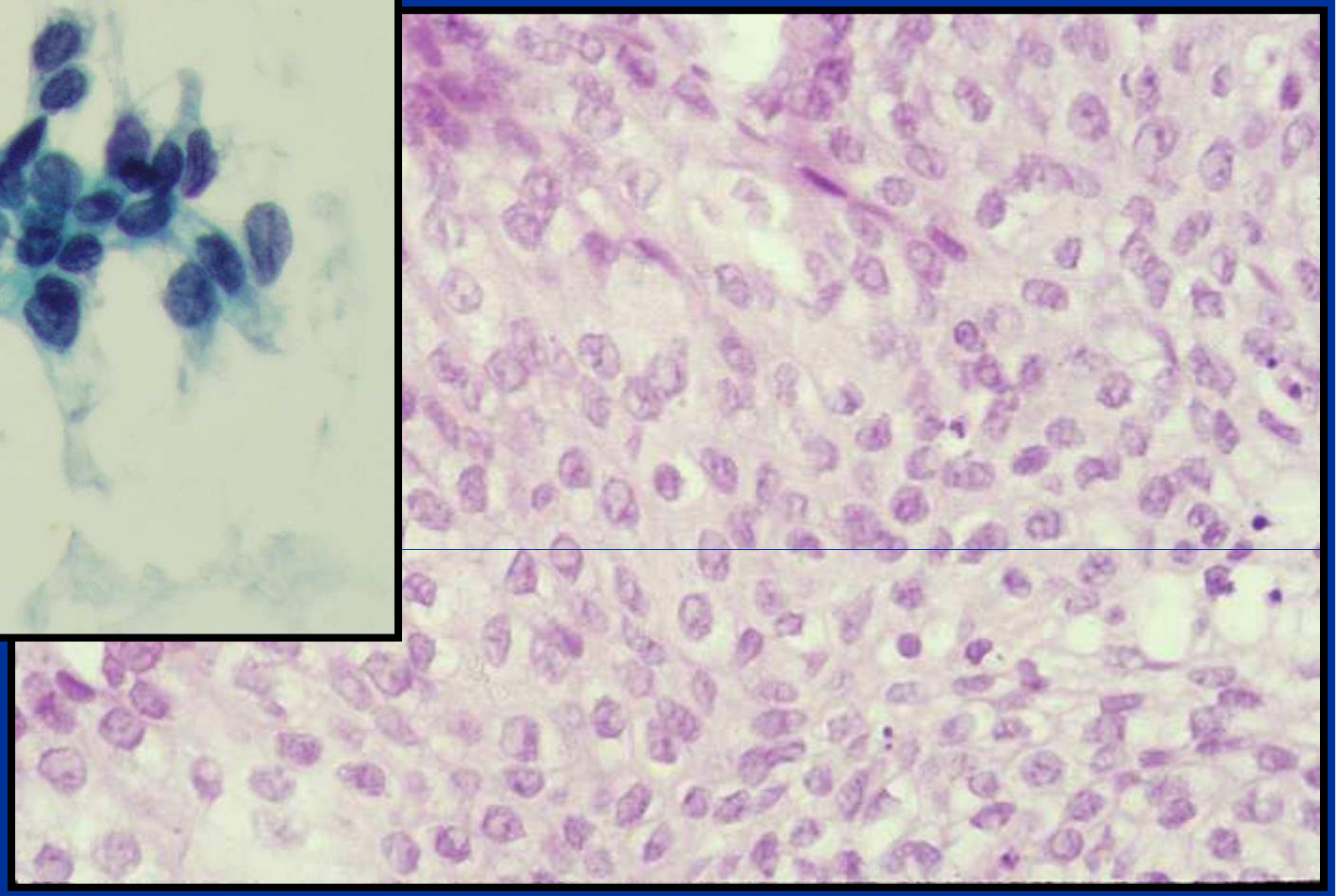
- Primary sites involving left SCLN *(Virchow's Node)* are different from those involving right SCLN
- *Cervin et al 1995,* FNA of 96 SCLN
  - Pelvic (16/19) & abdominal (6/6) malignancies → LSCLN
  - Thorax, breast, head/neck → no difference in metastatic pattern to LSCLN or RSCLN
  - Most common primaries: lung/breast > pelvis/testis > abdomen



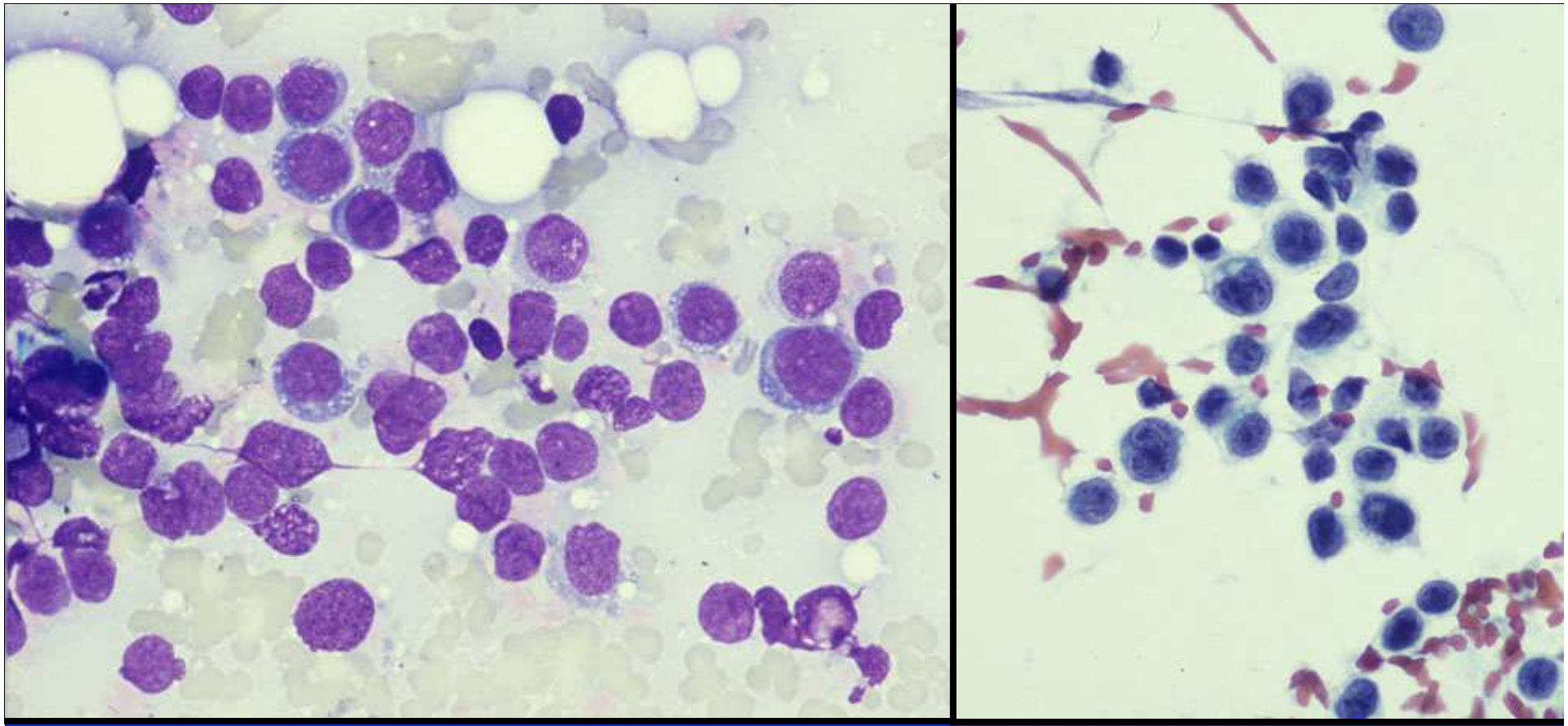


Case 7. FNA biopsy of left supraclavicular lymph node. The patient is a 65 year old man with a remote previous history of malignancy



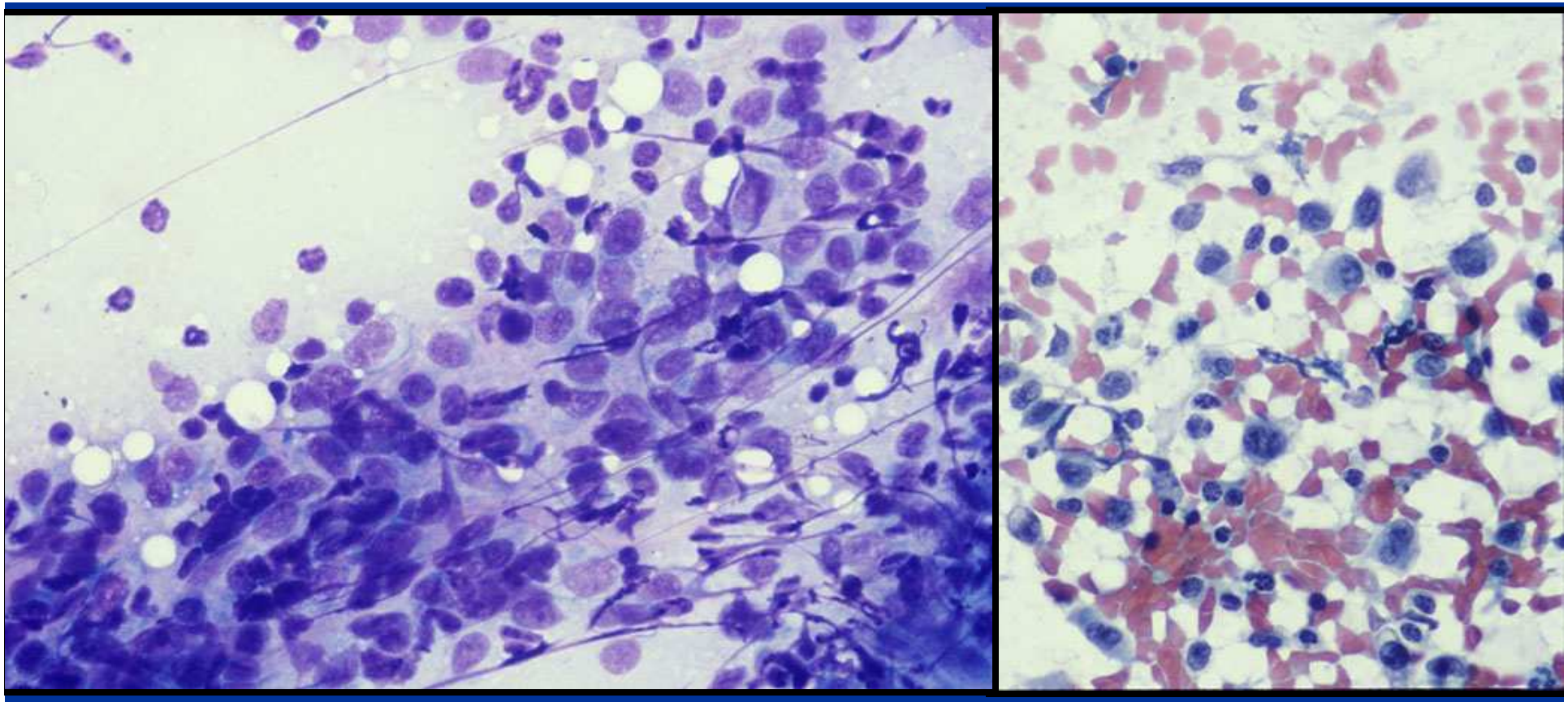


Diagnosis: Metastatic urothelial carcinoma. The patient had a previous history of bladder CA



- PD carcinoma may mimic lymphoma
- Diff Dx: large cell lymphoma, neuroendocrine CA, melanoma

Dx: Metastatic large cell CA, lung 1º, involving cervical lymph node

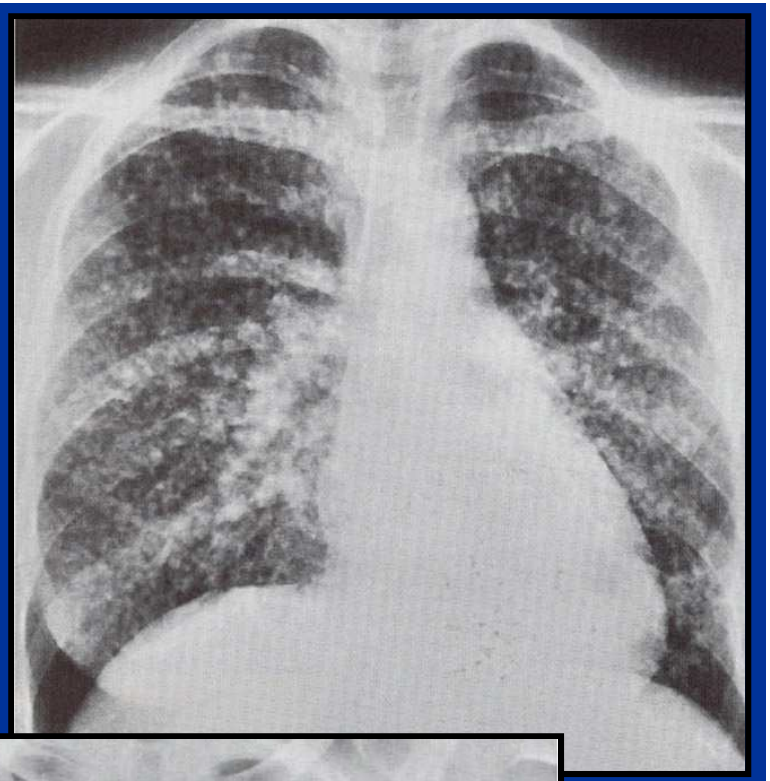


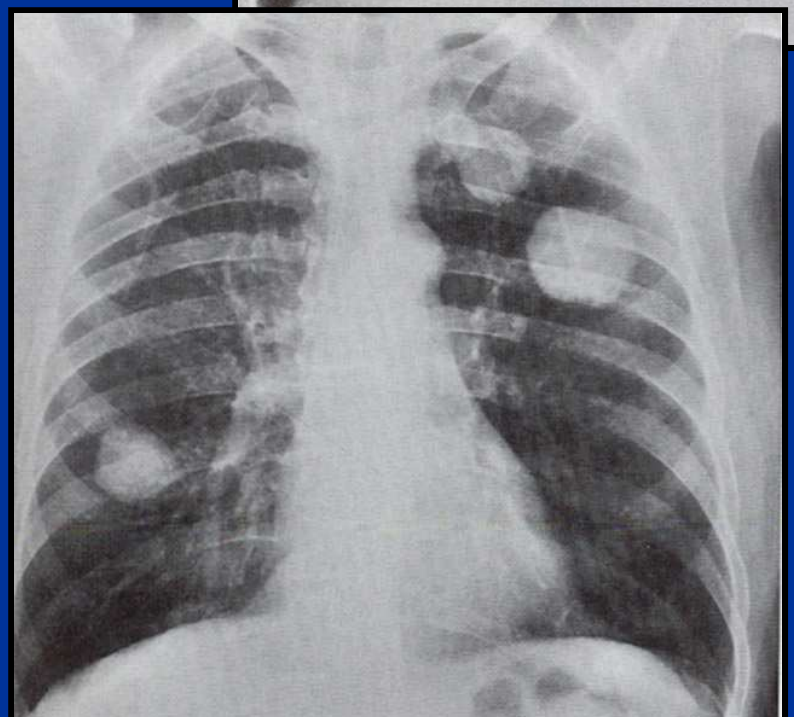
- Lymphoma may mimic carcinoma

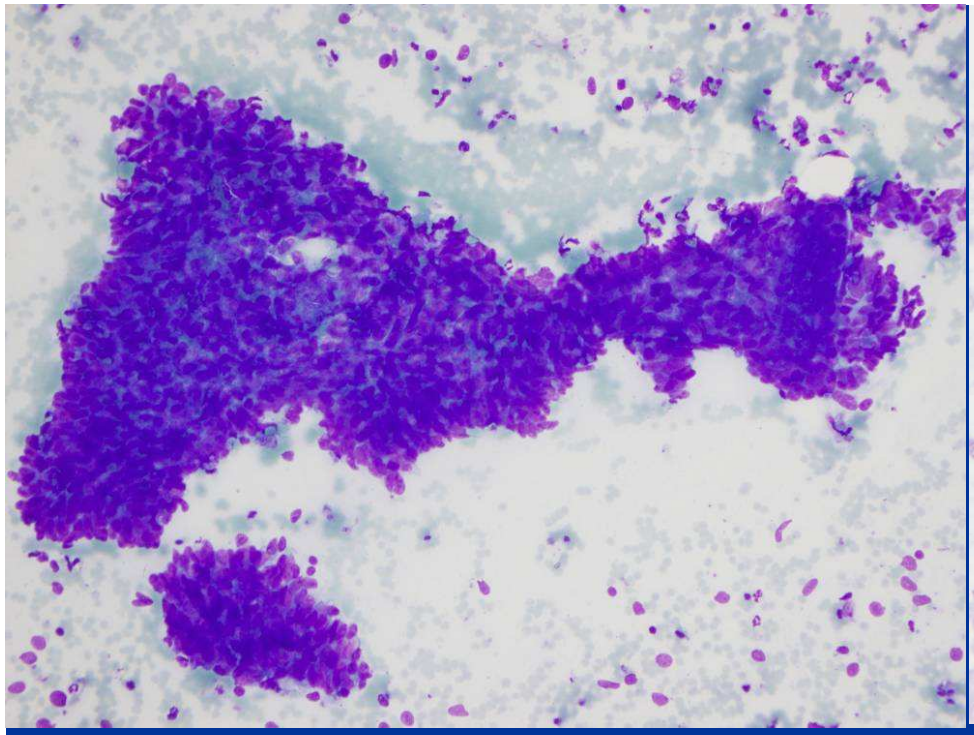
DX: Anaplastic large cell lymphoma (Ki-1), involving RSCLN

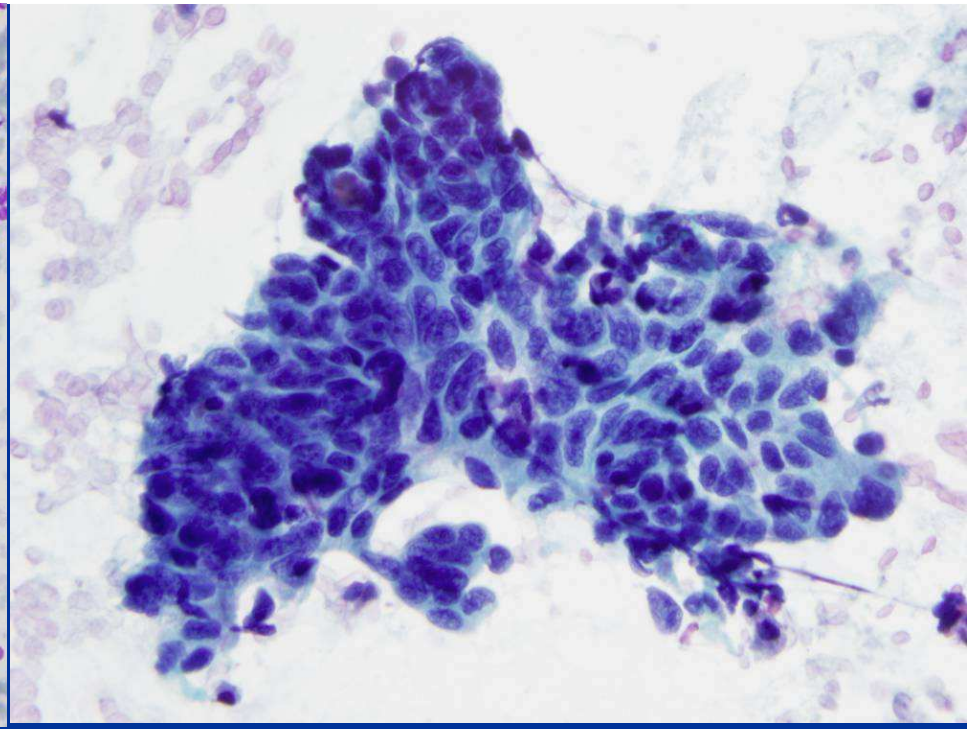
Lung Metastases

- Breast, GIT- common
- Any malignancy →lung
- Multiple nodules, most commonly
  - *Miliary*:
    - Melanoma, kidney, ovary, thyroid medullary CA
  - *Cannon ball*:
    - Sarcoma, kidney, melanoma, colorectal CA



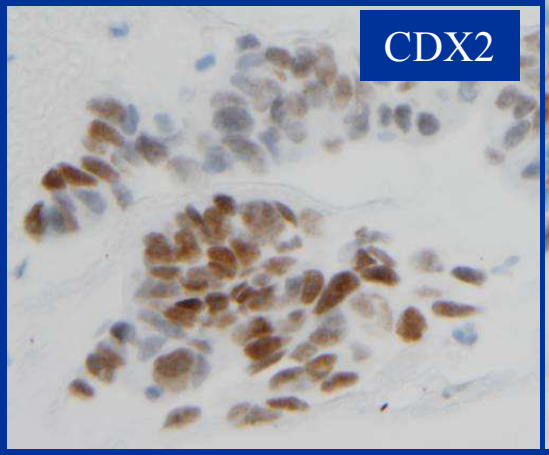


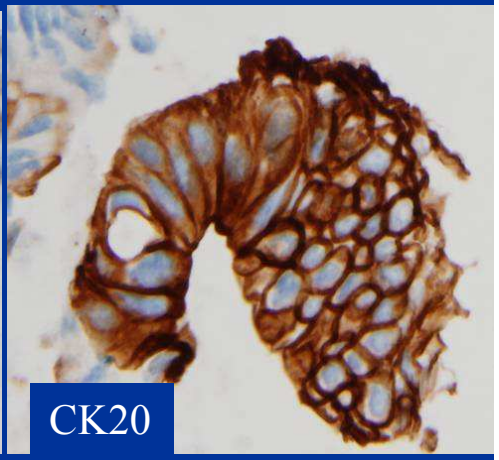




Multiple lung nodules (cannon ball) in 49 yr old woman.
No previous malig.

- CK7-, CK20+
- CDX2+, TTF1-

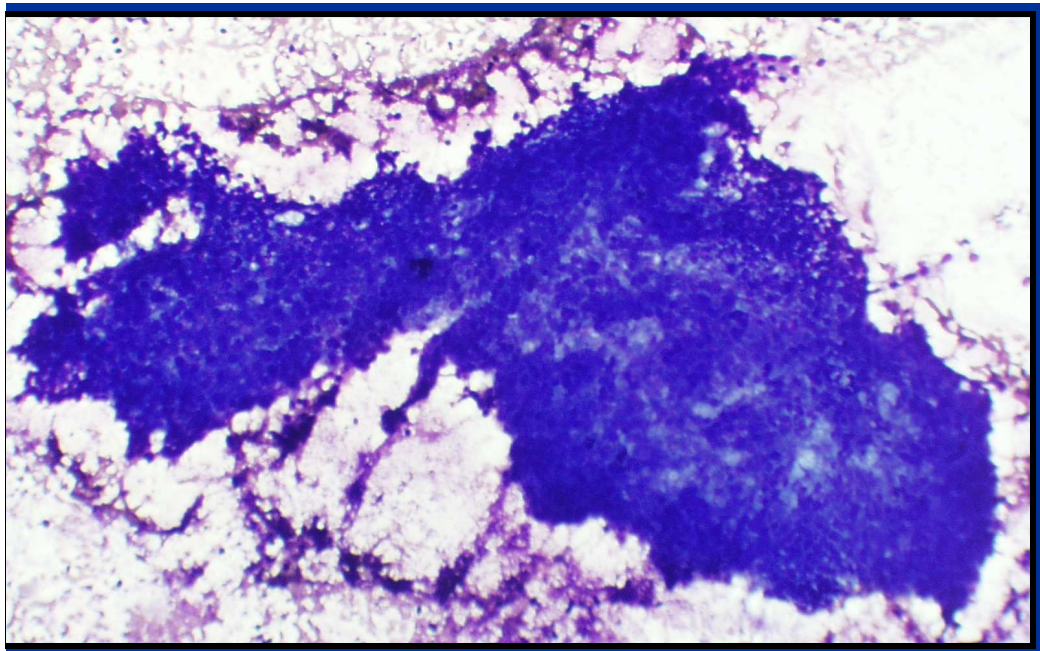


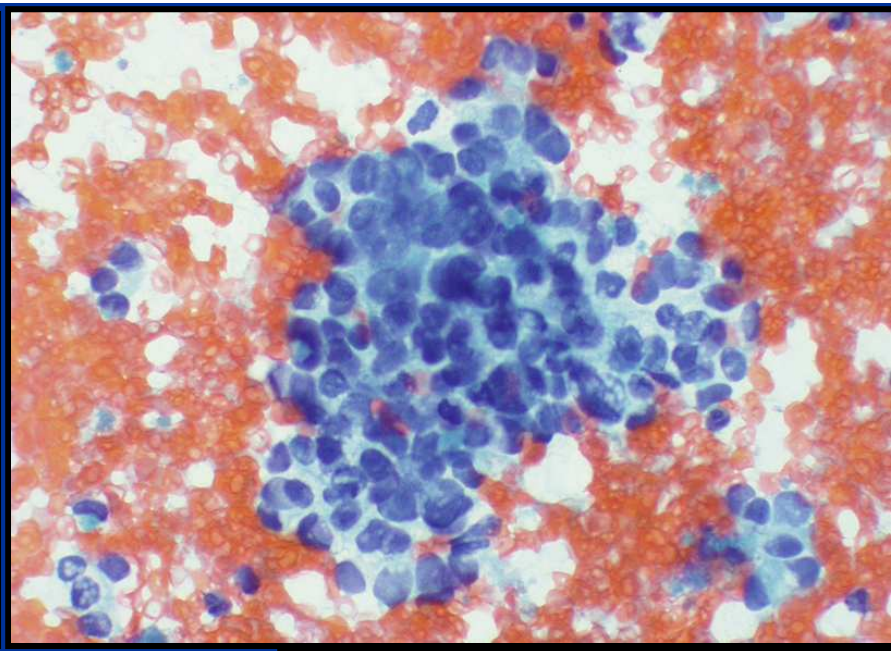


DX: Metastatic adeno CA c/w colon 1°

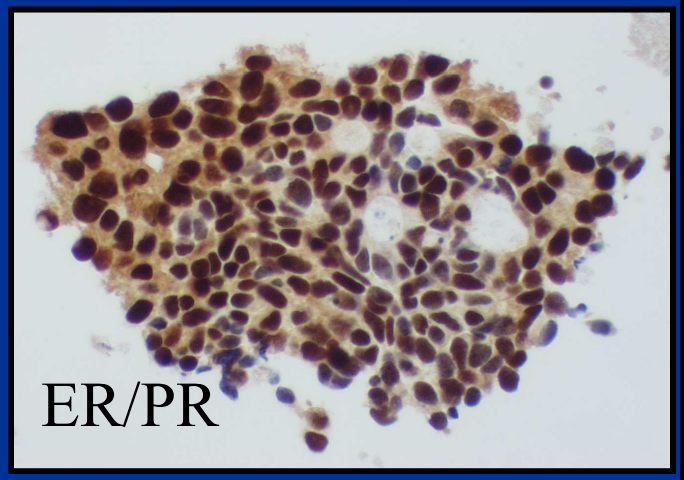
Lung Metastases (cont.)

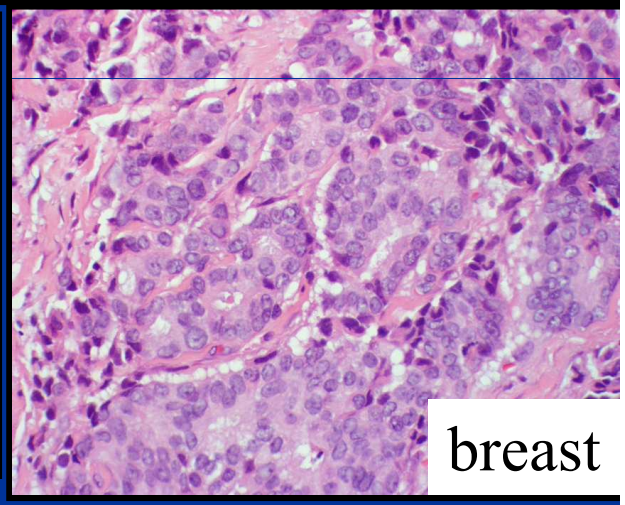
- Diffuse infiltrate or solitary coin lesion (more problematic) → rule out primary lung carcinoma
- Diffuse (6-8 % of pulmonary mets):
  - Lung, breast, GI tract, pancreas
- Solitary MET (3-9 % of all solitary pulmonary nodules):
  - Melanoma, breast, colon, kidney, sarcoma, non-seminomatous GCT
- FNA sensitivity =89%, specificity =96%





- *Solitary lung mass, 68y F*
- *Hx breast ca X 1 month, SBR I, 0/18 nodes*

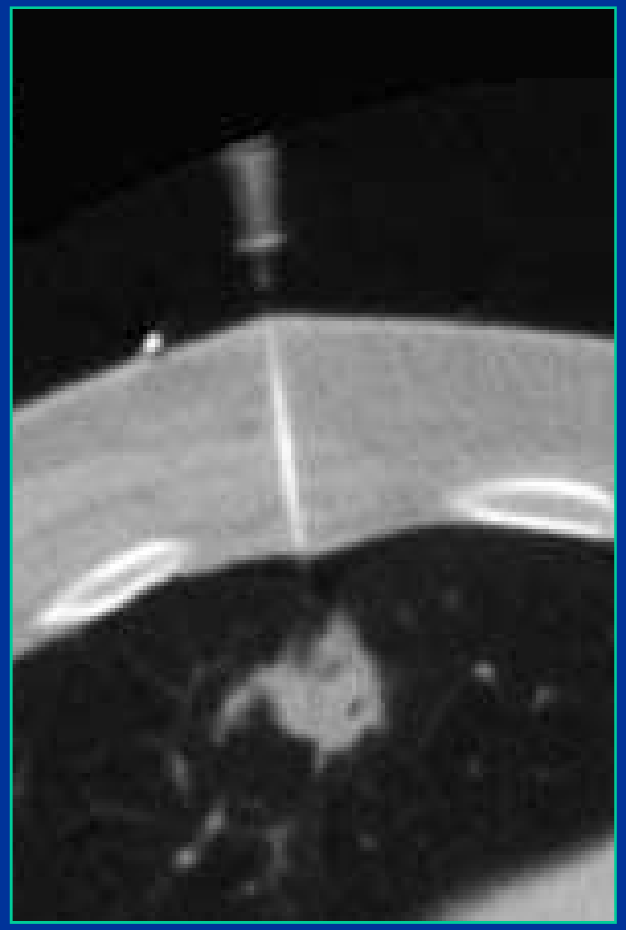




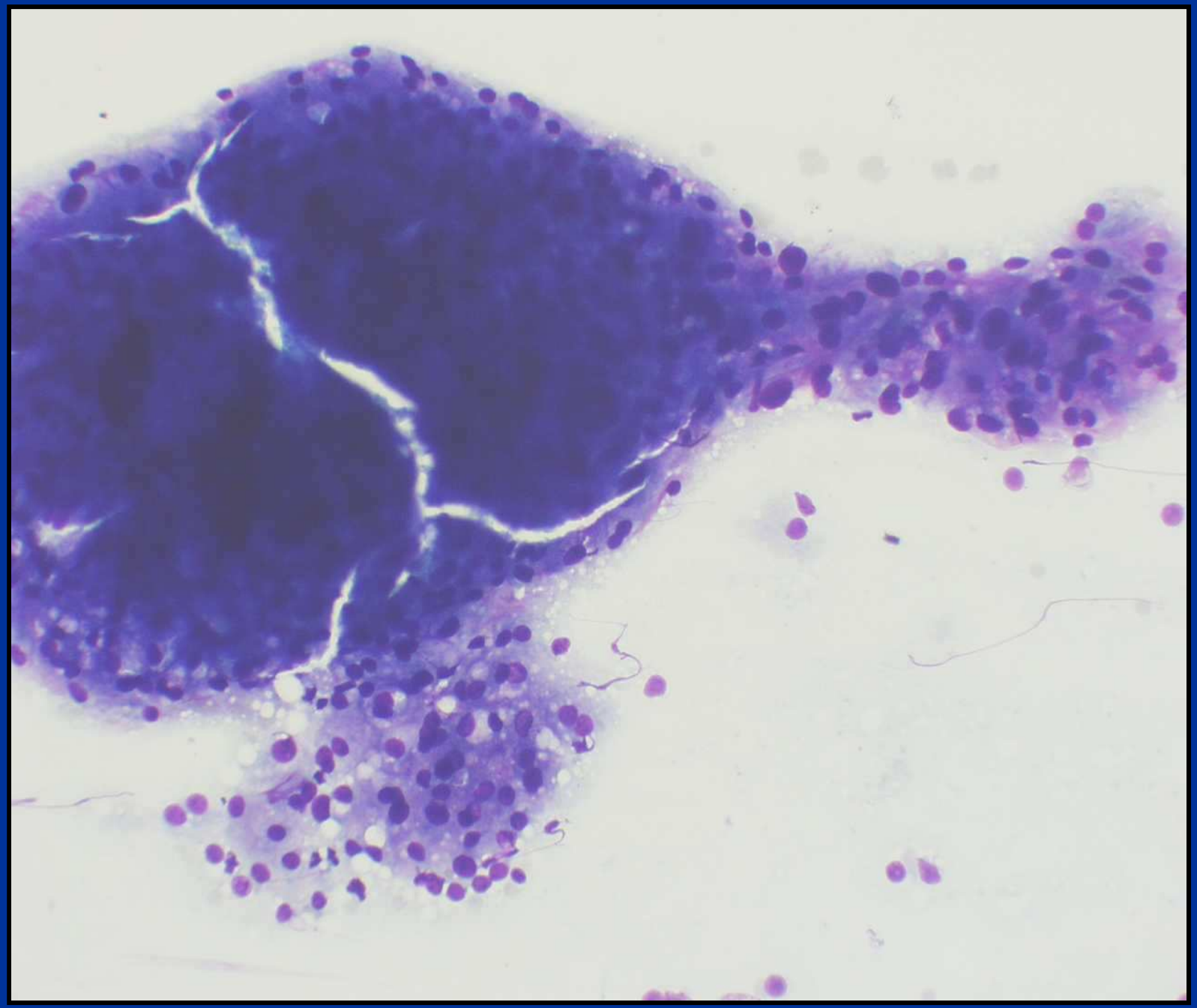
- IHC: CK 7+, CK 20-, TTF1-, ER+, PR+

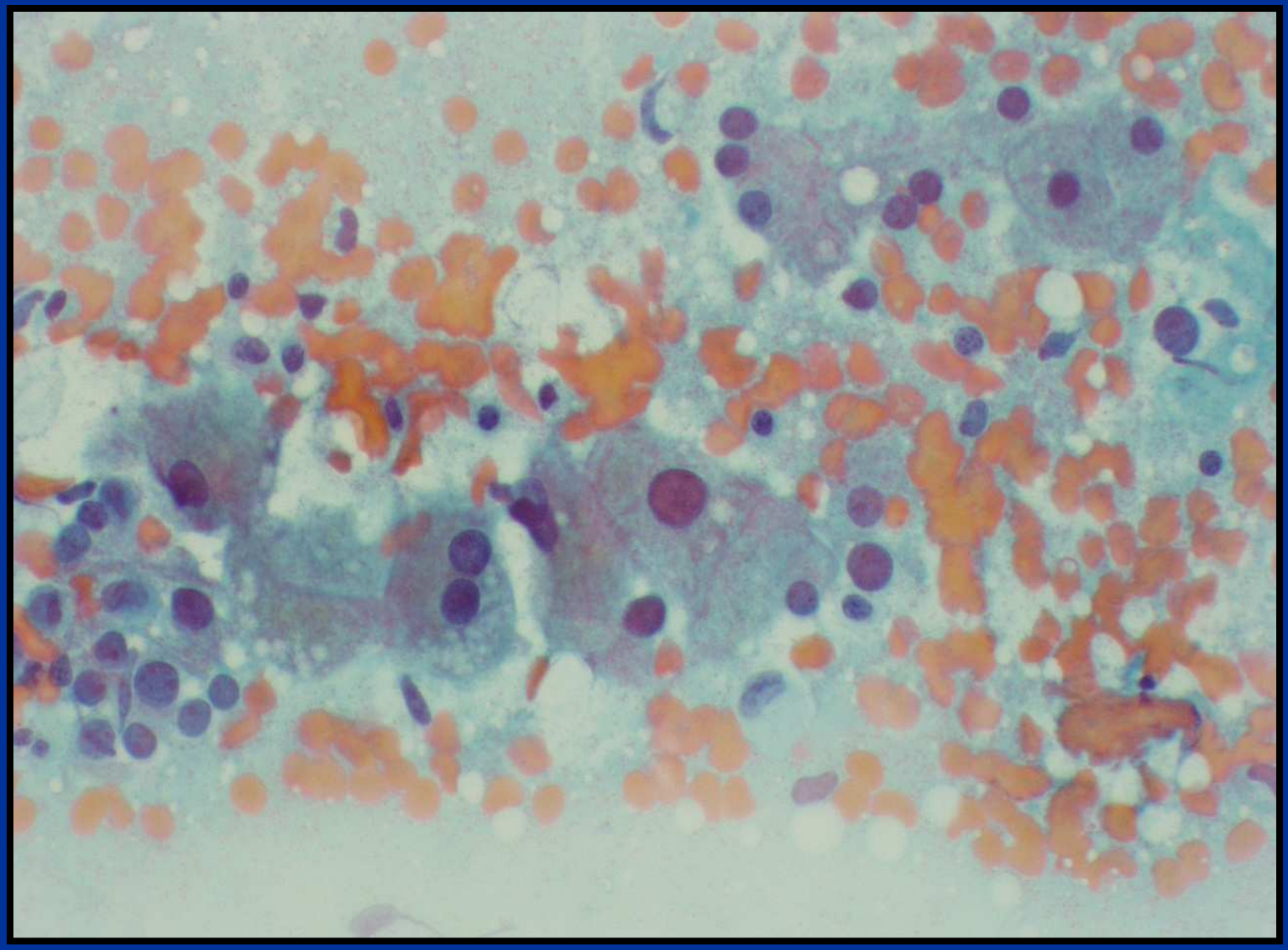
Diagnosis: Metastatic breast ca

Lung



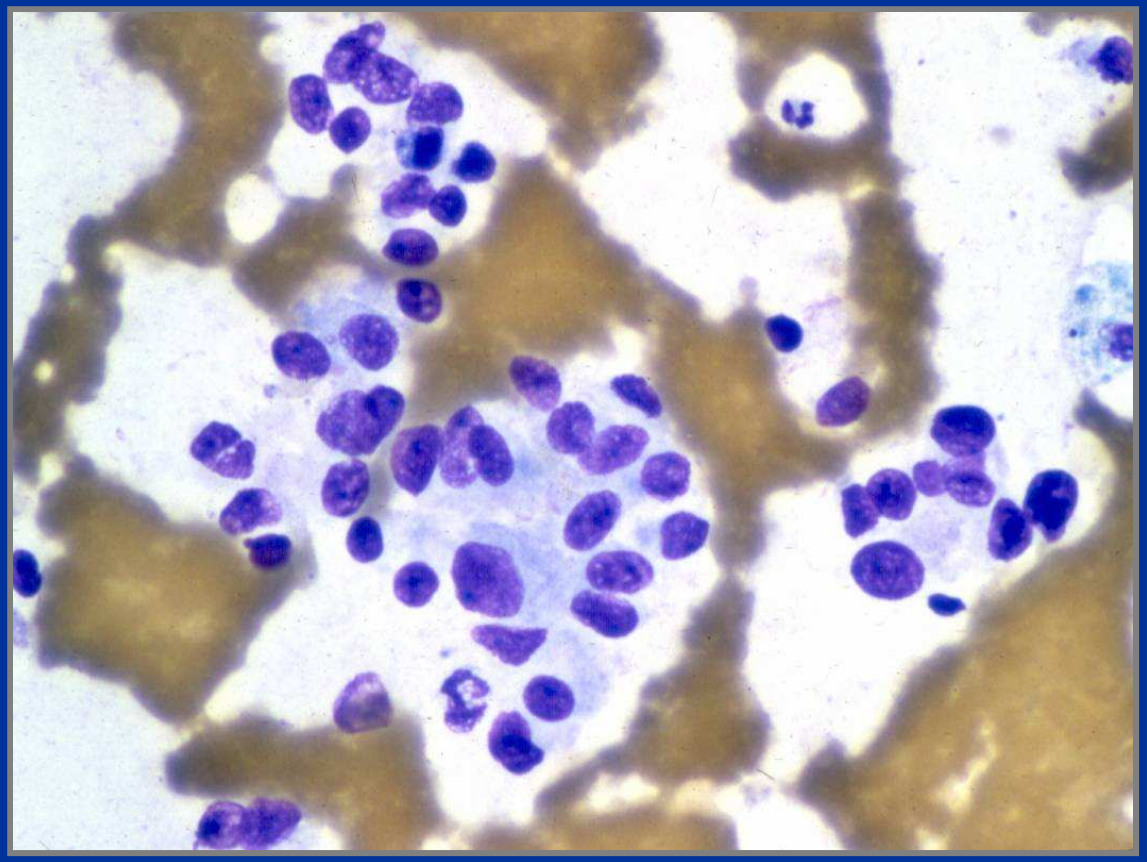
53 year old male presented with a solitary 3 cm lung mass. Patient also had an indistinct kindey mass

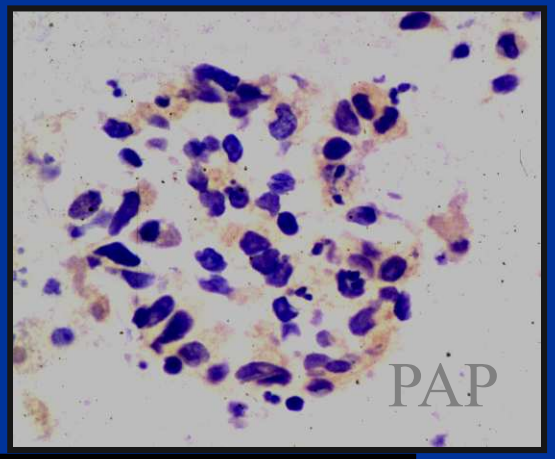


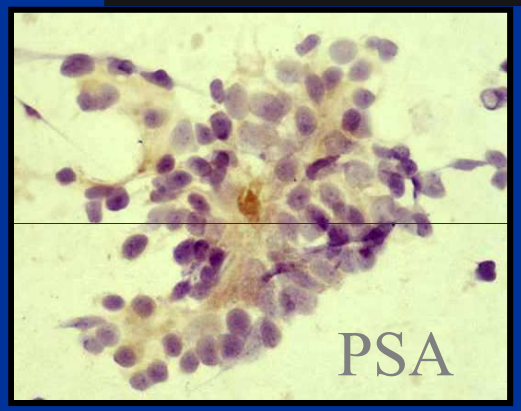


- FNA of right lower lobe lung masses may also inadvertently sample benign liver tissue

Lung







- Multiple lung nodules, 76 y M
- No previous hx of malignancy

5-10% of PD prostate CA either PSA- or PAP- (best to use both)

Unusual Sites of Metastasis

- Include breast, thyroid, pancreas, kidney, small bones, eye, spleen
- Uncommonly encountered
- May pose diagnostic difficulties and lead to confusion with primary neoplasms arising in these sites

Mechanisms of Metastasis to Unusual Sites

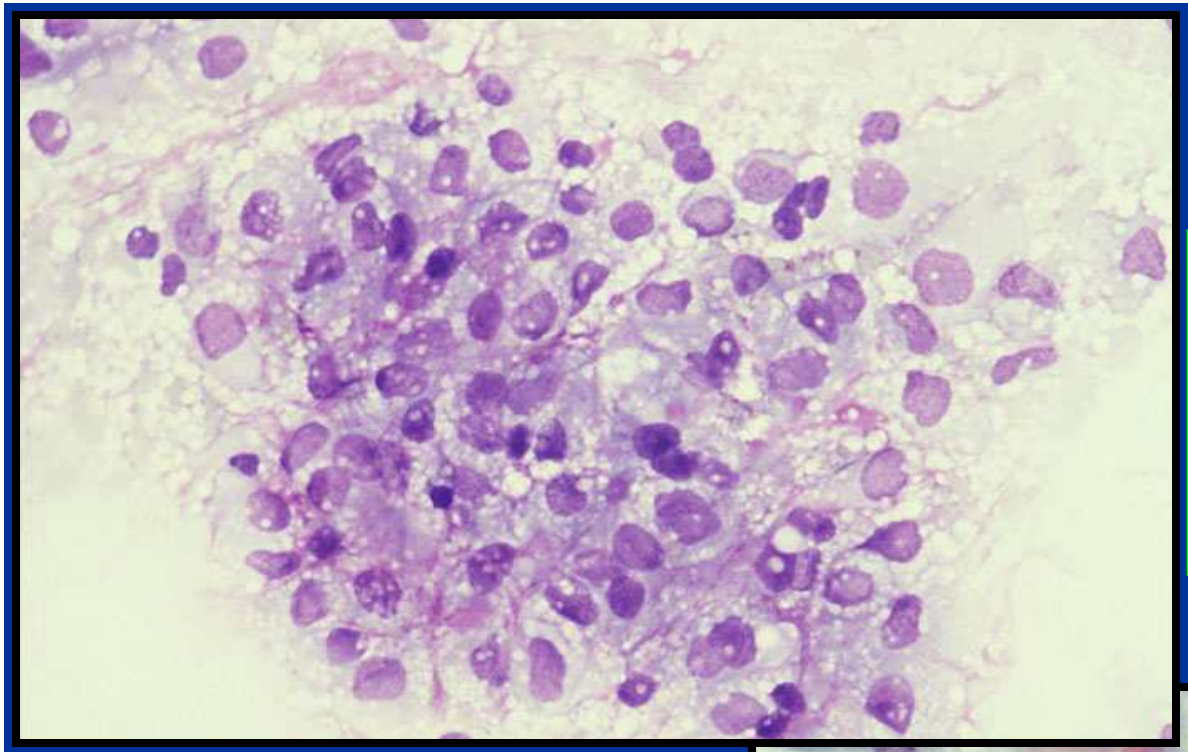
- Initial sites of metastasis → lymph nodes or venous (lung, liver)
- Subsequent (2°) widespread dissemination from initial metastatic site via arterial system →brain, endocrine glands, small bones, spleen

METS to Thyroid

- Unusual site of involvement in clinical practice; although autopsy series report 2-26% of patients with malignancy
- Solitary mass or multiple small nodules
- Direct extension – head & neck squamous cell CA, adenoid cystic CA
- Kidney > colon, lung, breast > melanoma

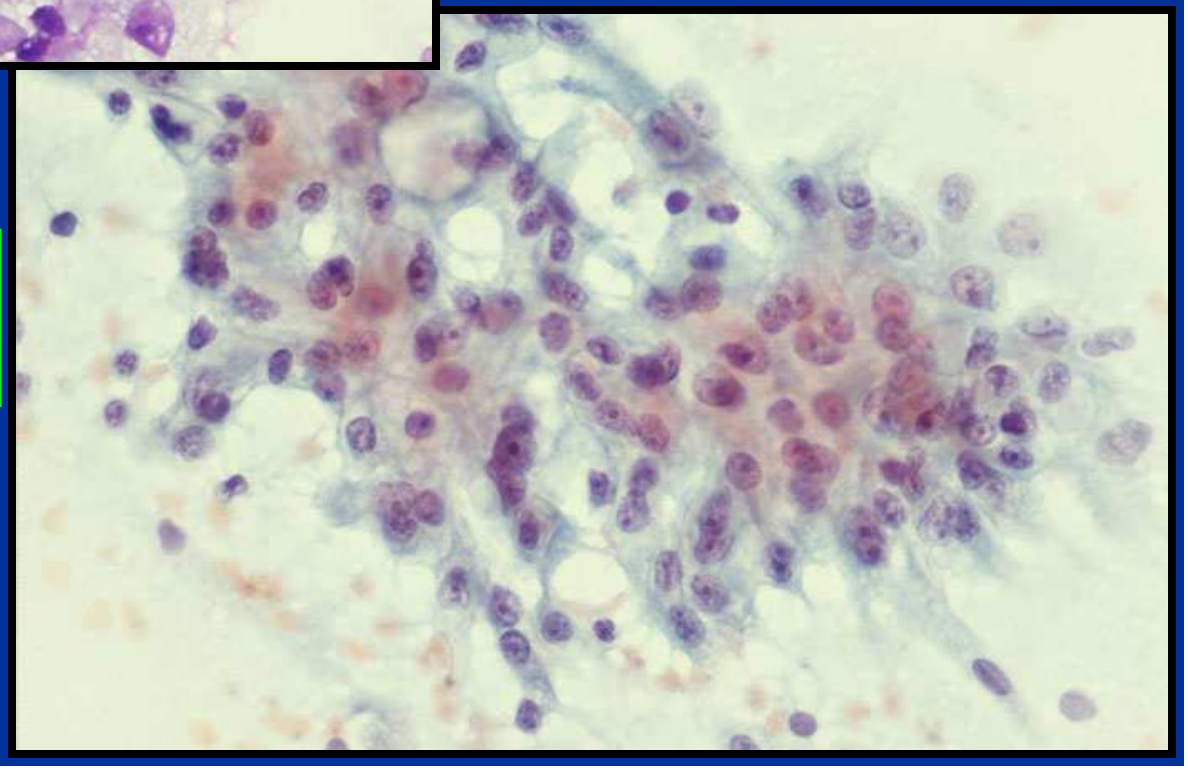
METS to Thyroid (2)

- Alien cytology
- Differential diagnosis:
  - Renal CC, clear cell type vs. thyroid CA with clear cells
  - RCC, granular type vs. Hurthle cell neoplasm
    - *RCA, TTF-1, thyroglobulin*
  - Plasmacytoma + amyloid vs. Medullary CA *(EMA, kappa/lambda, Calcitonin, CEA)*
- Dx of metastasis may prevent inappropriate thyroidectomy



FNA right thyroid nodule, 76 year old female.

Patient had previous Hx of malignancy X 15 yrs



•Diagnosis: Metastatic Renal cell CA

Summary
Cytopathologic Workup of MUP

- Clinico-pathologic approach
  1. Cytomorphologic patterns
     - Cell lineage: adenoca, squamous, etc.
     - Cytomorphologic classification: small cell, large cell, etc.
  2. Ancillary studies – IHC
  3. Clinical patterns of metastasis
     - Common metastatic sites
     - Uncommon metastatic sites

Gene Expression Profiling in MUP

- Confirm existing suspicions or provide new info?
  - High agreement with already available CP data
    - ? superiority to IHC + clinical info in unresolved cases: *not helpful (Personal experience w AviaraDx)*
    - Cost: $ 3,350 - 3,750
- Prospective studies are needed to assess:
  - Effect on patient outcome
  - Which profiling methodology /gene panel is best?
- IHC remains crucial component of workup. GEP may play supportive role in unresolved cases.

Promising future

General Principles Considered in Analysis of Suspected Metastasis

- Familiar with cytologic features of common malignancies originating in a primary site
- Unusual/alien cytology for a primary site
- Knowledge of common and unusual metastatic patterns of malignancies & possible diagnostic pitfalls
- Produce a potential short list of possible primary sites
- Cytomorphology and IHC can then help arrive at a more specific diagnosis

General Principles Considered in Analysis of Suspected Metastasis (2)

- Clinical history of previous malignancy
- Review of previous pathology material
- Tissue confirmation in unresolved cases before definitive treatment