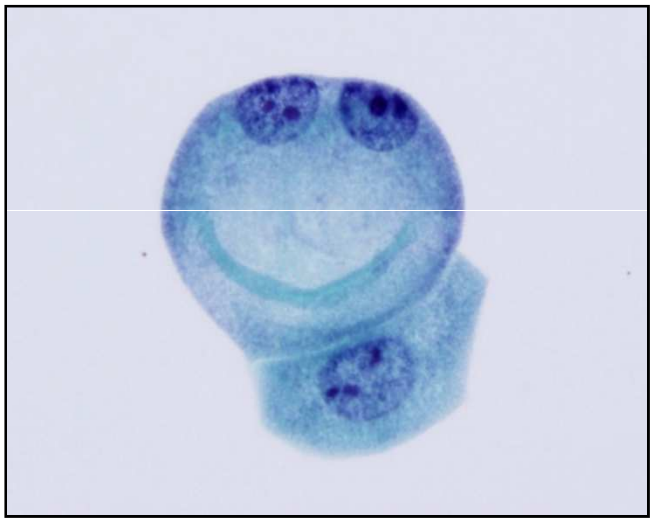
Understanding Genitourinary System Cytology



Part I: Urine Cytology Made Easy

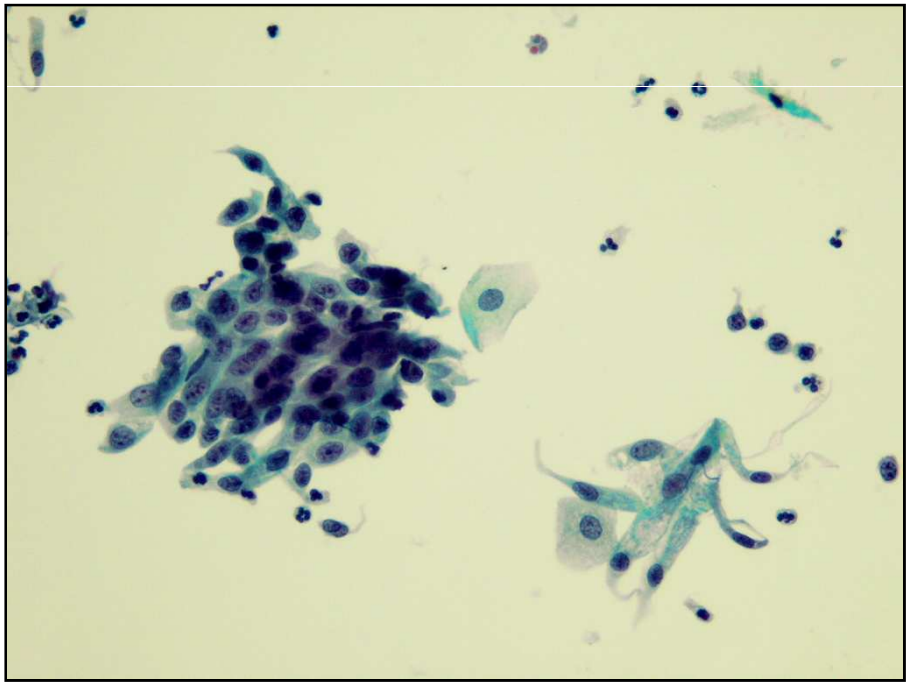
Eva M. Wojcik, MD
Professor of Pathology and Urology
Loyola University Medical Center
Chicago, IL

OBJECTIVES

- Recognize the pitfalls and limitations of routine urine cytology
- Understand the limitations of cytologic-histologic correlation
- Recognize the importance of correlating results with clinical and cystoscopic findings
- Evaluate the current role of ancillary techniques in the diagnosis of urothelial carcinoma

Case 1

- Voided urine from a 41 year old female who presented with a hematuria.

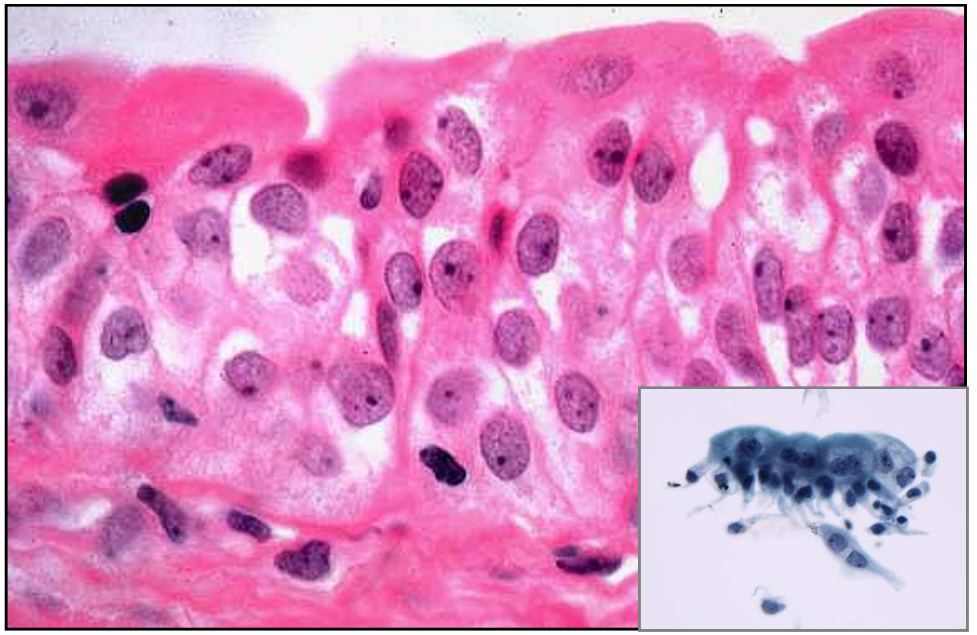


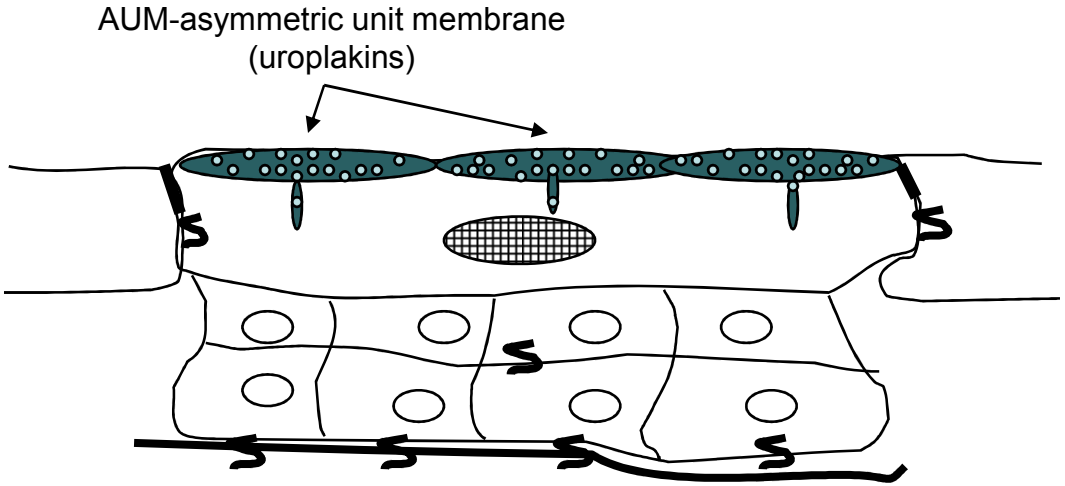
What will you do?

1. Sign out as “Negative”
2. Sign out as “Atypical”
3. Sign out as “Low grade UC can not be excluded”
4. Call a urologist/nurse

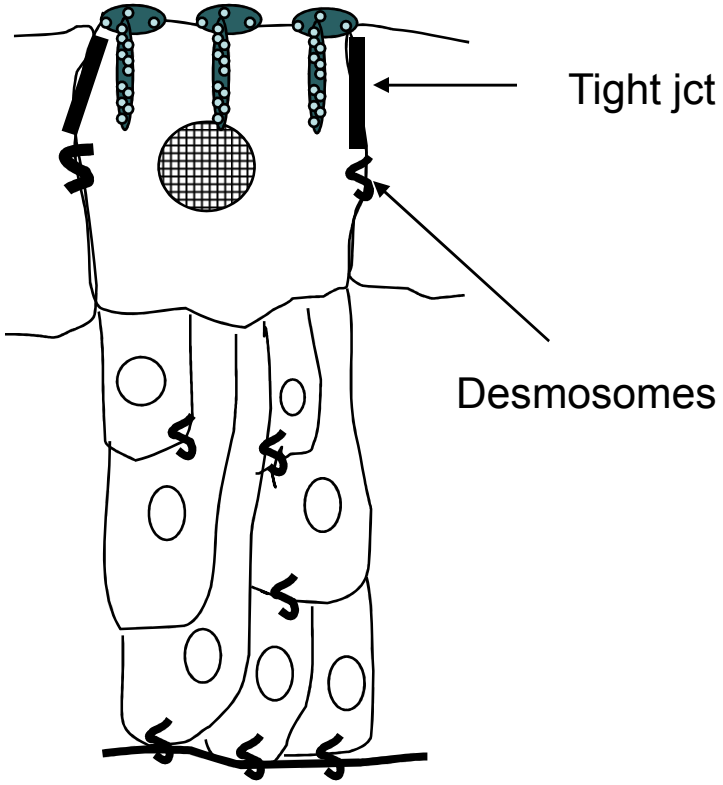
Urothelium - function

- Urine - blood barrier
- Ability to dilate and contract



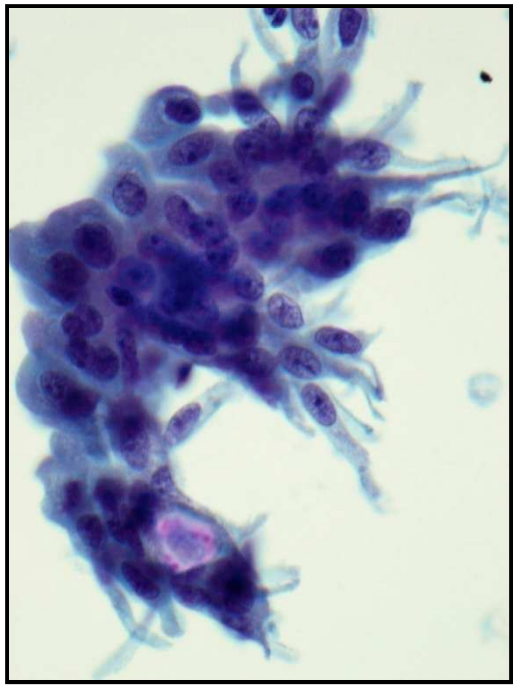
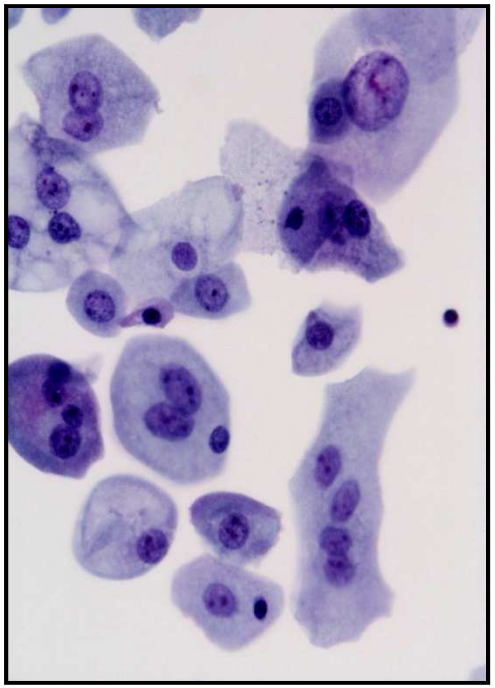
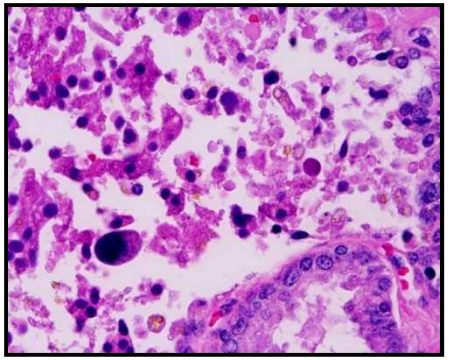
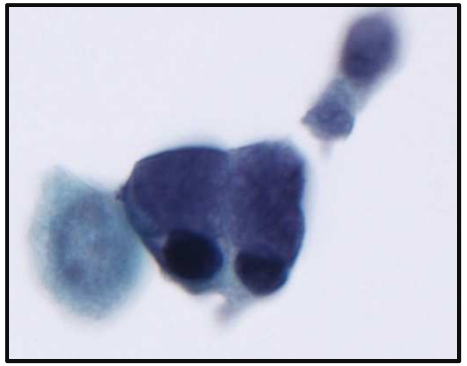
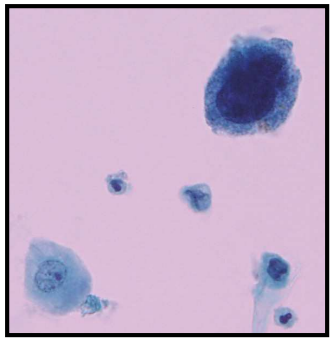
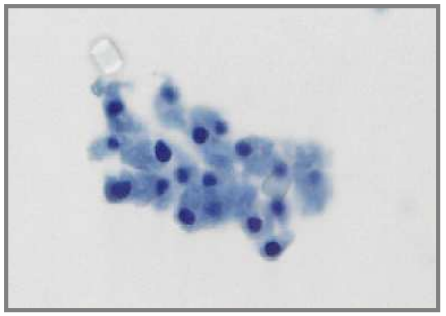


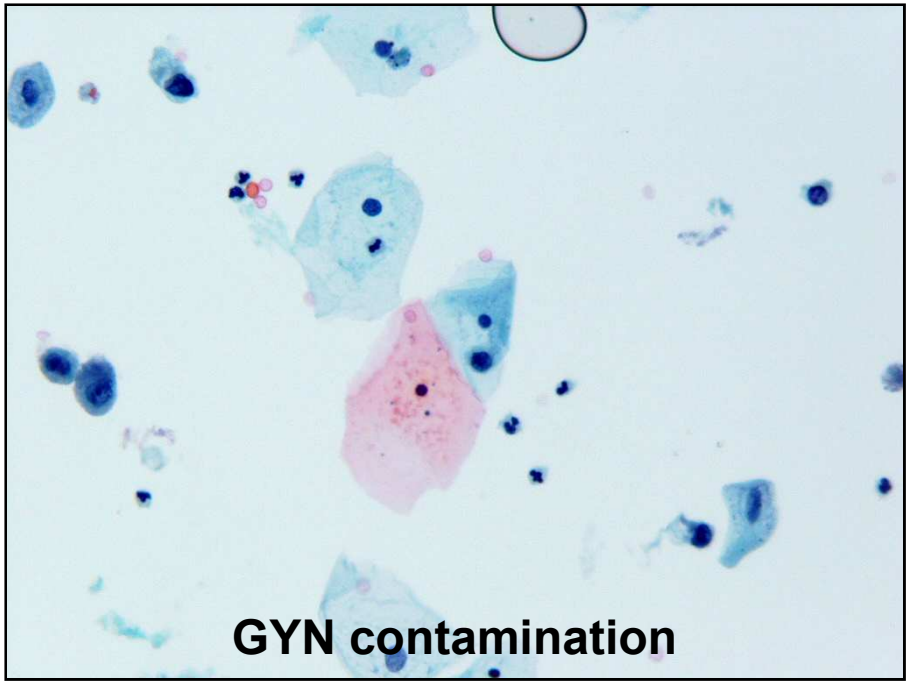
Adopted from Koss

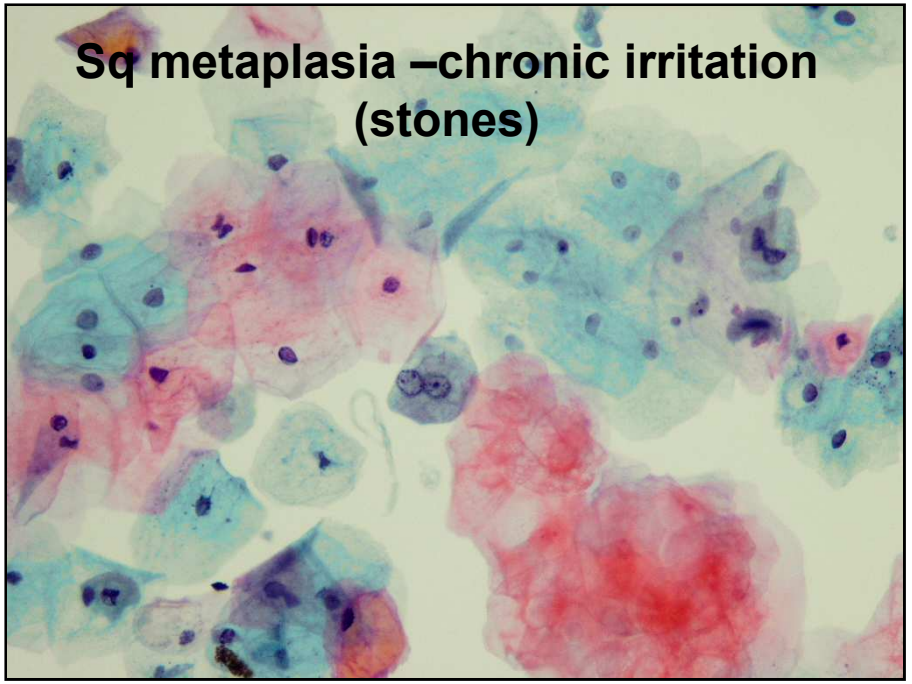


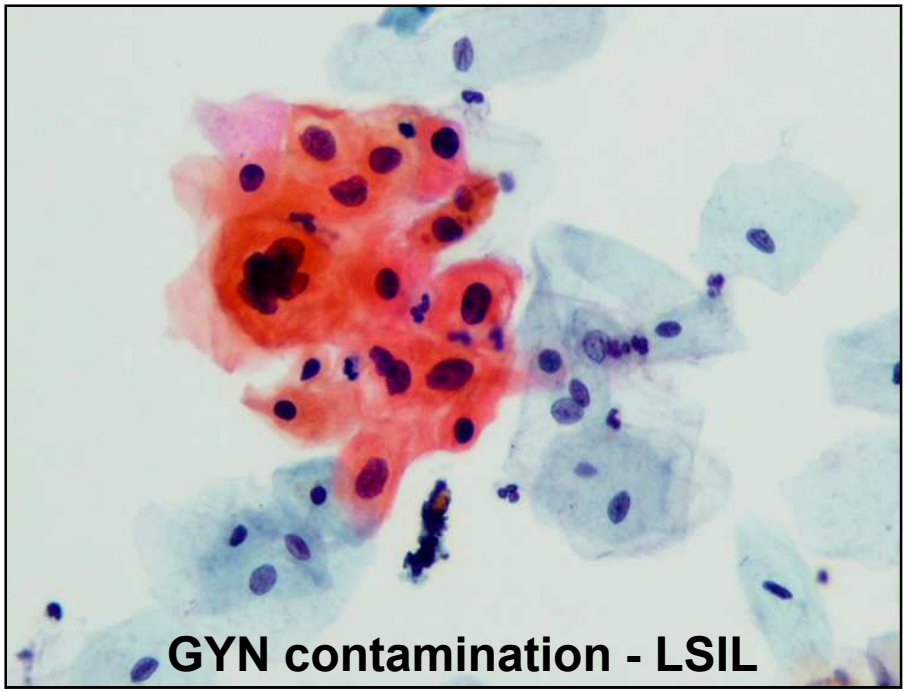
What cells to expect

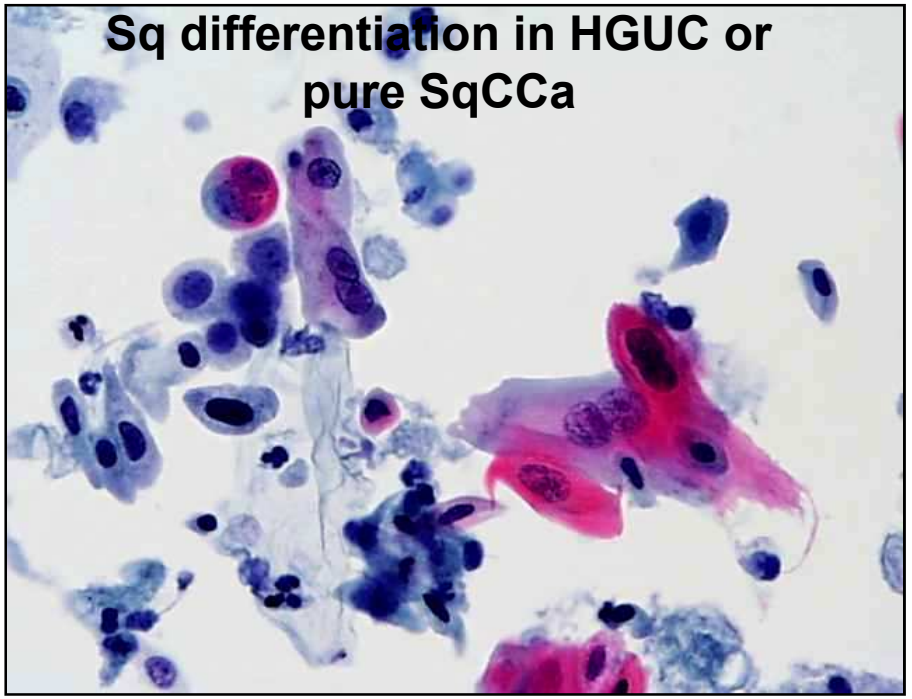
- Urothelial cells – superficial (umbrella cells), intermediate/basal cells
- Squamous cells – GYN tract, trigone, metaplasia, dysplasia
- Glandular epithelium – cystitis glandularis, metaplasia, prostatic glandular cells, seminal vesicle cells
- Renal tubular cells
- Hematopoetic cells – RBC, PMN, plasma cells, macrophages


GYN contamination


Sq metaplasia –chronic irritation
(stones)


GYN contamination - LSIL

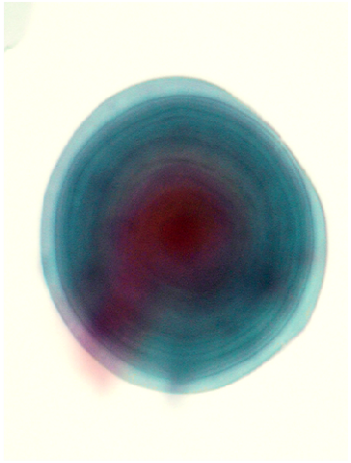

Sq differentiation in HGUC or
pure SqCCa

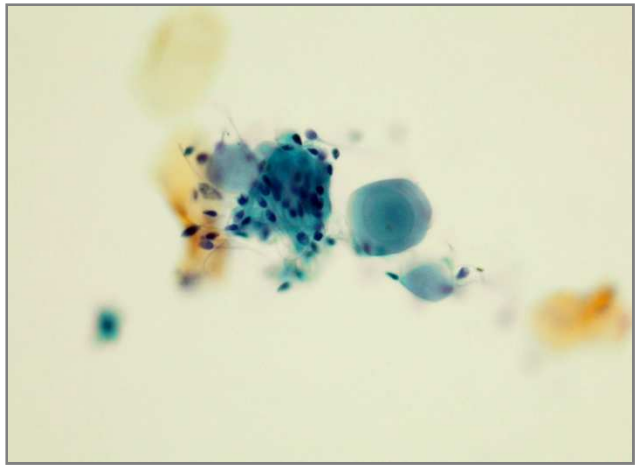
Take home message

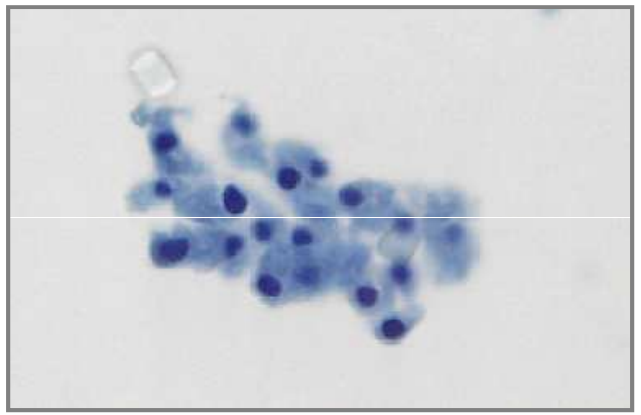
- Benign squamous cells – Females - GYN contamination; Males – squamous metaplasia – chronic irritations
- Dysplastic squamous cells – Females – GYN origin, Males – urethra, older females and males – “tip of an iceberg” - ?HG UC with squamous differentiation
- Malignant squamous cells - HG UC with squamous differentiation (statistically more likely) or squamous cell carcinoma (primary or secondary)

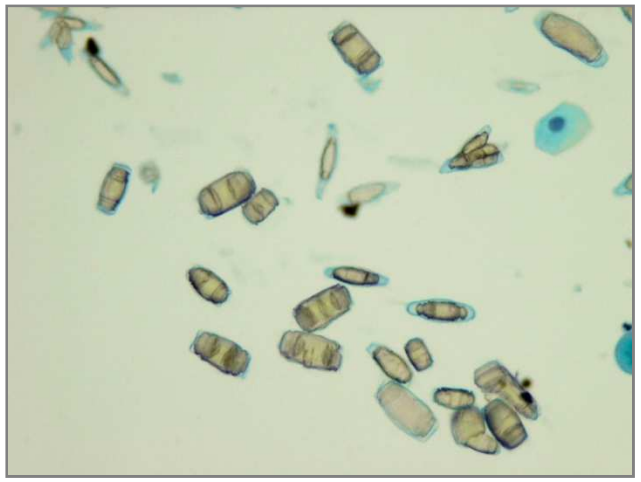
Urinary sediment

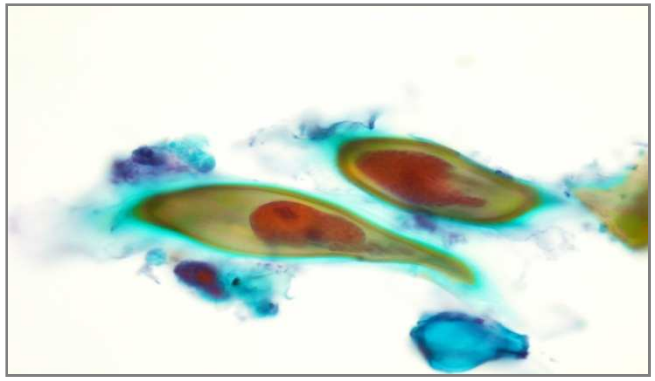
- Crystals
- Renal casts
- Sperm
- Corpora amylacea
- Lubricant
- Contamination











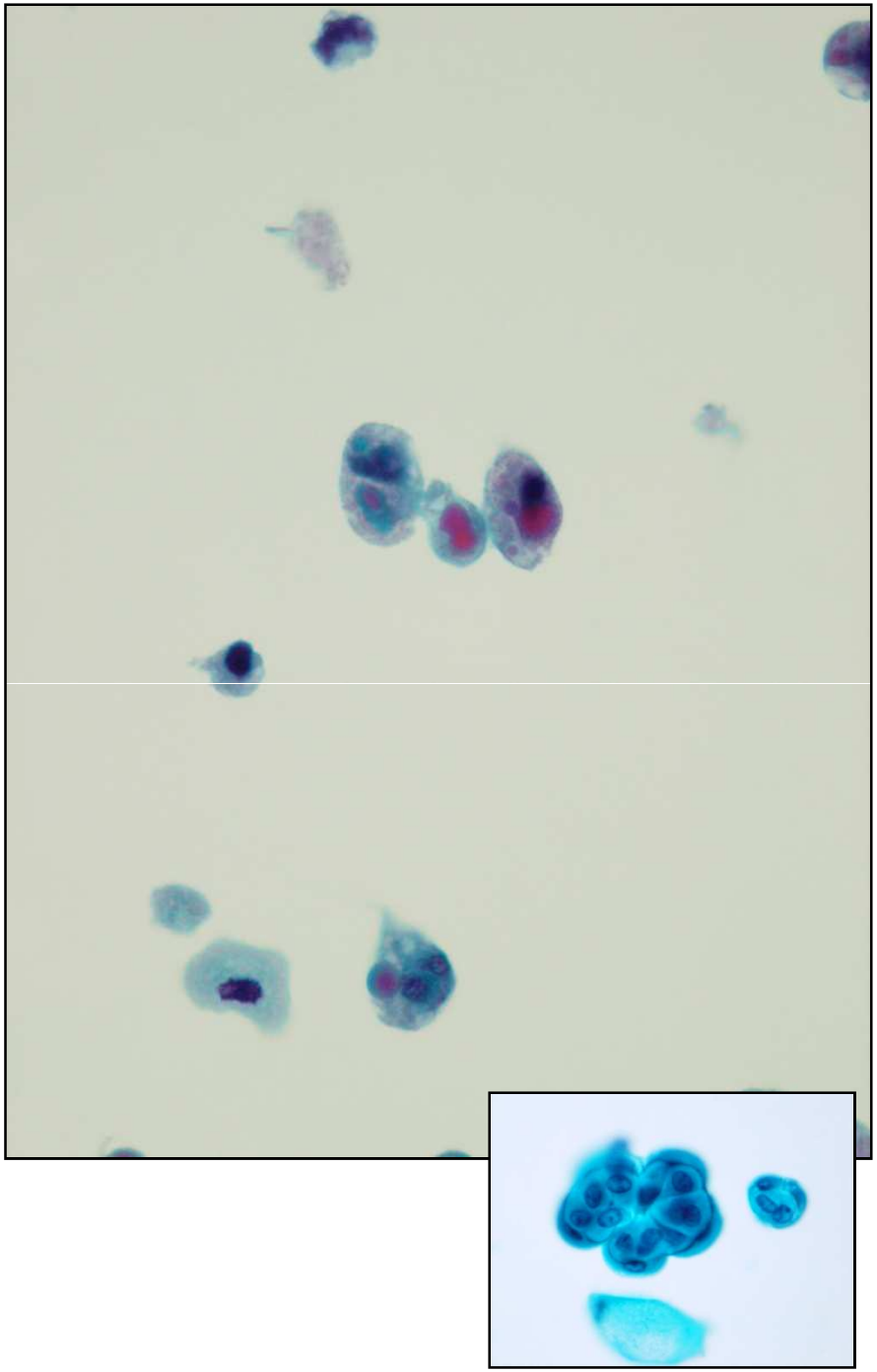
How to approach urine specimen?

What do I need to know first?

What is the type of specimen?

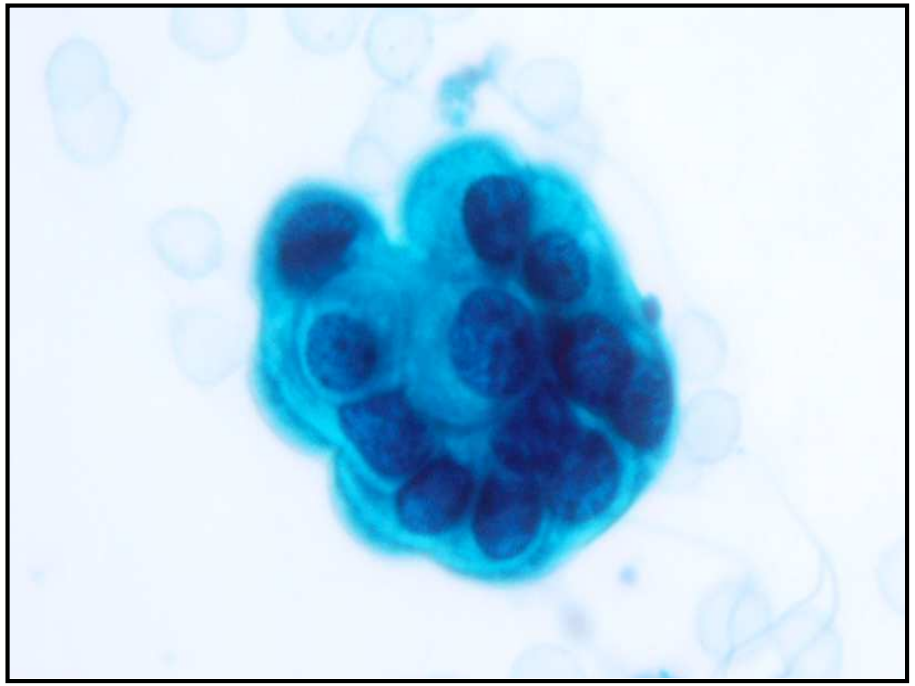
Voided urine

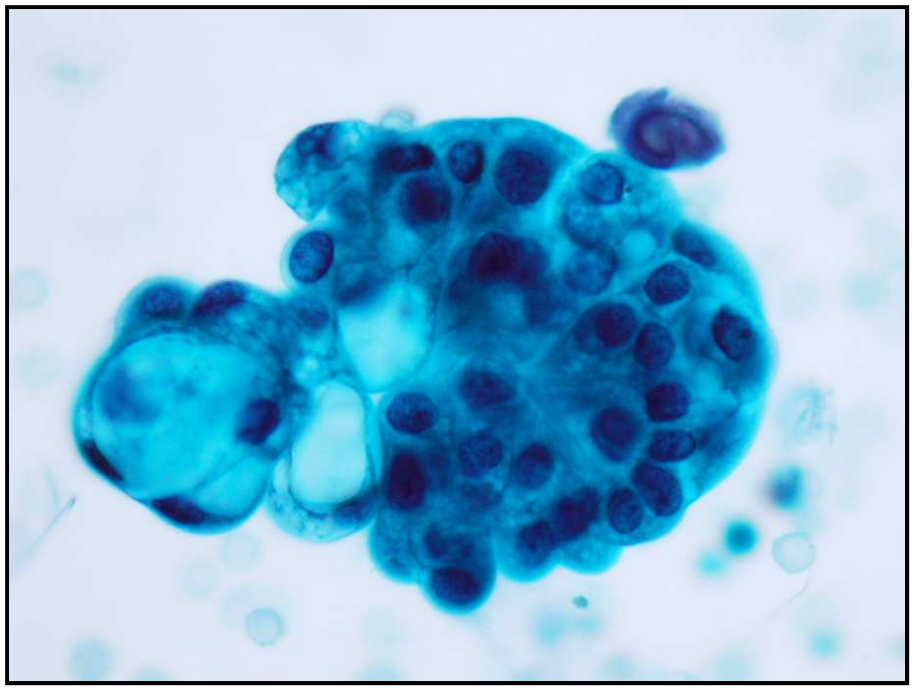
- 2nd morning midstream
- Low cellularity – umbrella cells, few intermediate/basal cells, squamous cells (women)
- Rare cell clusters
- Eosinophilic cytoplasmic inclusions - degeneration



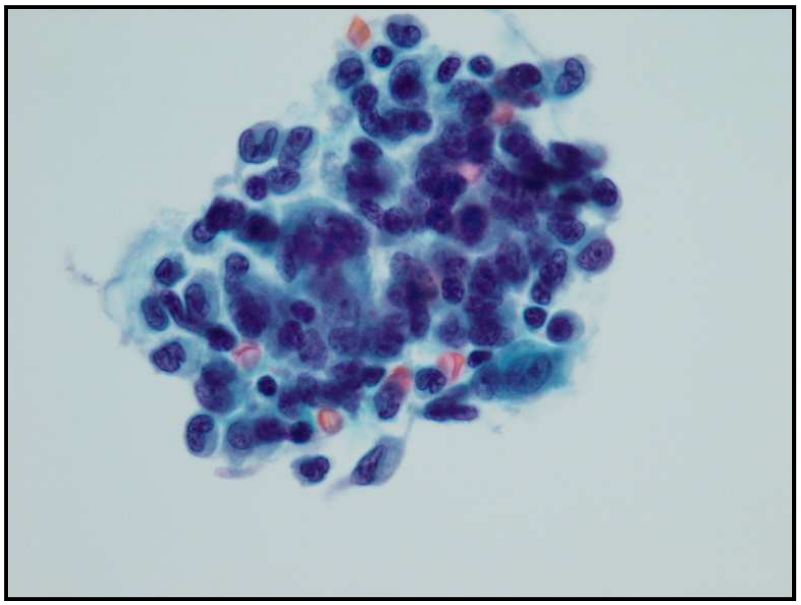
Nephrolithiasis

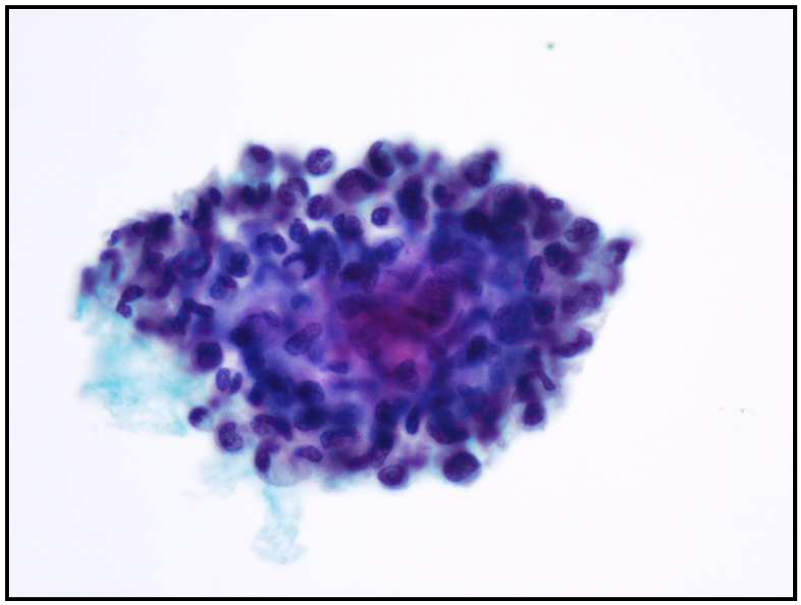
- #1 pitfall in urinary cytology
- Patients may present with hematuria and/or filling defect
- Cytology specimens may be cellular and three dimensional fragments composed of cells exhibiting significant pleomorphism may be seen
- Chronic irritation – squamous metaplasia
- Clinical history is crucial to avoid a false positive diagnosis
- Stones can co-exist with a neoplasm

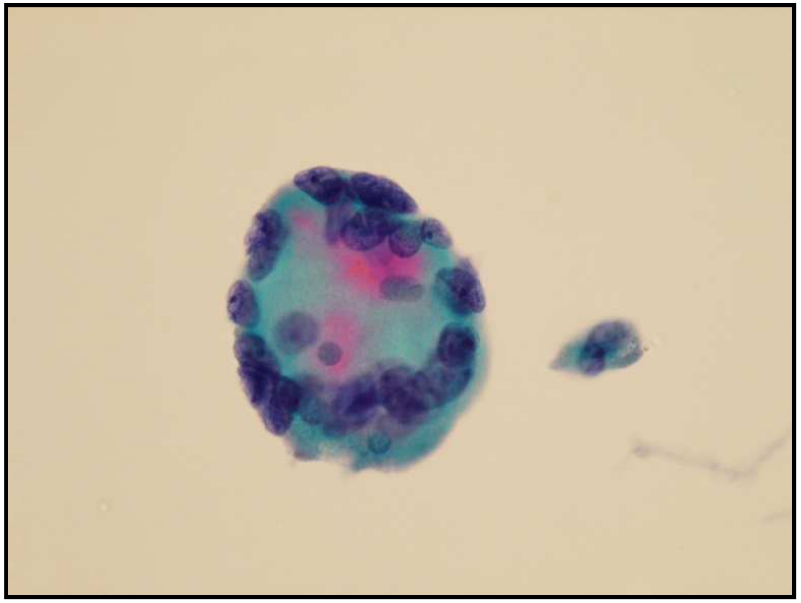


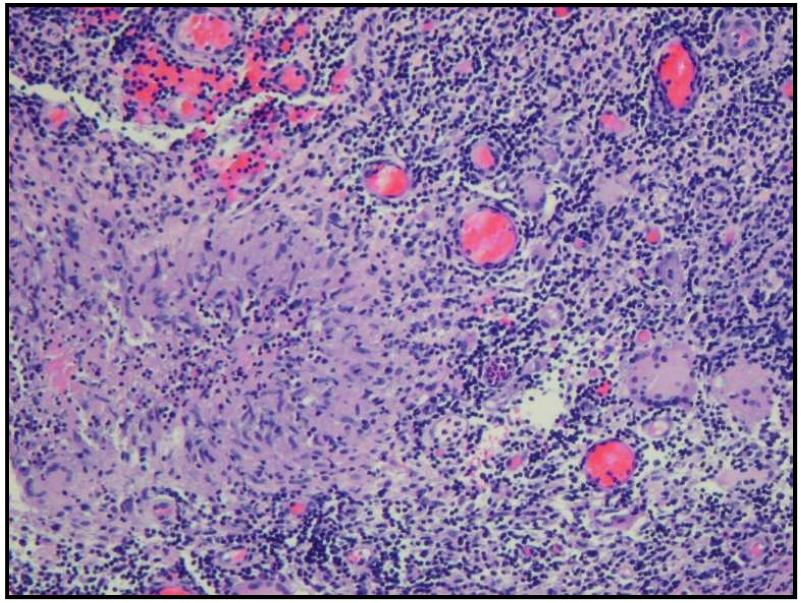


Treatment effect - BCG





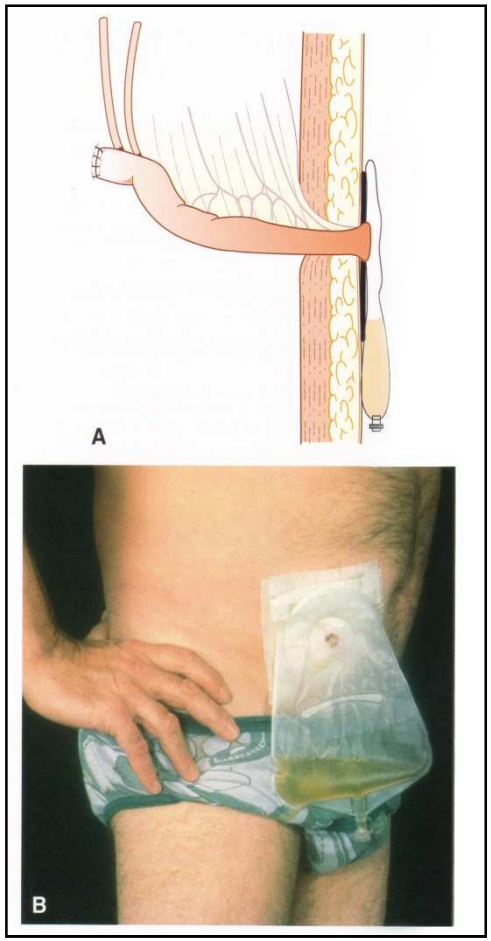




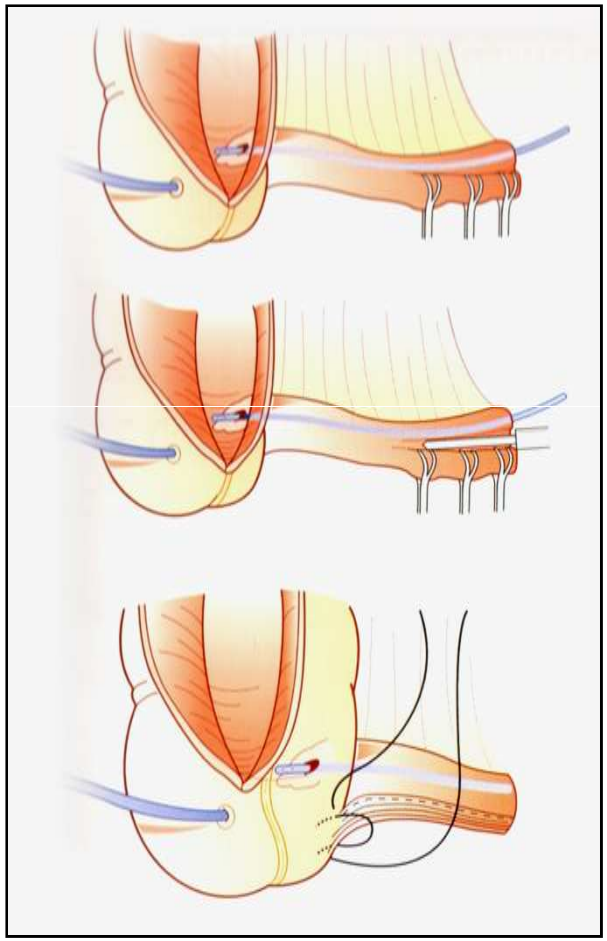
Take home message

- RARE cell clusters can be seen in voided urine
- Check for hx of stones, diverticuli
- In pseudopapillary clusters look for “cellular collars”
- Squamous metaplasia with anucleated squames – chronic irritation - stones

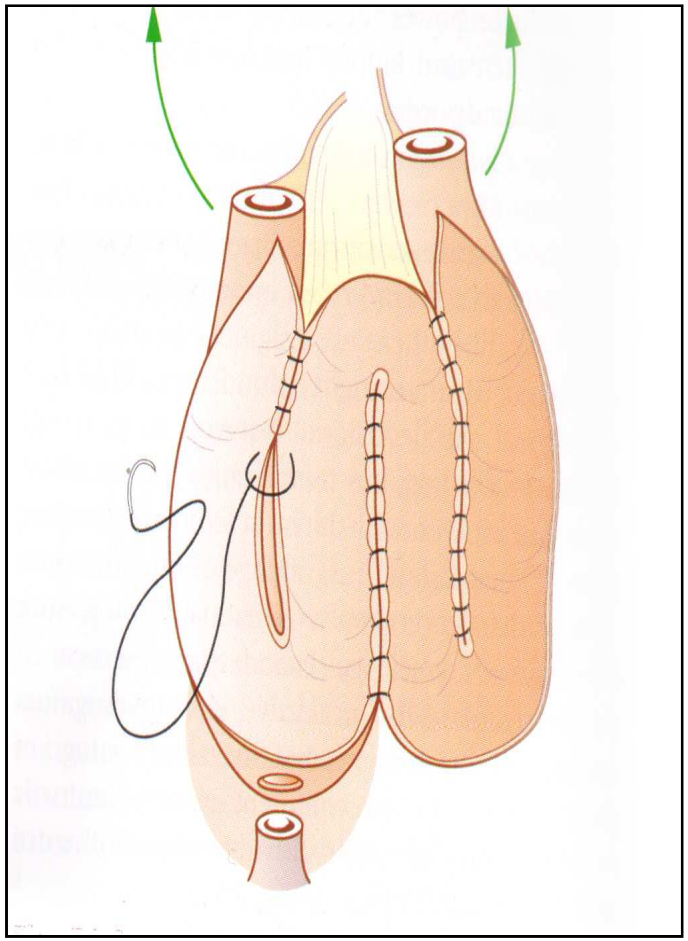
Urinary diversions



Ileal conduit



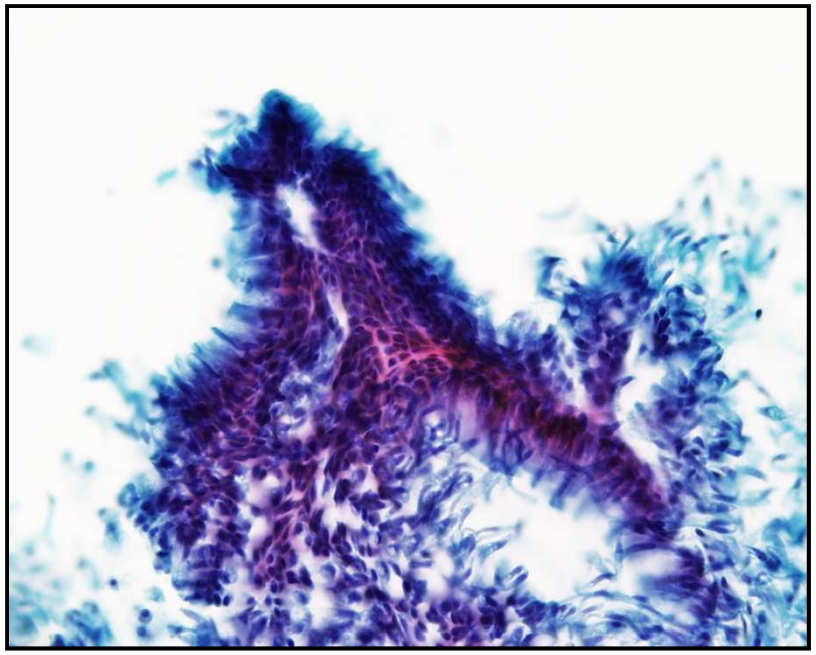
Indiana pouch



Neobladder

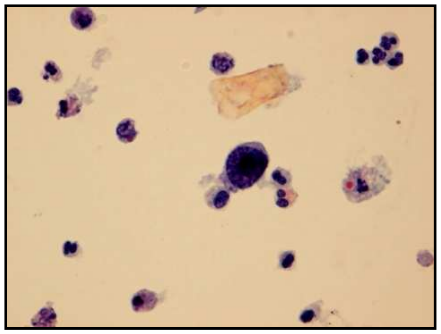
Urinary diversion

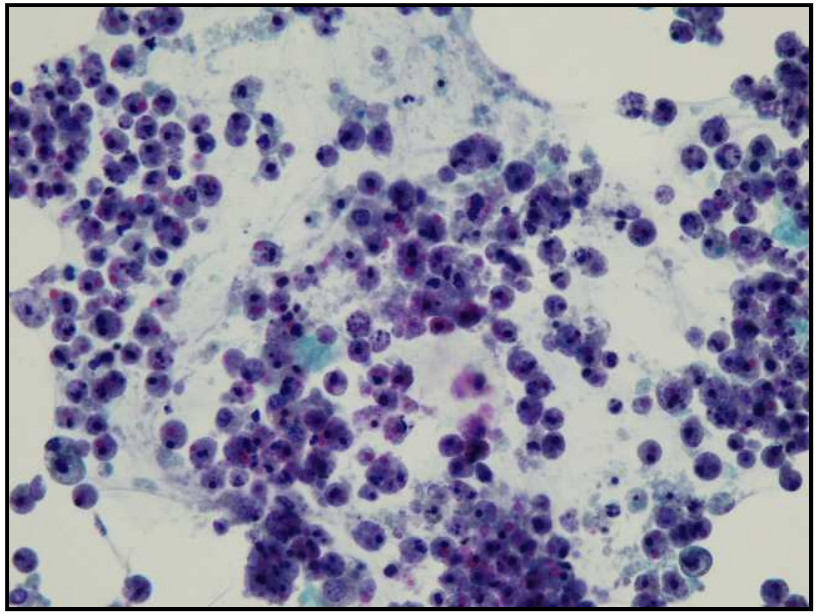
- To monitor upper urinary tract
- Numerous poorly preserved glandular cells, mucus, inflammatory cells



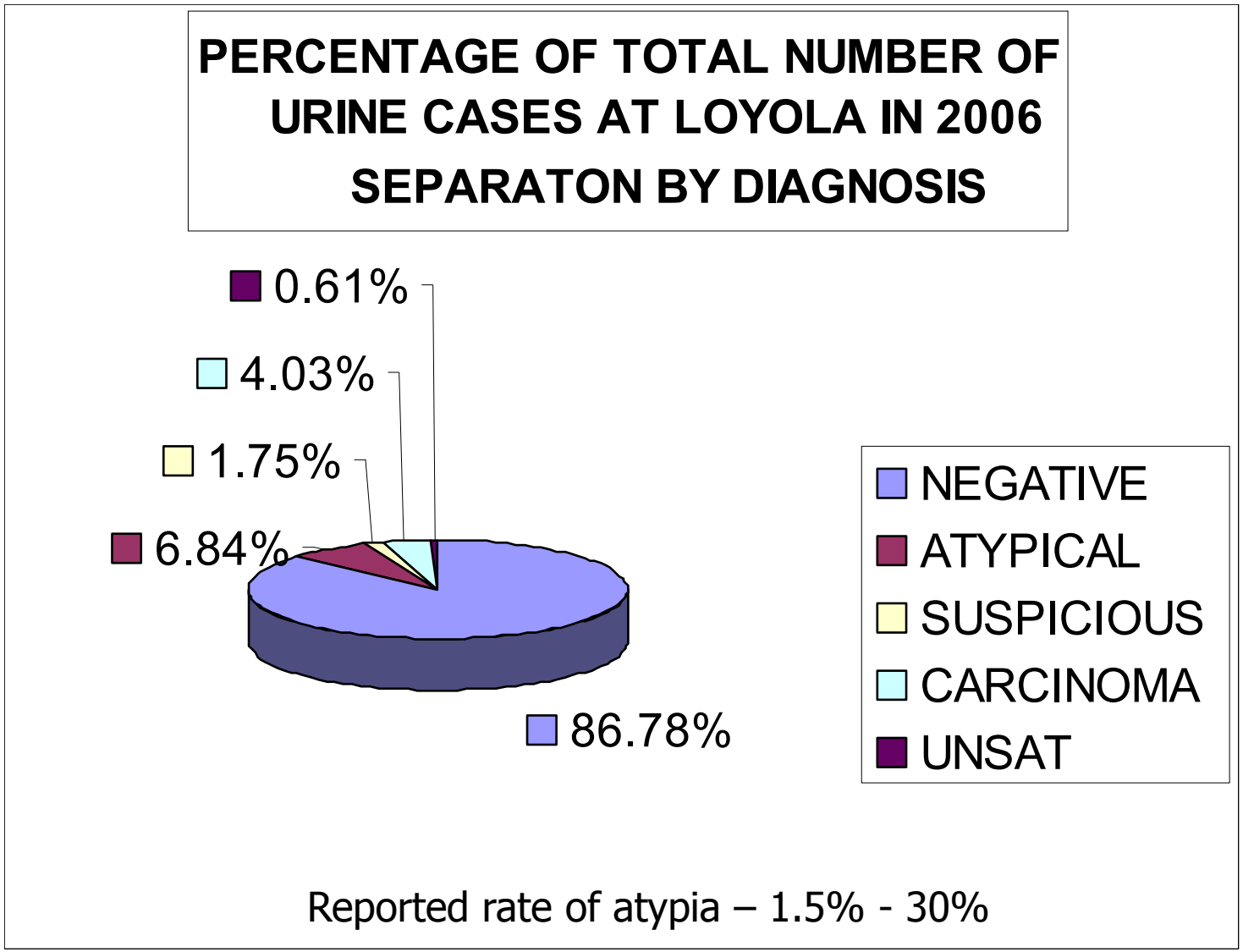
Systematic Study of Urine Cytology Following Urinary Diversion *Liu et al. 2007*

- 305 urine specimens from 105 patients
- Positive – 4.6%
- Suspicious – 2%
- Atypical – 5.9%
- Sensitivity – 80%
- Specificity – 98%
- PPV - 63%
- NPV – 99%





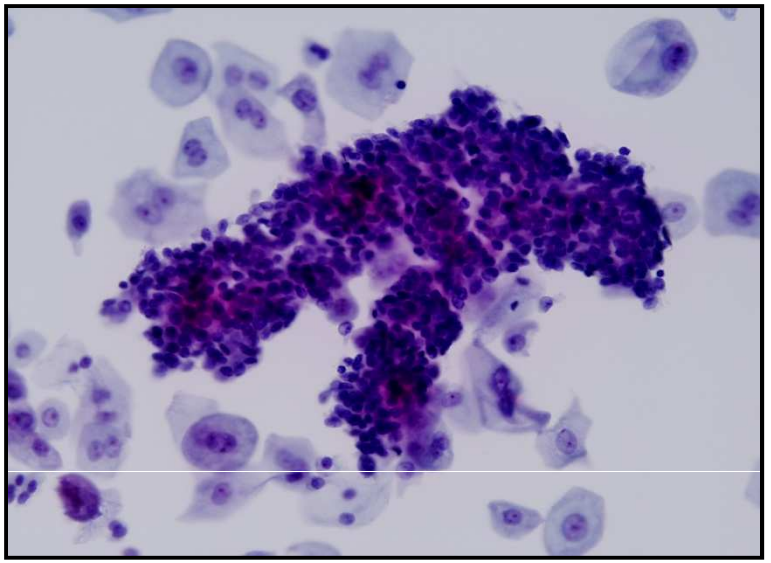
How about atypia?

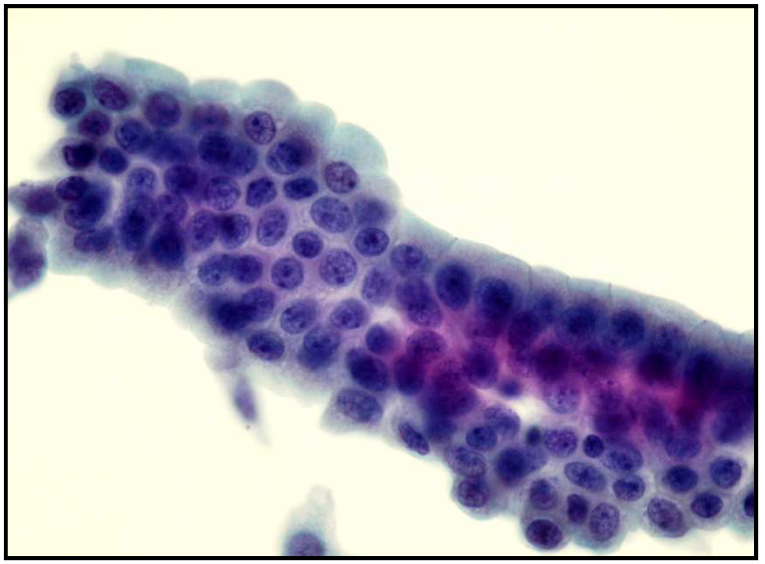


Reported rate of atypia – 1.5% - 30%

Instrumented urine

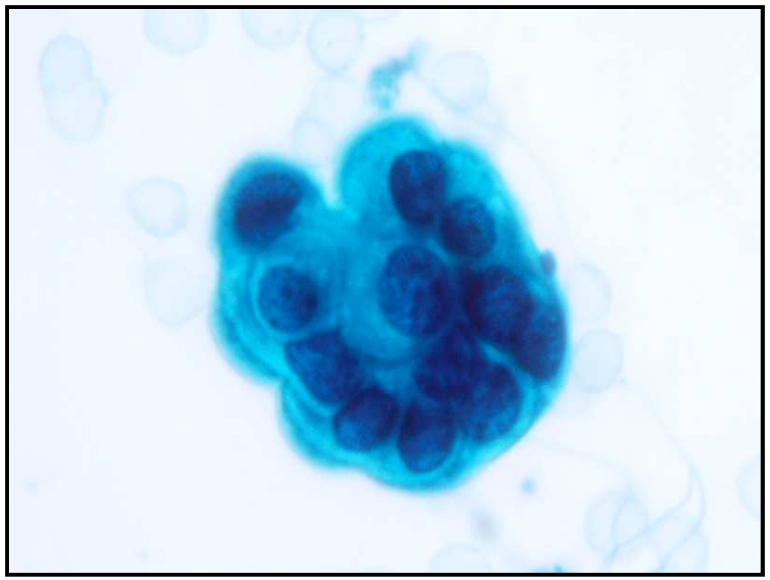
- High cellularity – umbrella cells and intermediate/basal cells
- Better cellular preservation
- Numerous cell clusters
- Similar findings in urolithiasis and low grade carcinomas



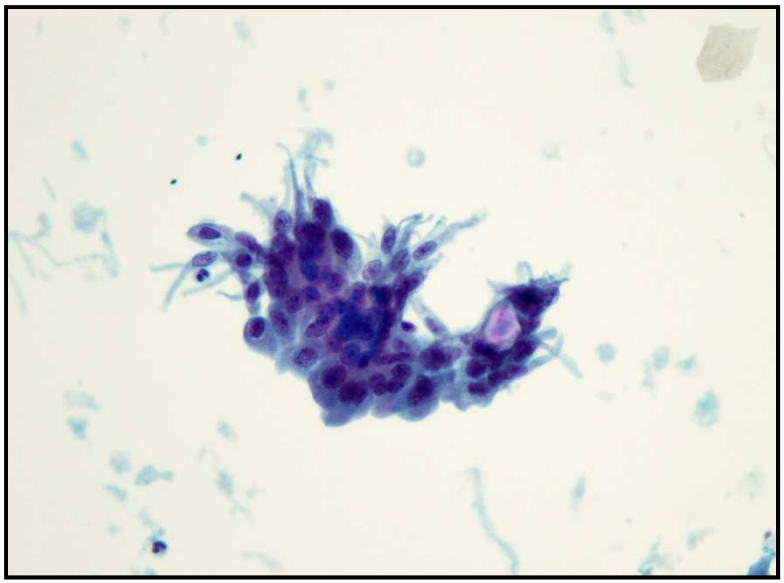


Take home message

- If a specimen looks like instrumented urine and is labeled as “voided” – call a nurse – most probably patient voided after the procedure

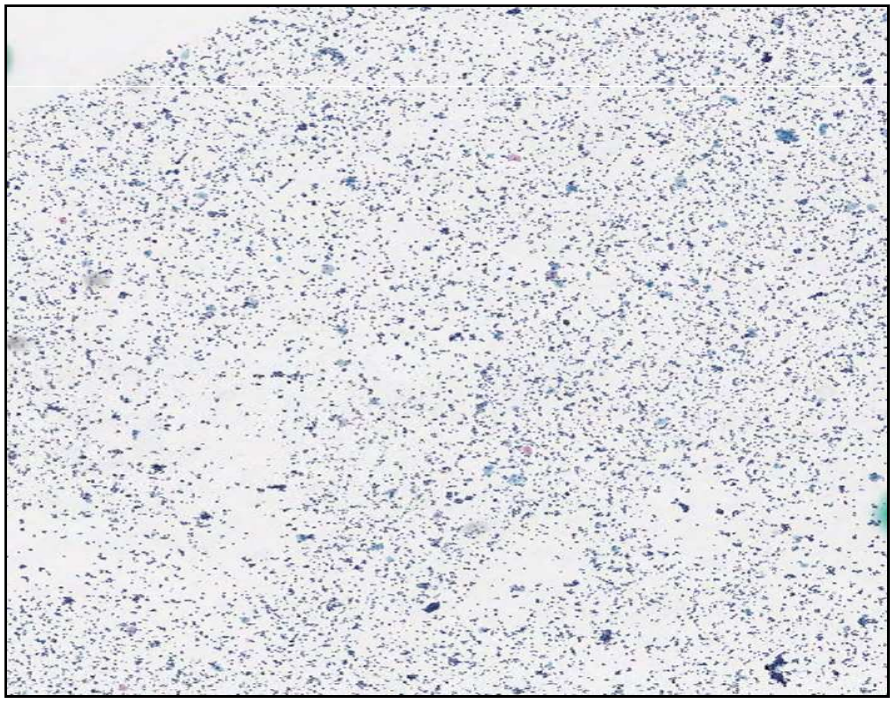


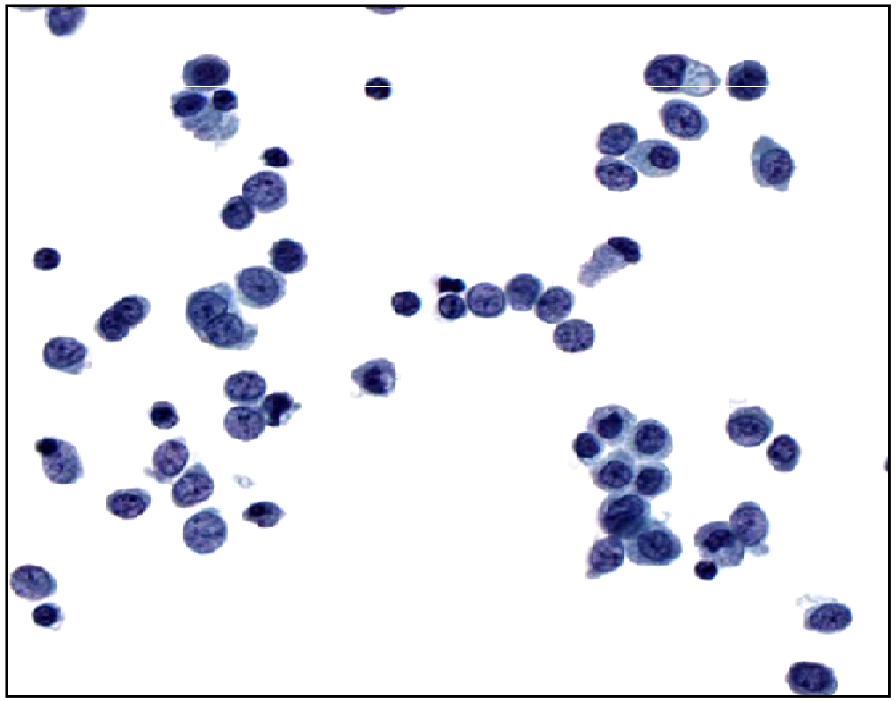
vs.



Case 2

- Bladder barbotage from a 58 year-old man with hematuria.





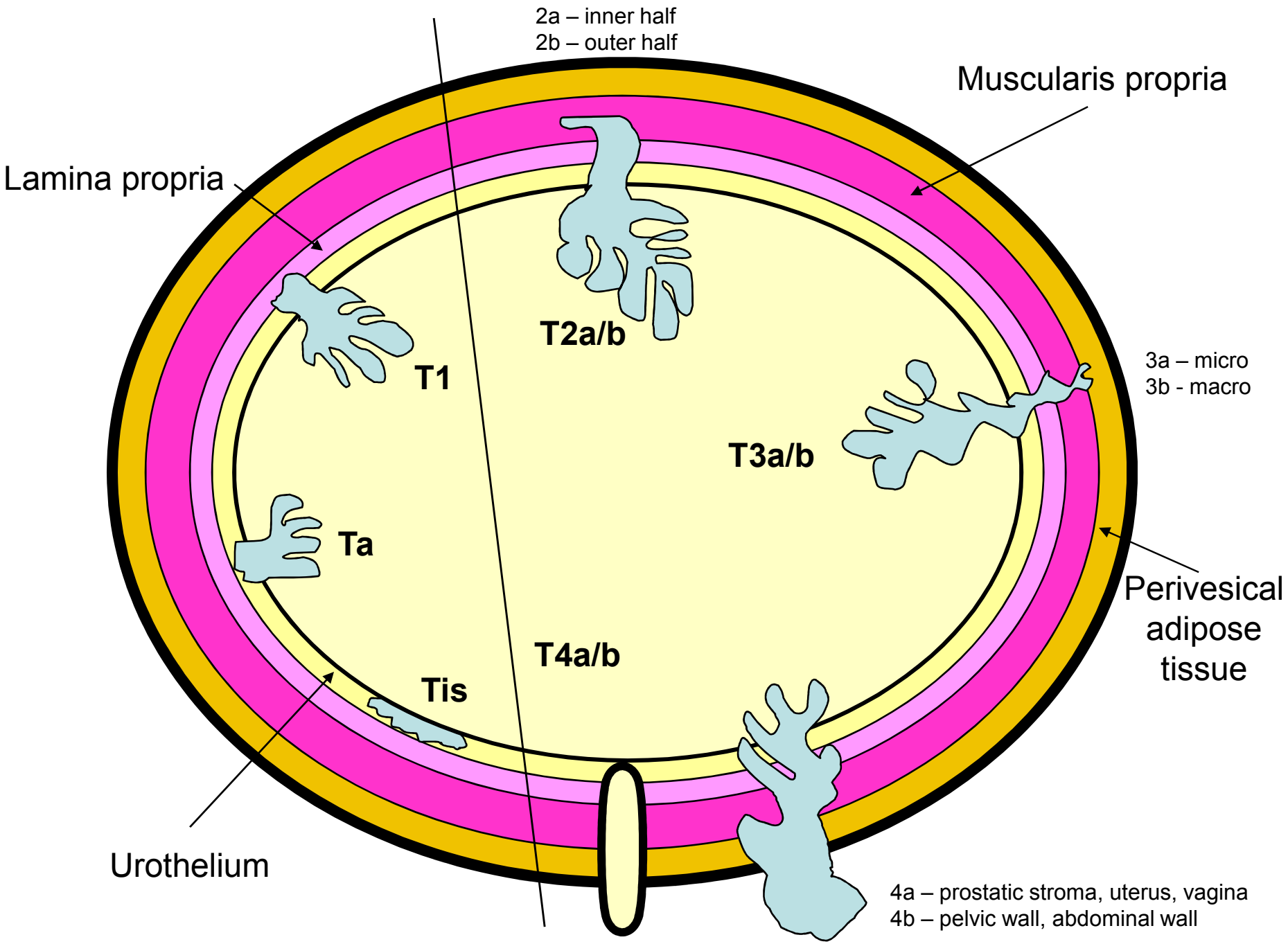
Questions

- Can we make a diagnosis of a low grade urothelial carcinoma?
- What features are necessary to make this diagnosis?
- What is a low grade urothelial carcinoma?
- Does it make a difference to differentiate between low and high grade UC in cytology?

First – we have to understand urothelial carcinoma

Bladder cancer - current status

- Worldwide – 7th most common cancer
- 260,000 new cases each year in men
- 76,000 new cases each year in women
- The chance of a man developing bladder cancer at any time during his life is about 1 in 30 and for a woman, 1 in 90 (USA)
- Highest incidence – Western Europe, North America, Australia
- ~ 50% detected by routine cytology
- ~ 75% superficial bladder cancers
- ~ 50% - 70% - recurrence
- ~ 5% - 10% - progression
- > 500,000 people in the US are survivors of this cancer
- The highest cost/patient from diagnosis to death
- The fifth most expensive cancer to treat
- ~ $3.4 billion/year is spent for bladder ca treatment (USA; 2003)


2a – inner half
2b – outer half
Muscularis propria
Lamina propria
T2a/b
T1
3a – micro
3b - macro
T3a/b
Ta
Perivesical adipose tissue
T4a/b
Tis
Urothelium
4a – prostatic stroma, uterus, vagina
4b – pelvic wall, abdominal wall

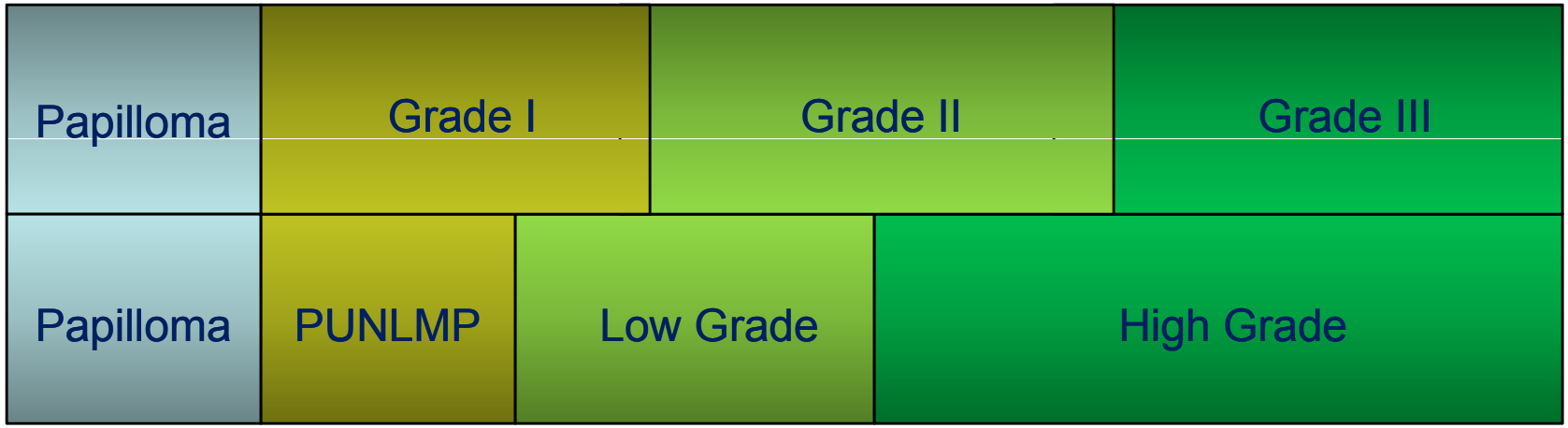
Can we make a diagnosis of LG UC?

Noninvasive Papillary Tumors	Sensitivity %
Grade I	16.6[1] and 39.0[2]
Grade II	70.6[1] and 56.0[2]
Grade III	93.5[1] and 89.0[2]
Total	78.6[1] and 71.0[2]

[1]*Koss et al. Acta Cytologica. 1985*
[2]*Wiener et al. Acta Cytologica. 1993*

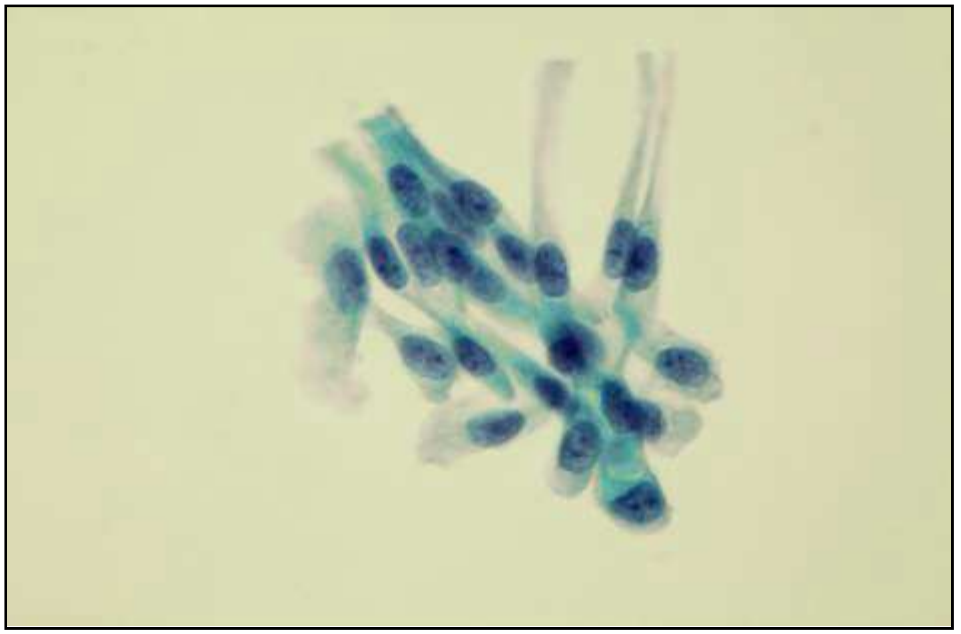
Classifications

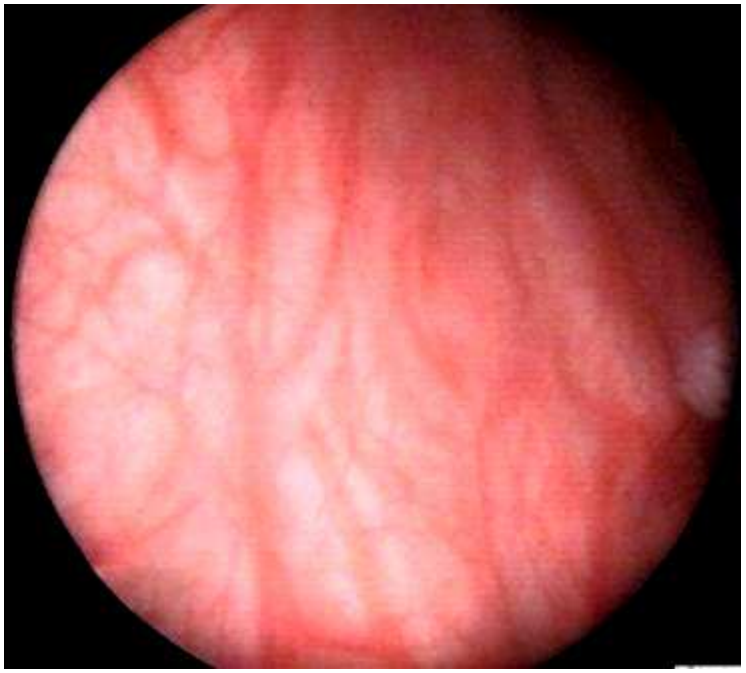
WHO 1973

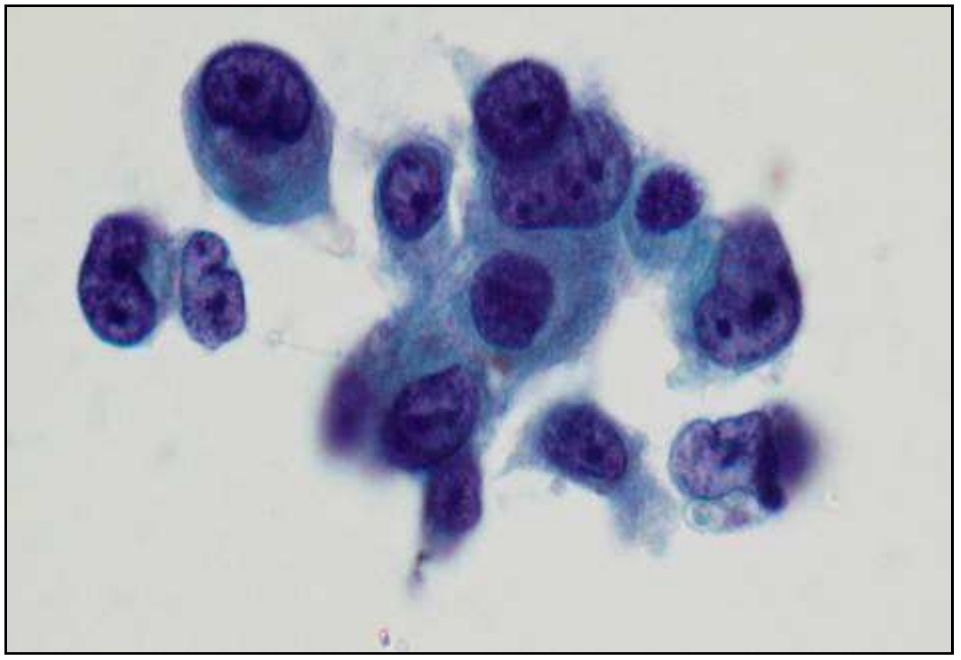


WHO/ISUP 2004

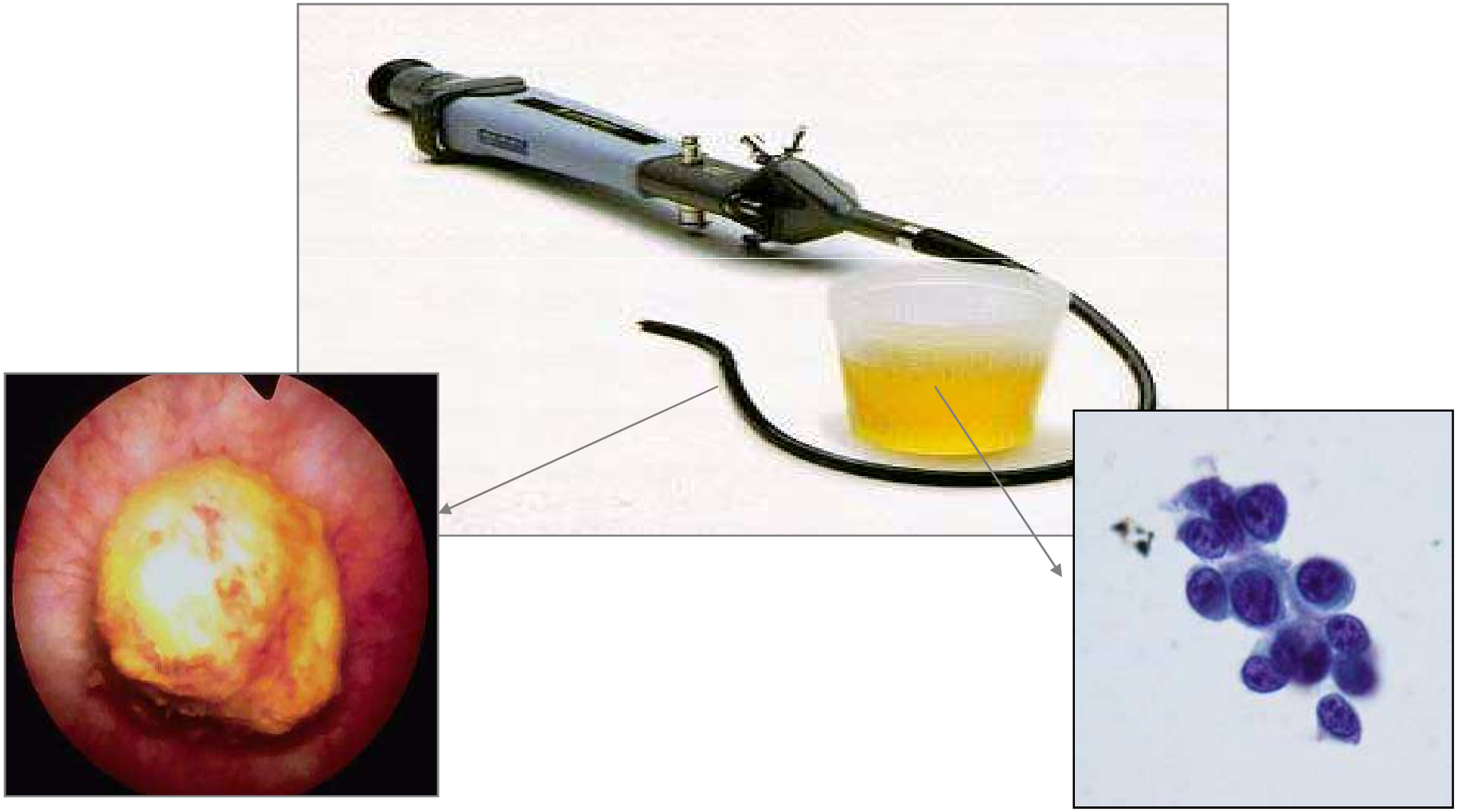
Most of the time - NOT





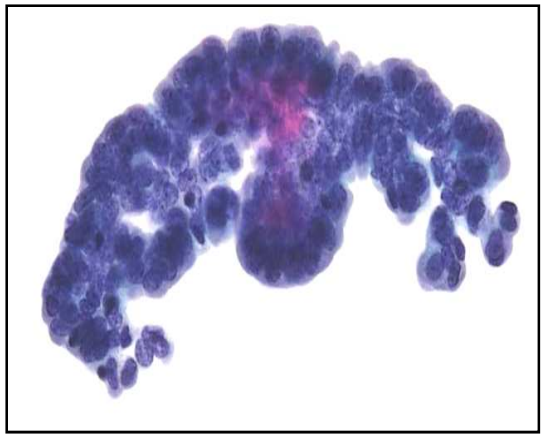


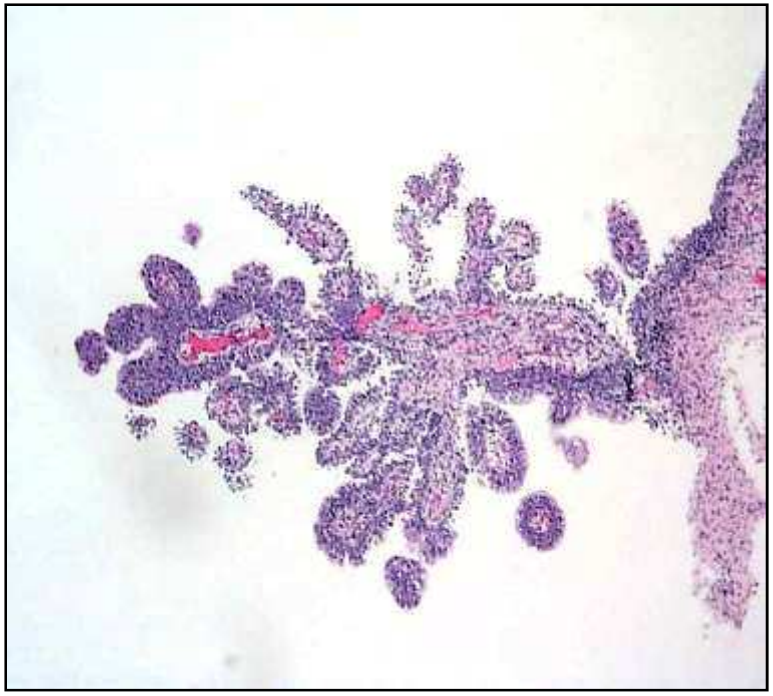
Urothelial Carcinoma
Diagnosis and Follow-up

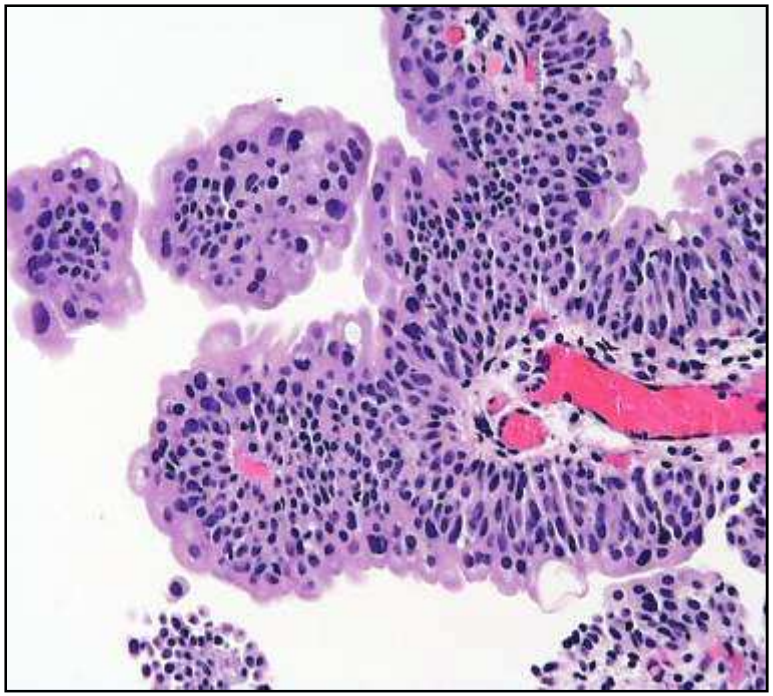


Urothelial papilloma

- < 2-3 % of papillary urothelial tumors
- < 50 years of age
- HISTOLOGY - delicate fibrovascular stalks covered by cytologically and architecturally normal urothelium

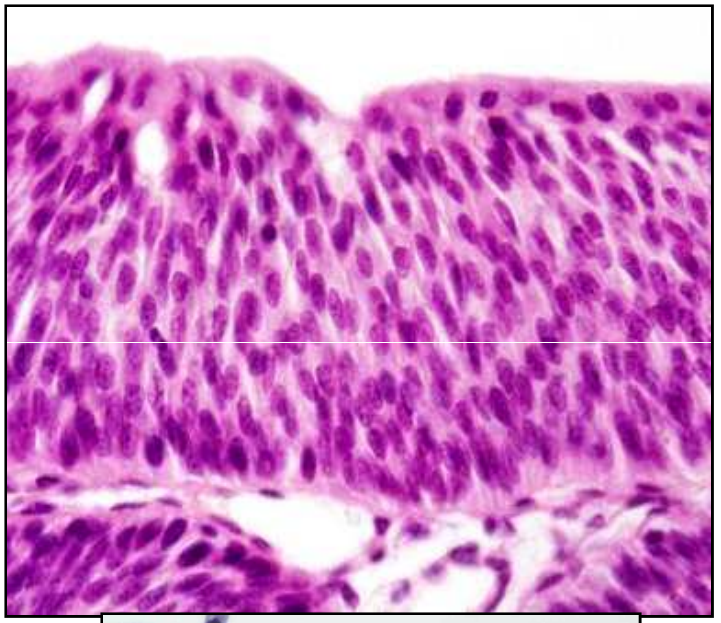


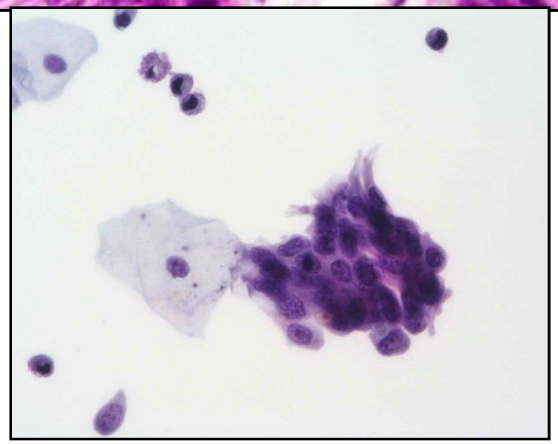




Papillary urothelial neoplasm of low malignant potential (PUNLMP)

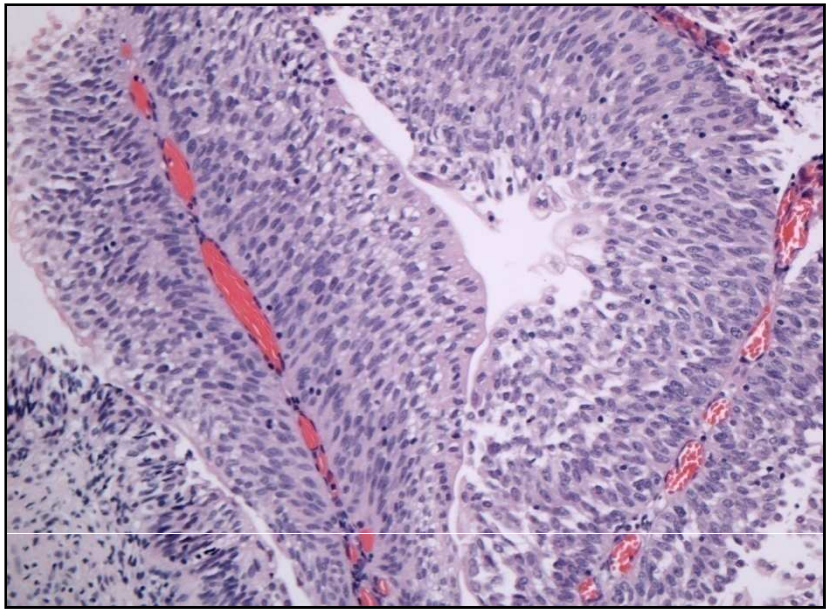
- “papillary urothelial lesion with orderly arranged cells within papillae with minimal architectural abnormalities and minimal nuclear atypia” *Epstein et al., 1998*
- Local recurrence (30%), progression (<10%), death from bladder cancer (3-4%)

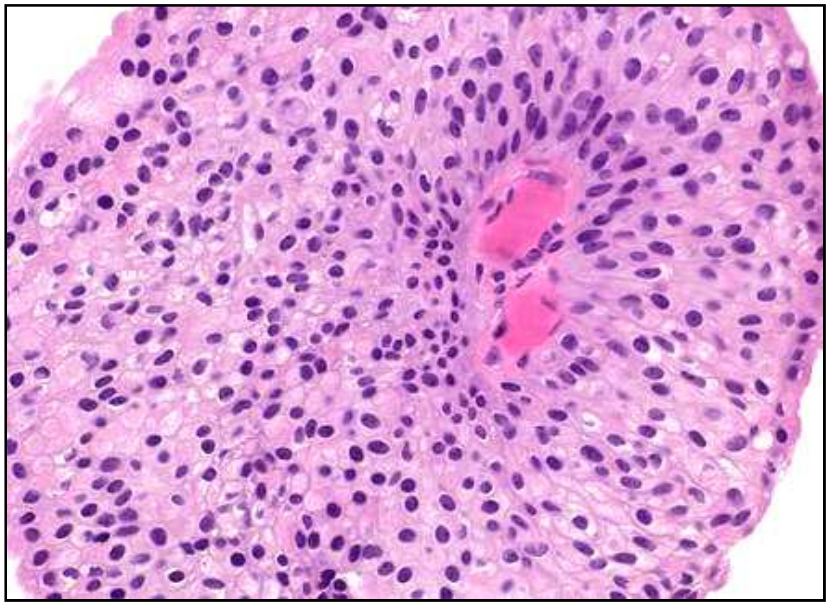


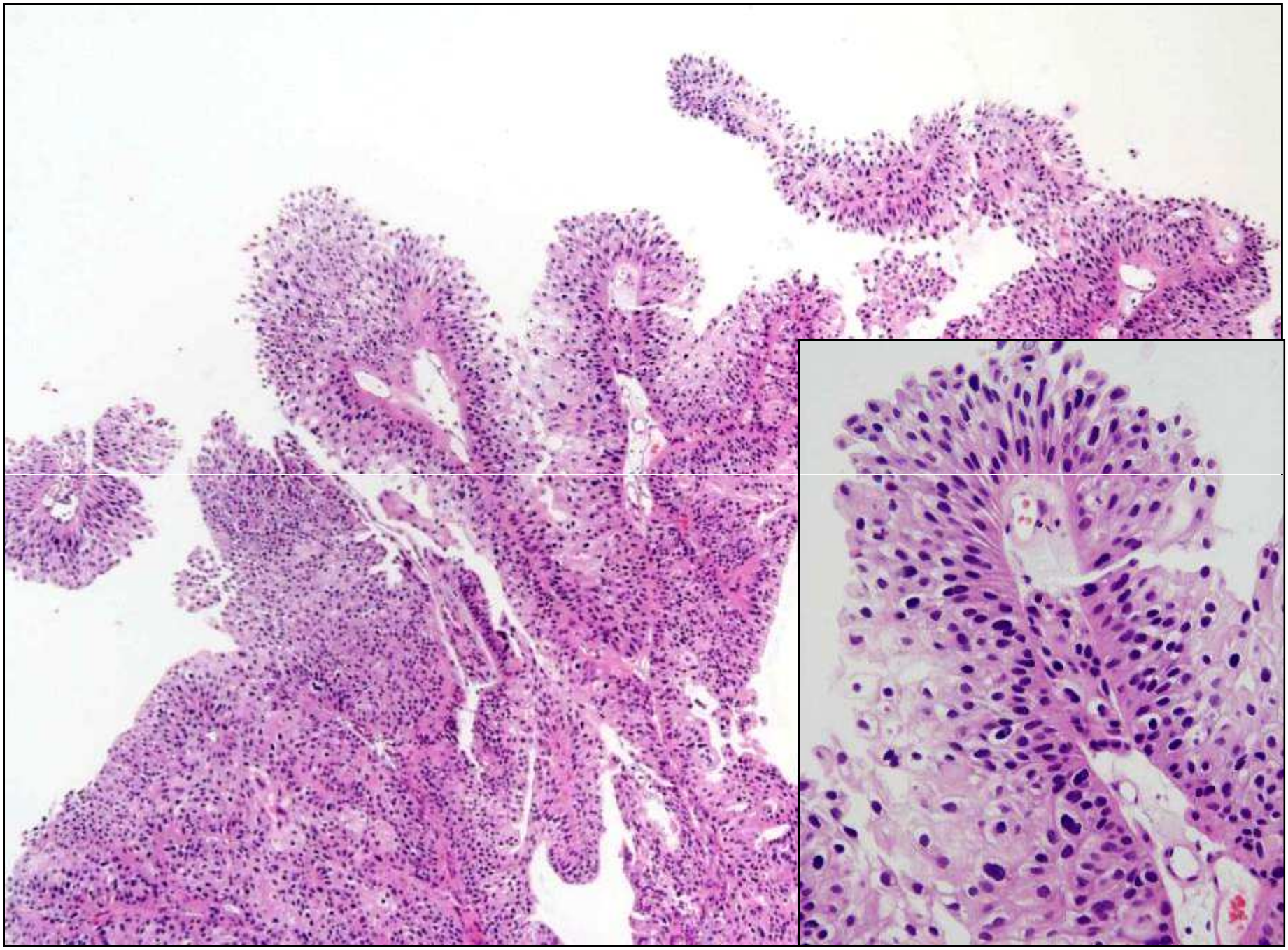


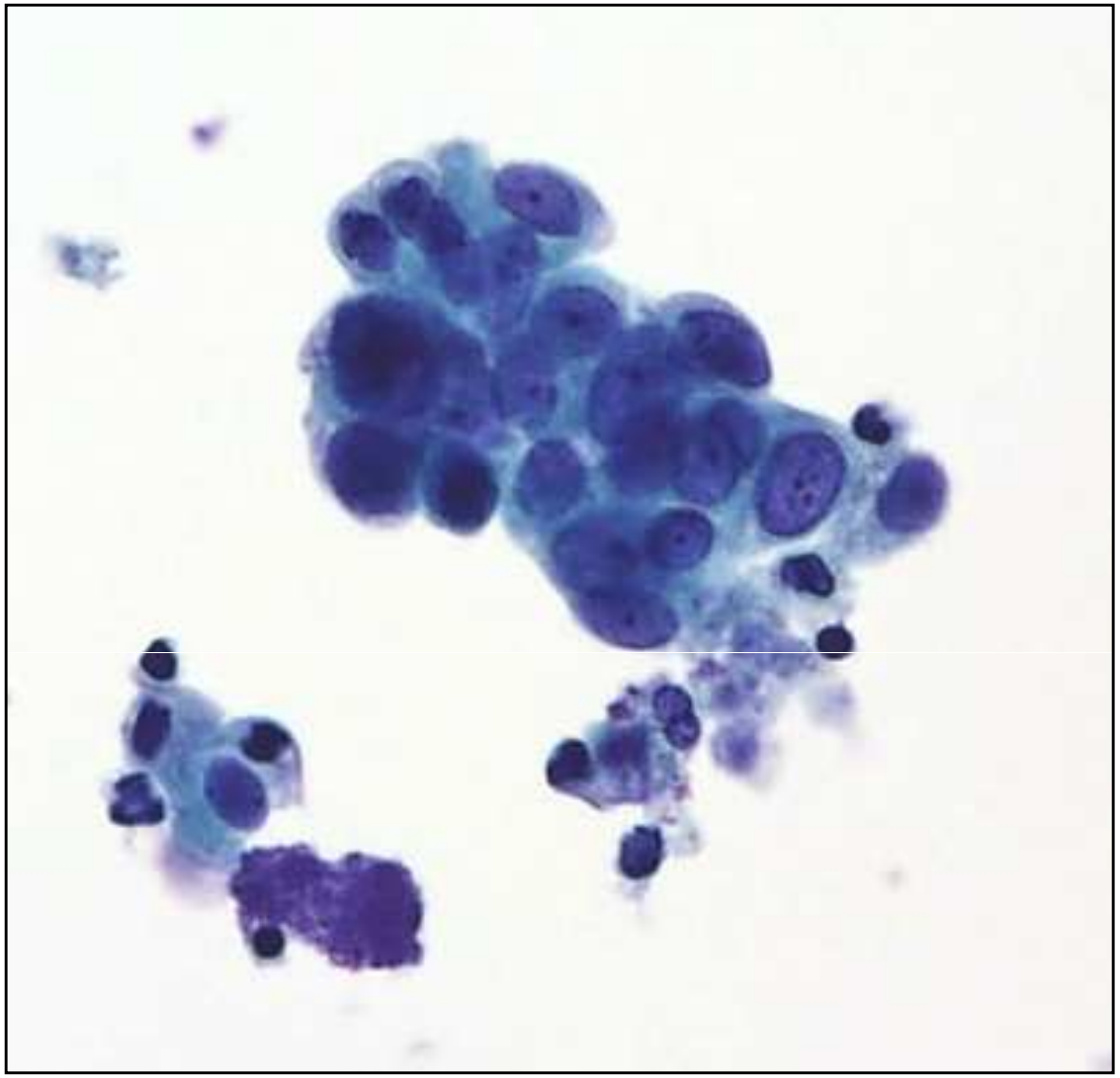
Low grade urothelial carcinoma

- LG UC – slender papillary branching fronds with minimal fusion. Easily recognized variation in architectural and cytological features – nuclear enlargement
- Local recurrence ~ 50 - 75%, progression >10%, death <5%

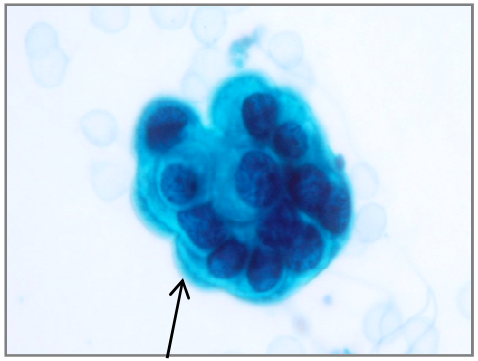




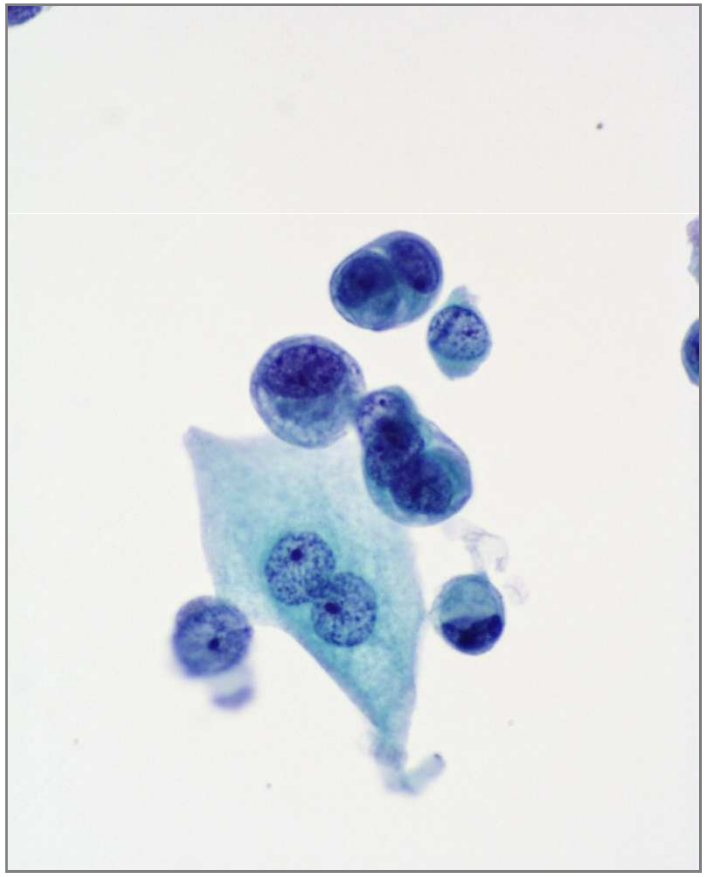


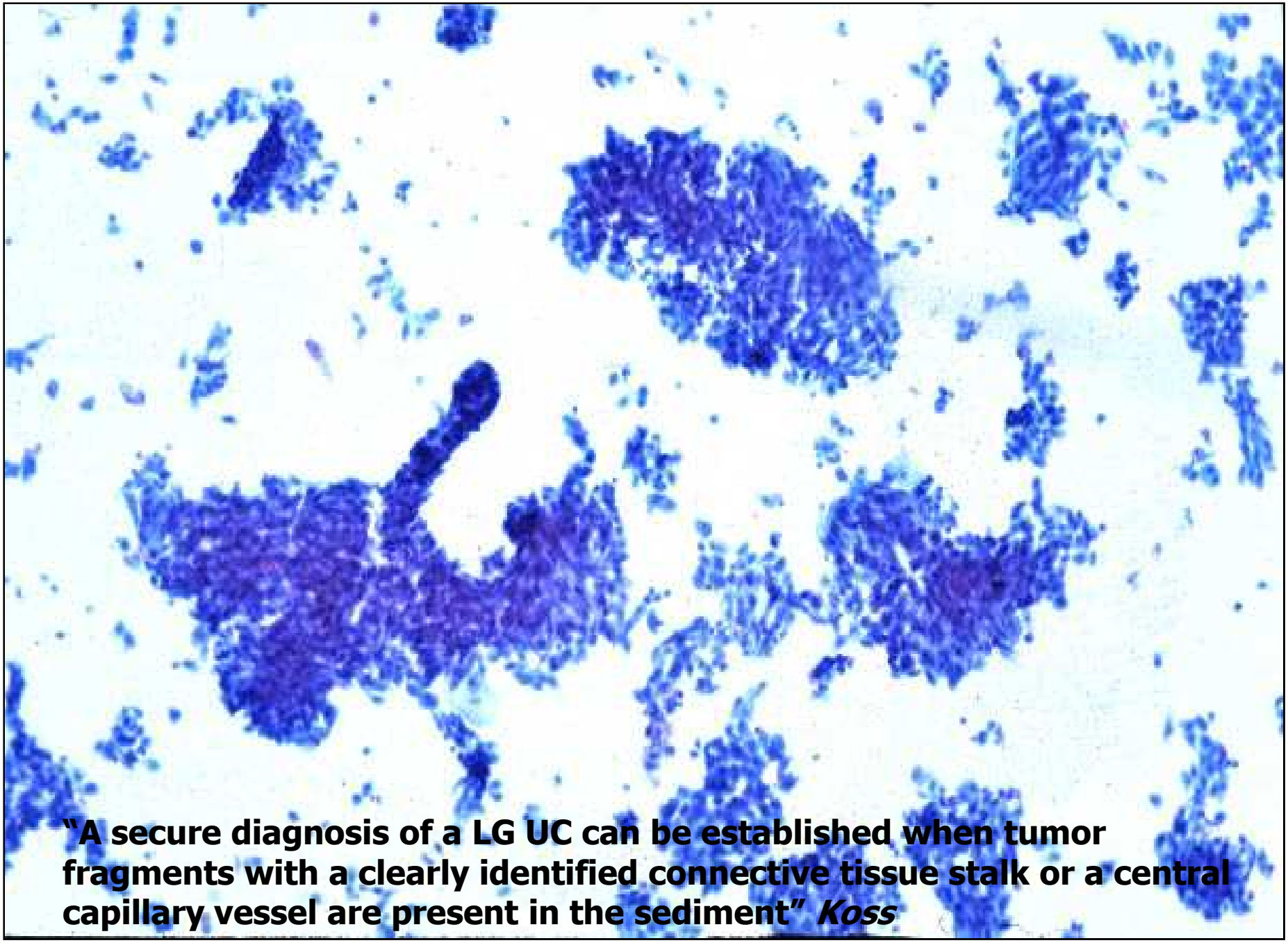


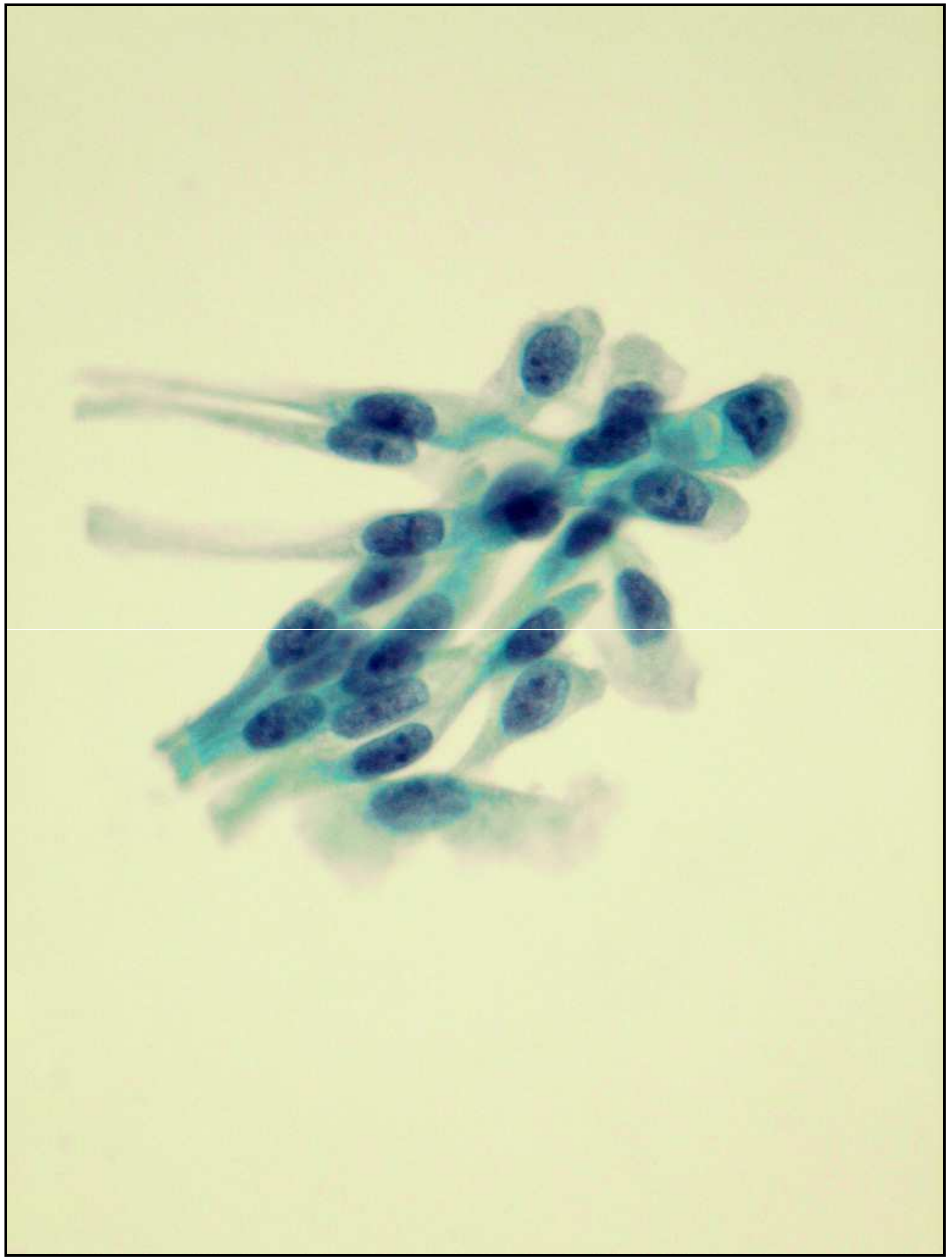
Vs.

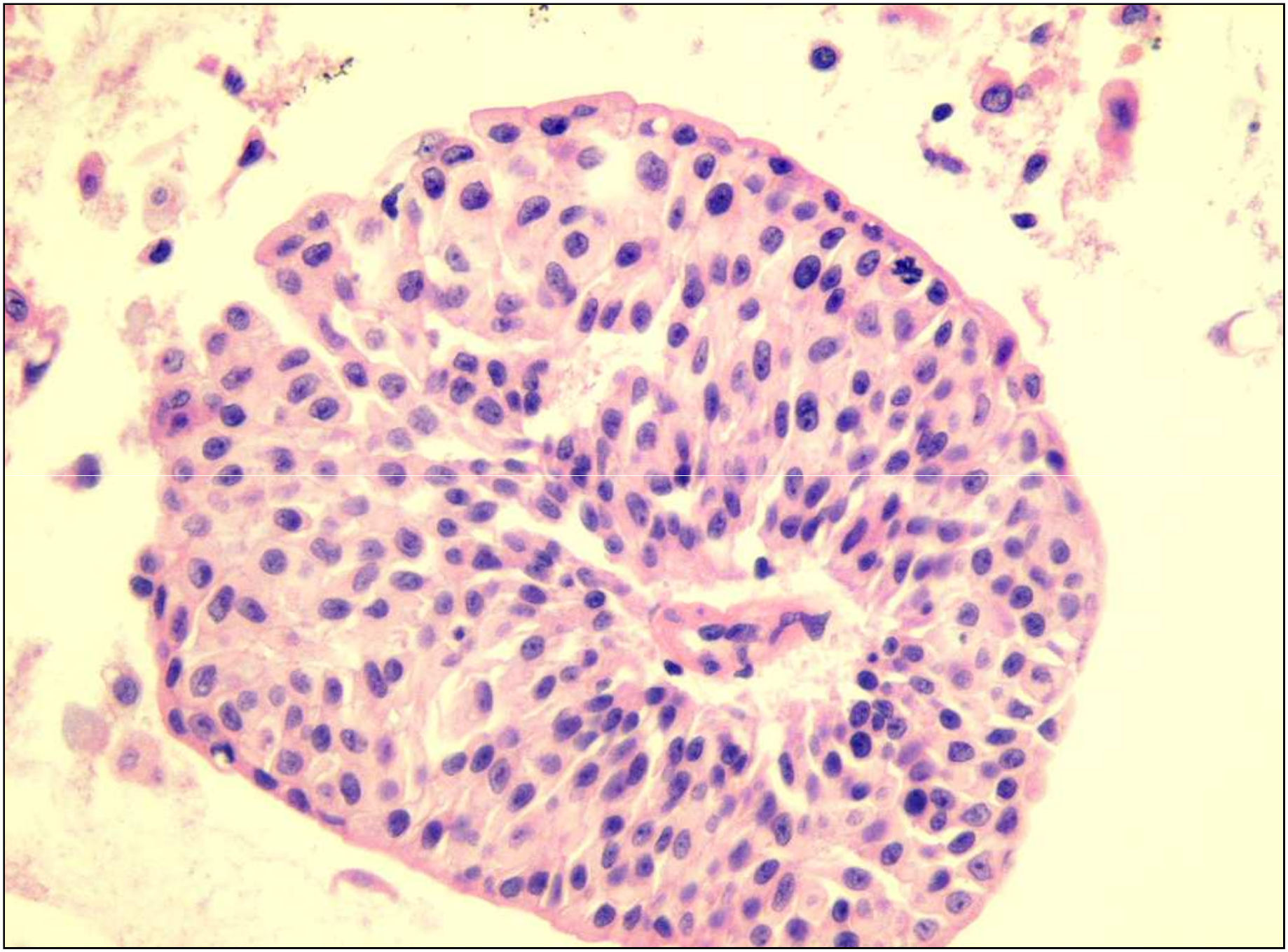


Cytoplasmic collar



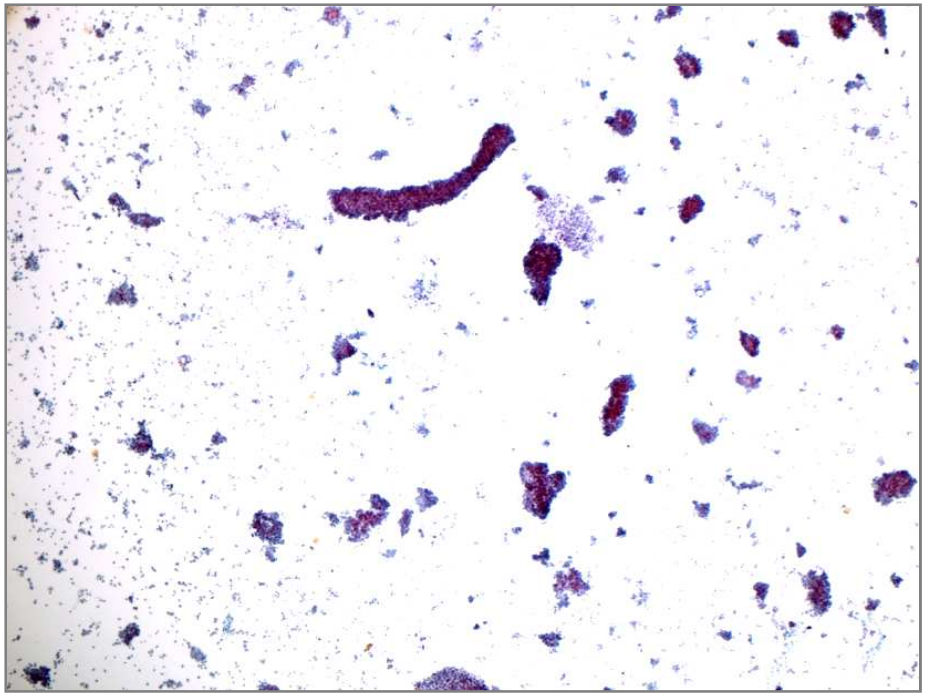

"A secure diagnosis of a LG UC can be established when tumor fragments with a clearly identified connective tissue stalk or a central capillary vessel are present in the sediment" *Koss*

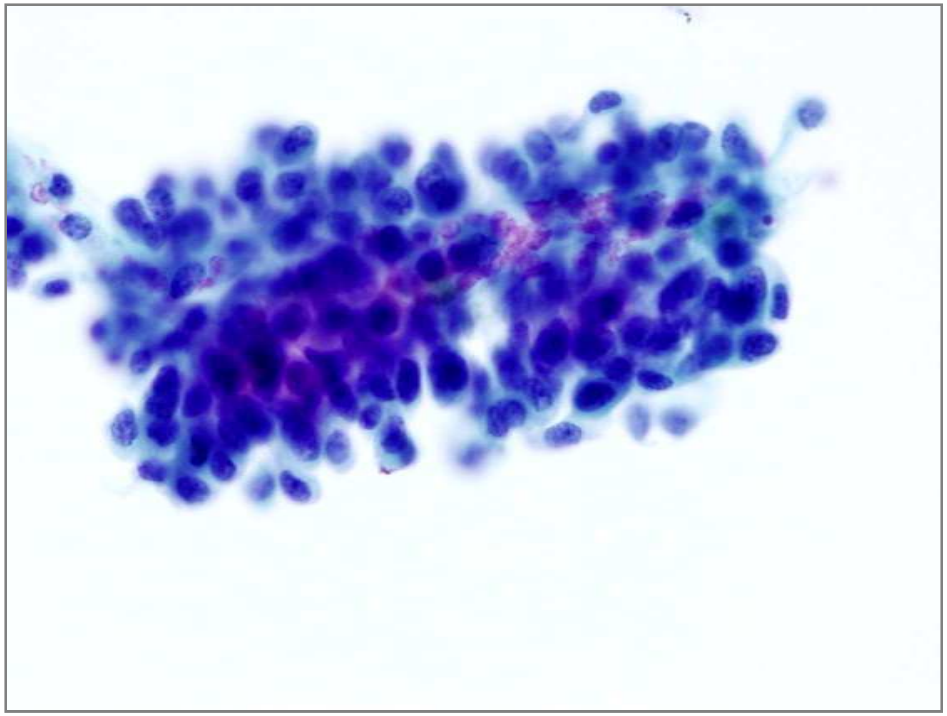


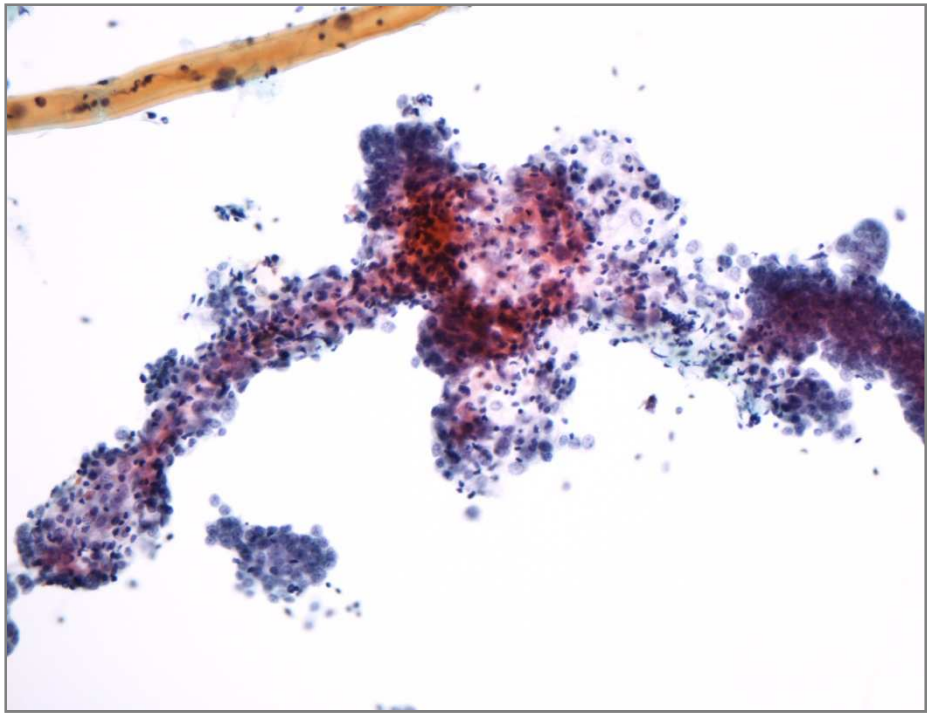


“Architecture”

– Fibrovascular cores
– Central capillary vessel

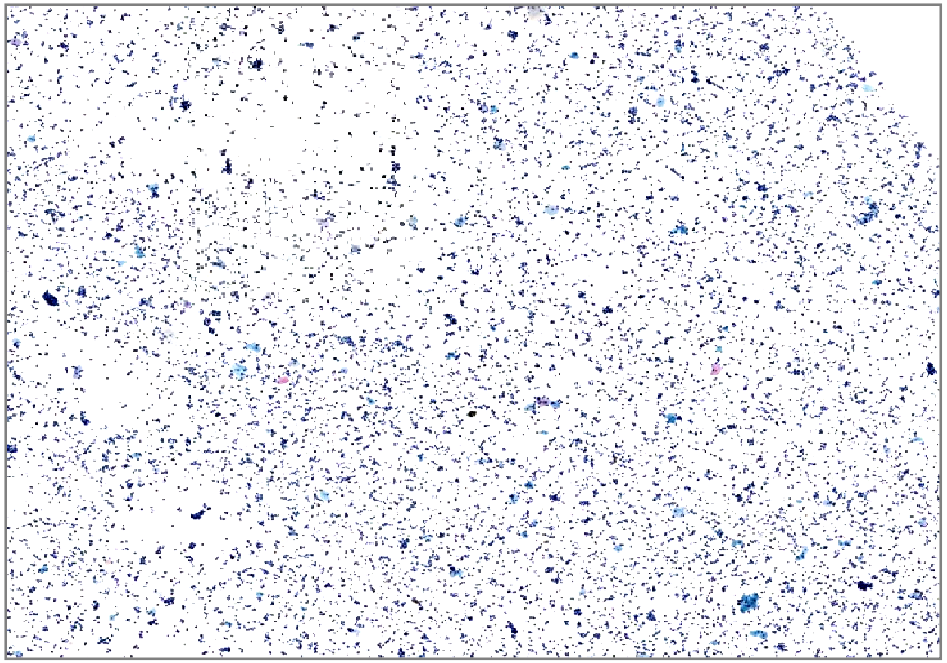


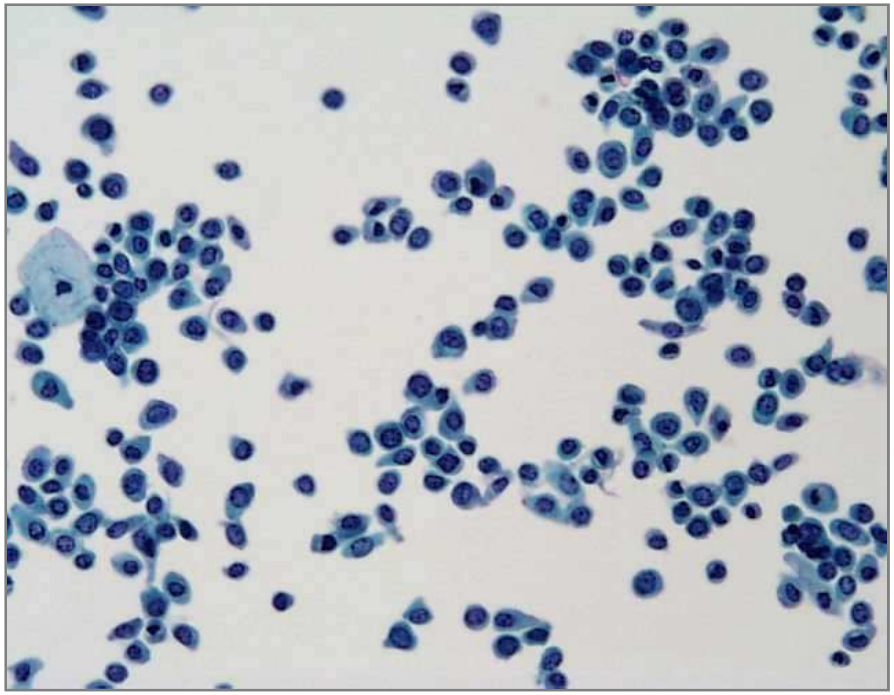


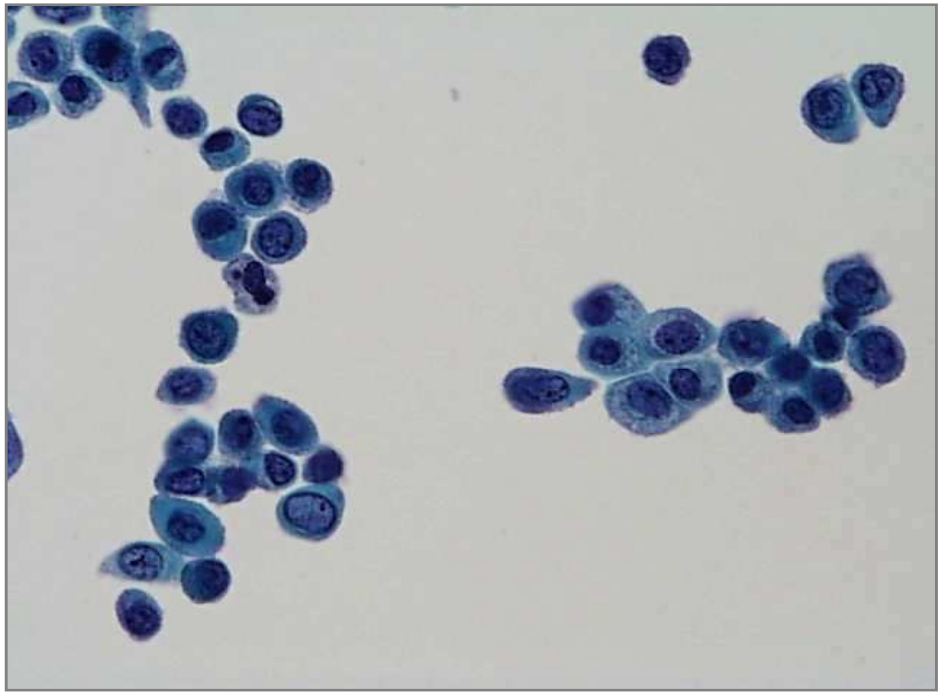


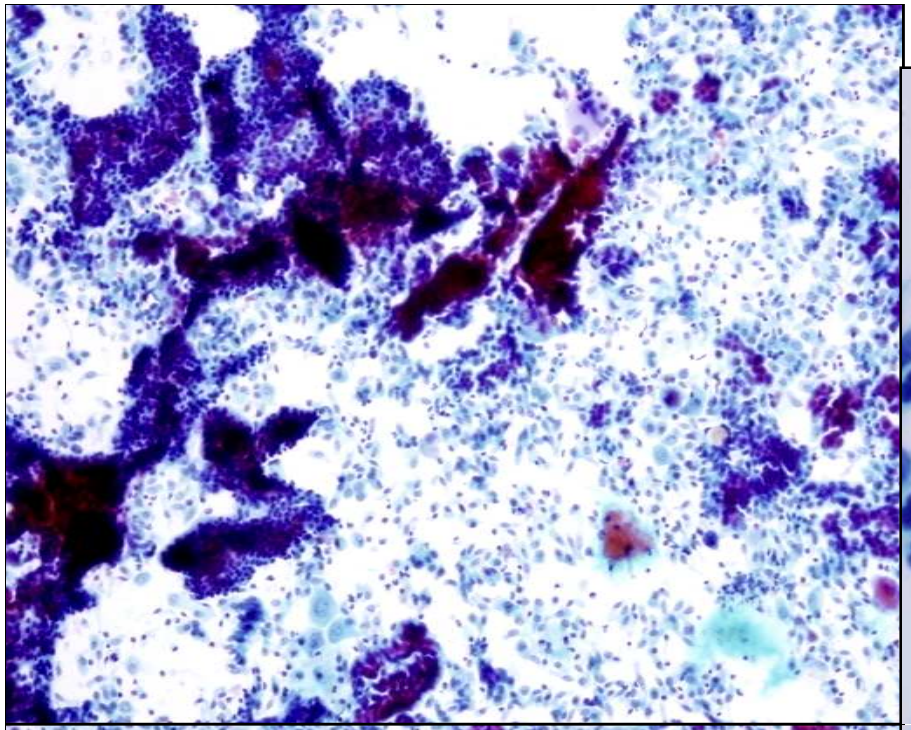
“Architecture”

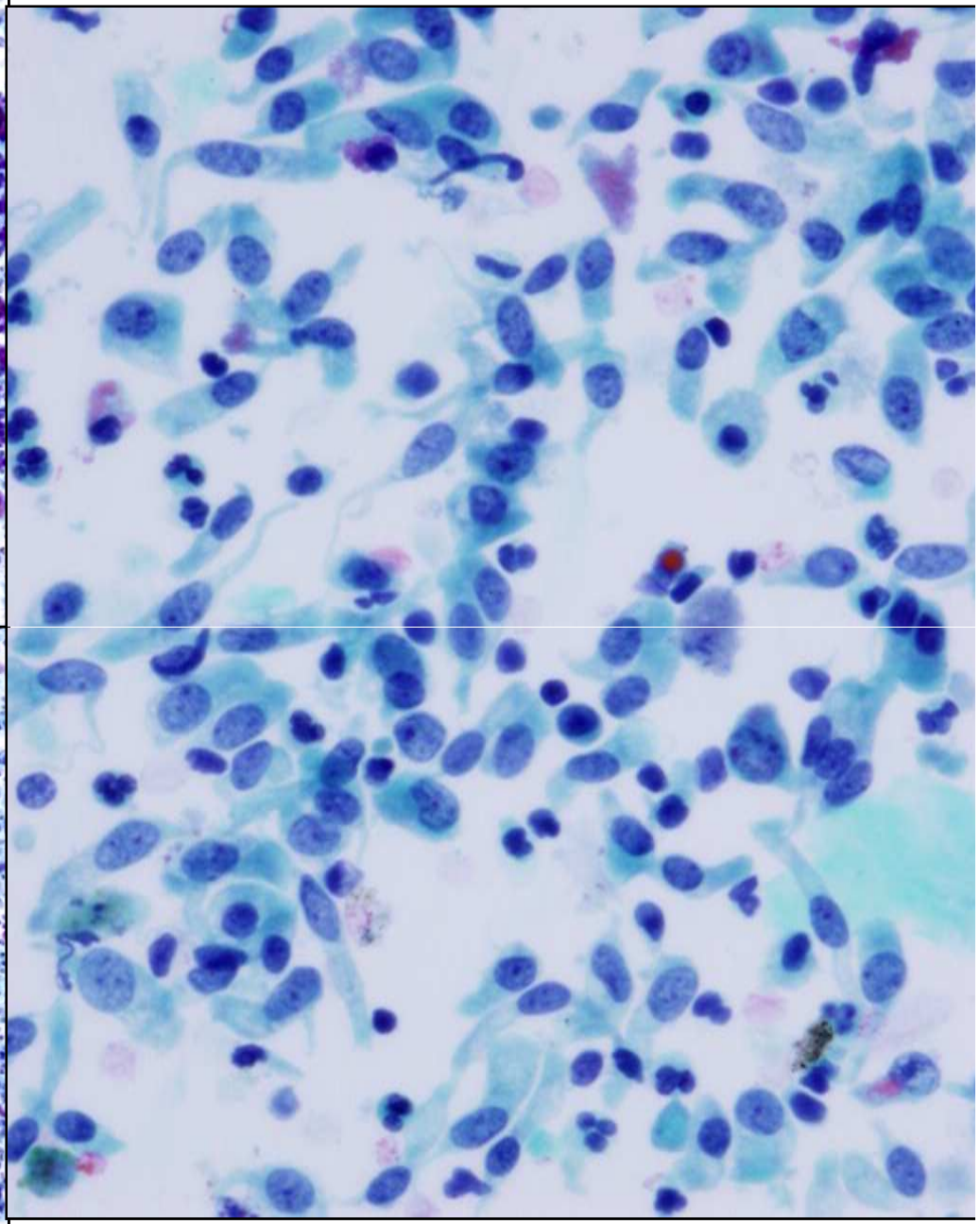
– Cellularity - “an ocean of cells”

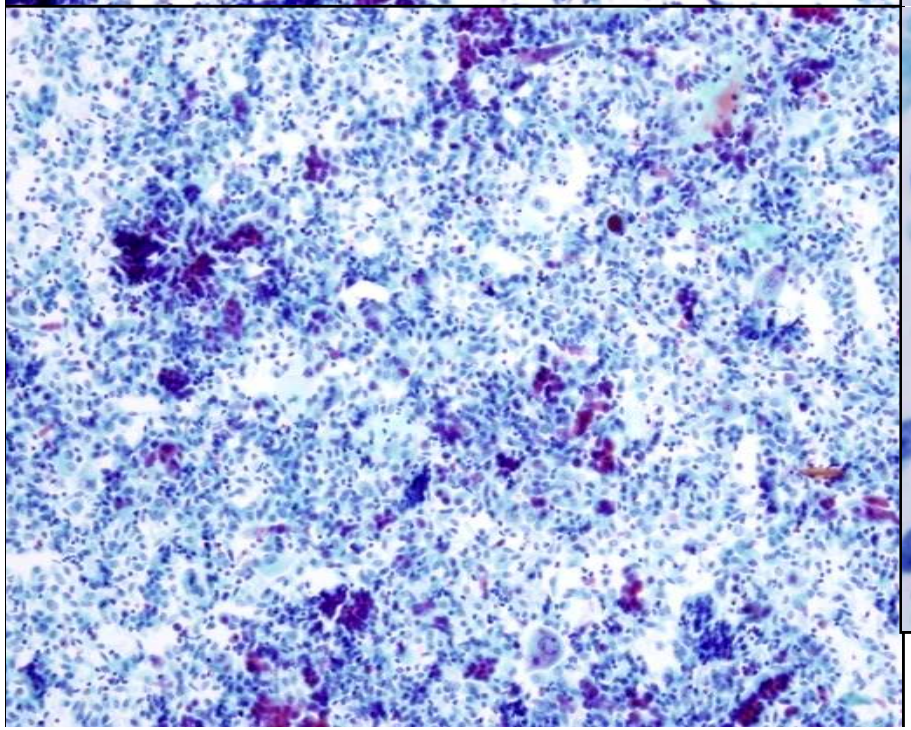






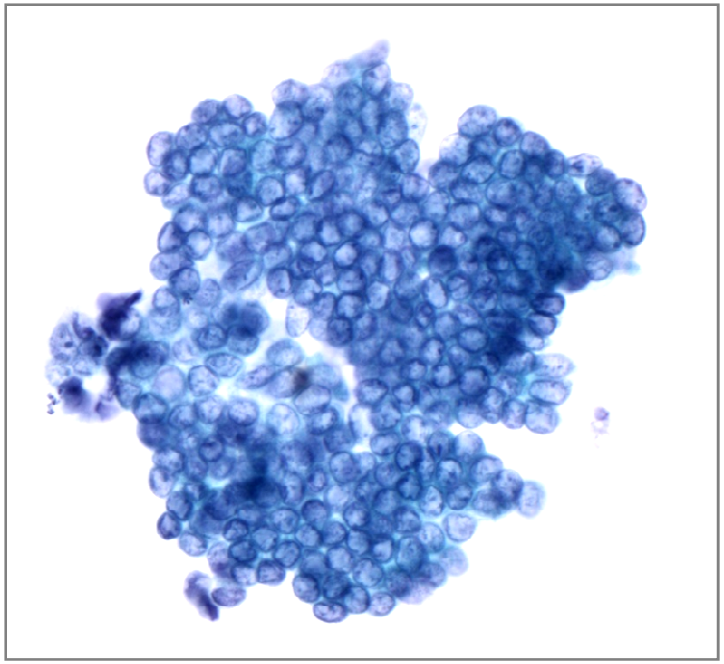


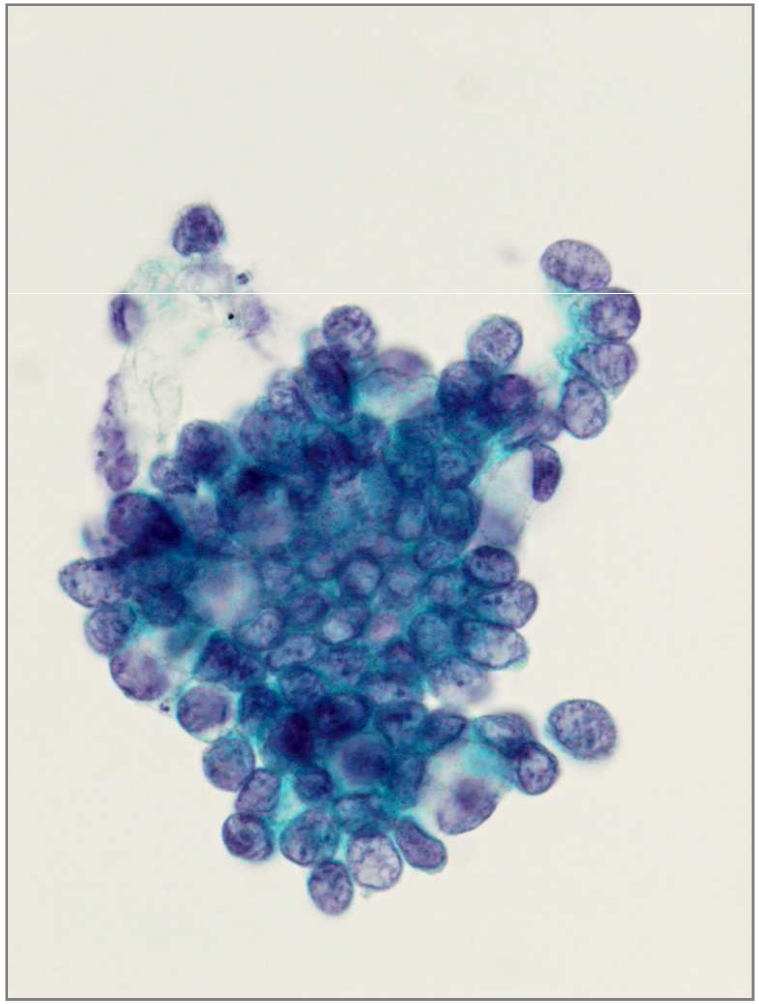




Urothelial carcinoma low grade

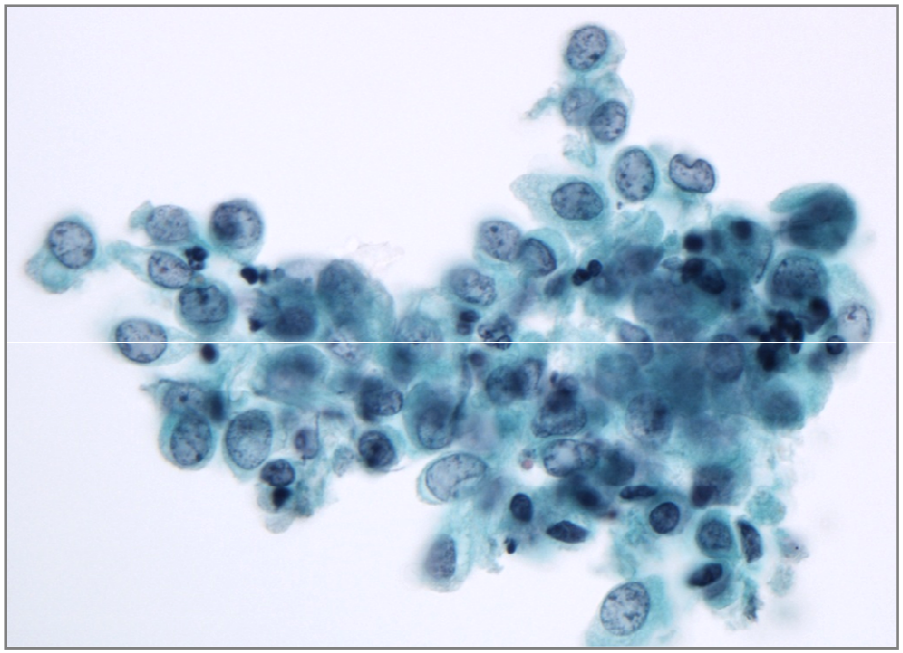
- Increased cellularity
- Presence of papillary, cohesive clusters
- Mild to moderate pleomorphism
- Increased N/C ratio
- Eccentric, mildly enlarged nuclei

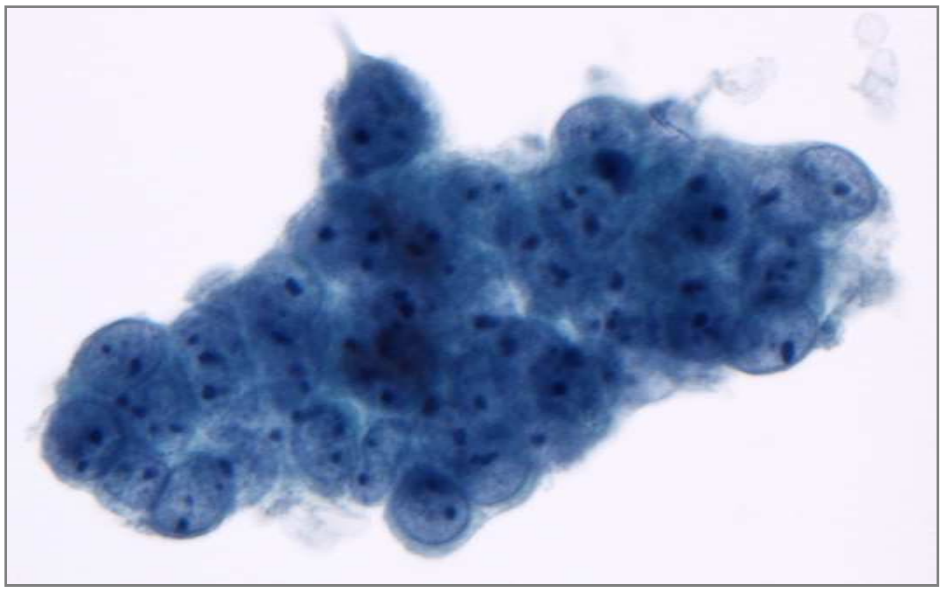




Urothelial carcinoma low grade

- Mild irregularity in nuclear membrane
- Granular, even chromatin
- Homogenous cytoplasm
- Inconspicuous nucleoli



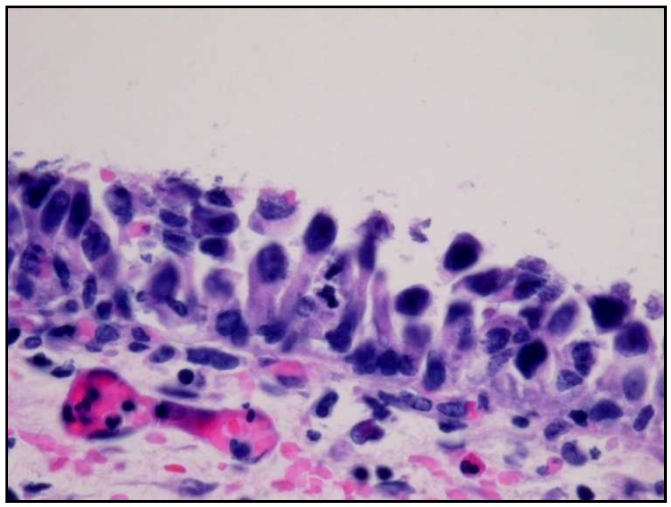


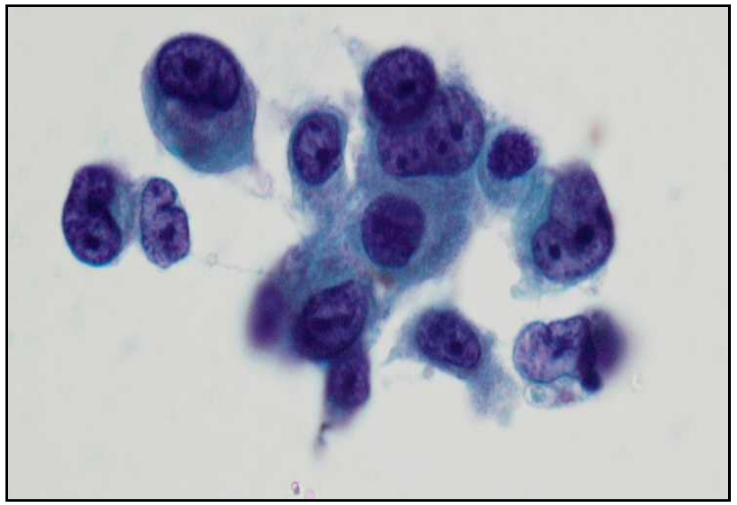
Take home message

- Cyto dx of LG UC on instrumented urines is possible (“low power diagnosis” - cellularity, fibrovascular cores) but unlikely
- If you are considering LG UC on instrumented urine check if biopsy has been taken
- If cyto+ and bx LGUC – urologist will look for CIS
- Our job is to look for HG UC

Dr. Leopold Koss, "The Father of Urine Cytology":

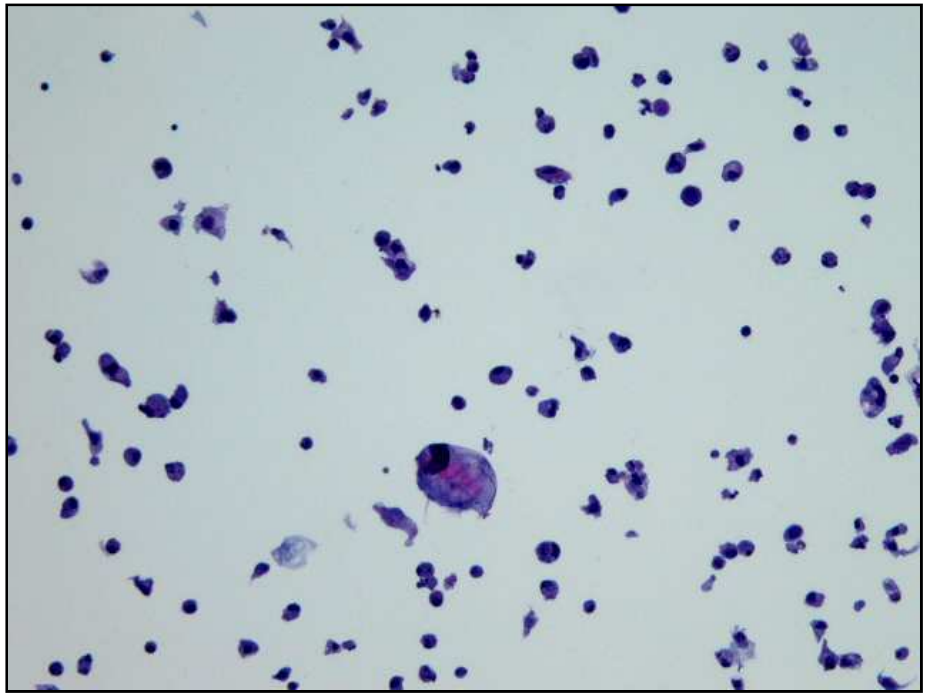
- "the principal target of cytologic evaluation of the lower urinary tract is the detection, diagnosis and monitoring of flat cancerous abnormalities of the urothelium"

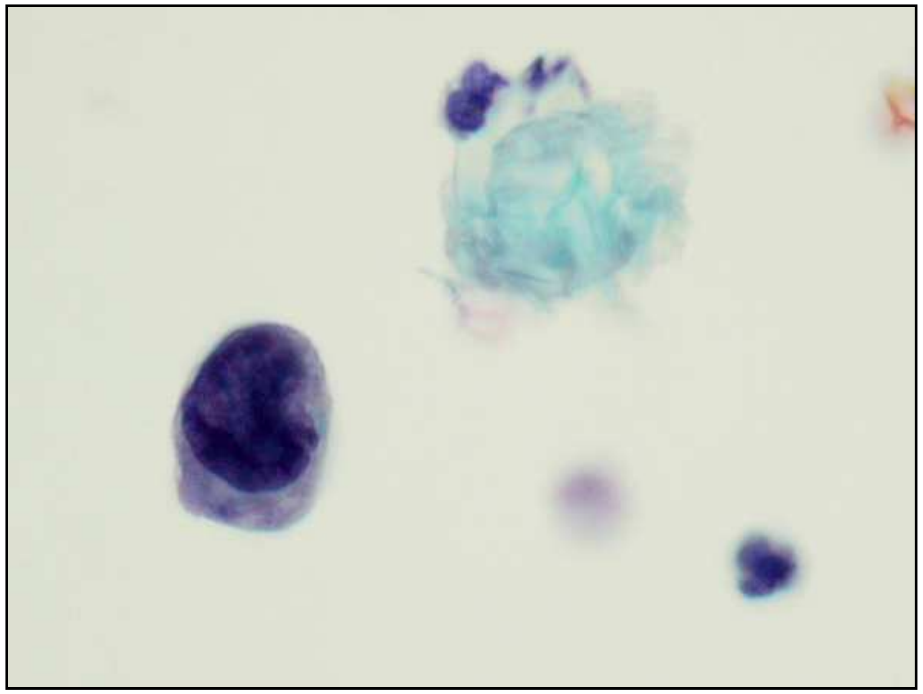




Case 3

- Voided urine from a 73 year old man with a history of a papillary low grade urothelial carcinoma. His two previous urine cytology specimens were diagnosed as – Polyoma.



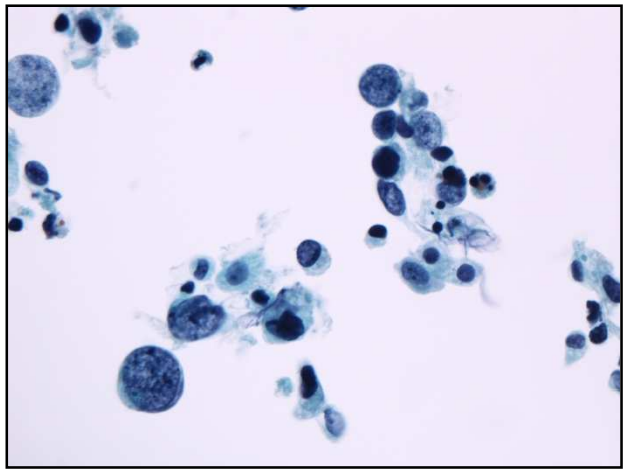


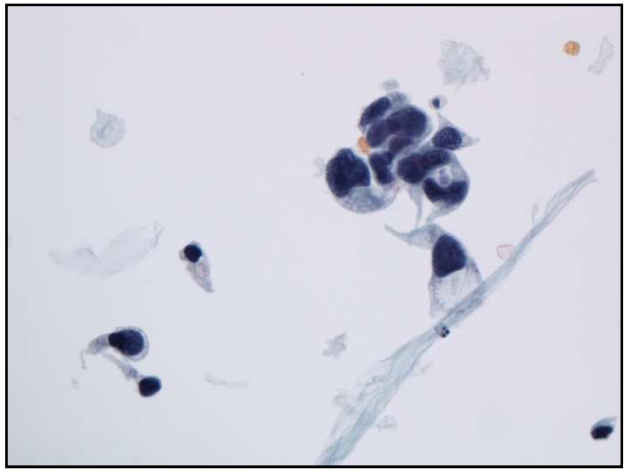
What is your diagnosis?

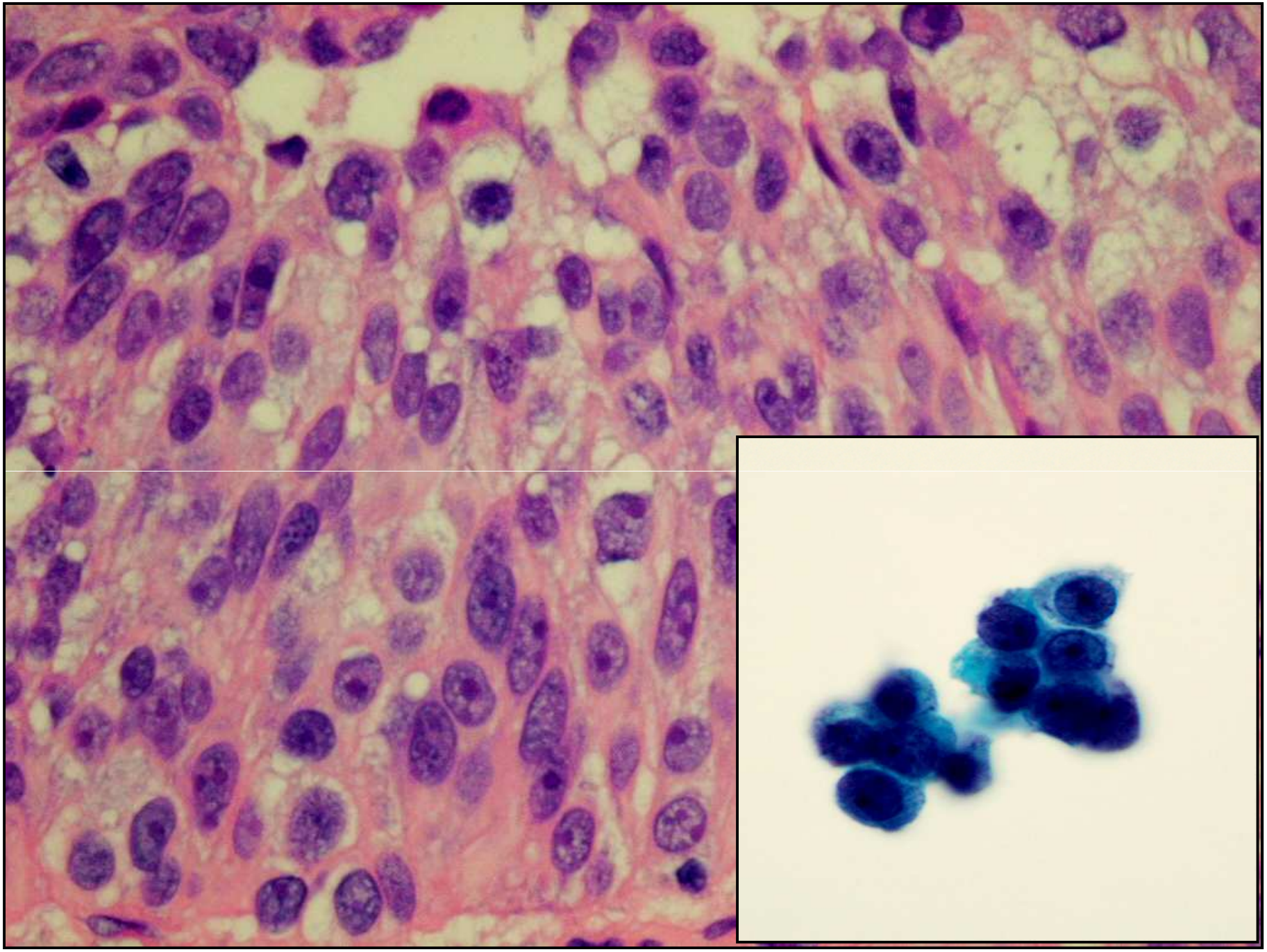
1. Urothelial carcinoma, high grade
2. Urothelial carcinoma, low grade
3. Urothelial carcinoma in situ
4. Polyoma virus infection
5. Suspicious for malignancy

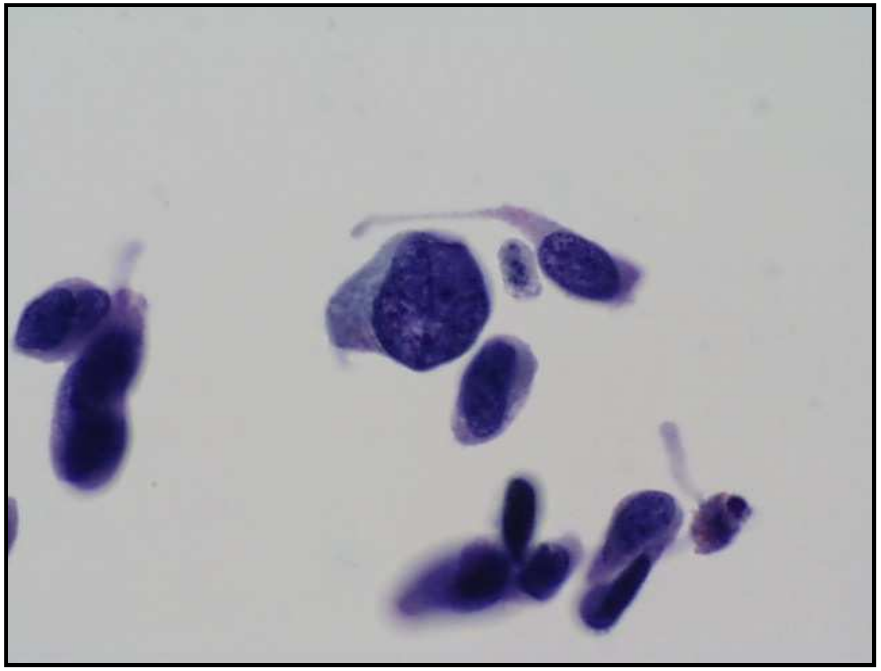
Urothelial carcinoma high grade

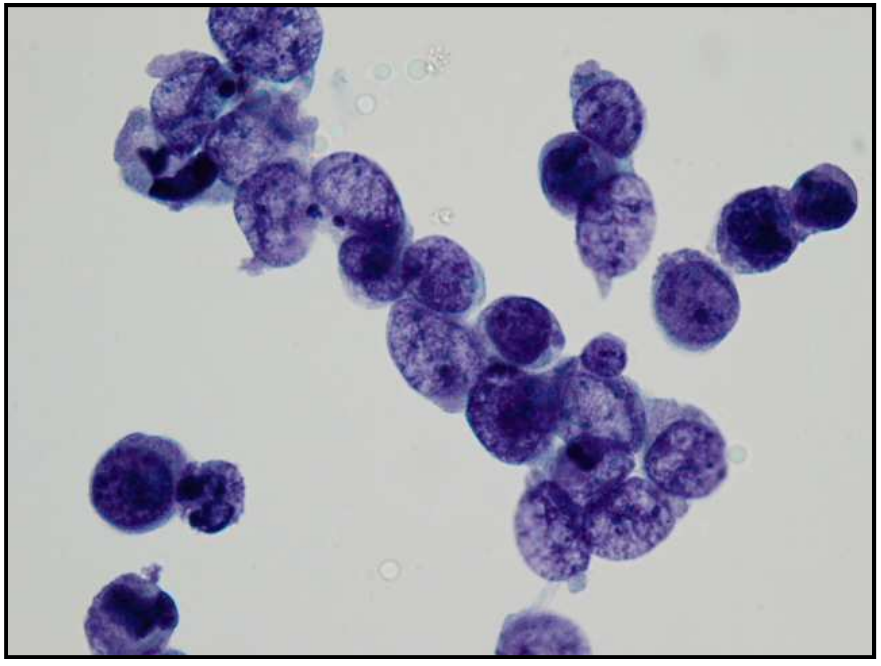
- Increased cellularity
- Presence of loose clusters and single cells
- Moderate to marked pleomorphism
- Eccentric, enlarged, pleomorphic nuclei
- Irregular nuclear membrane
- Coarse chromatin
- +/- prominent nucleoli
- Squamous or glandular differentiation



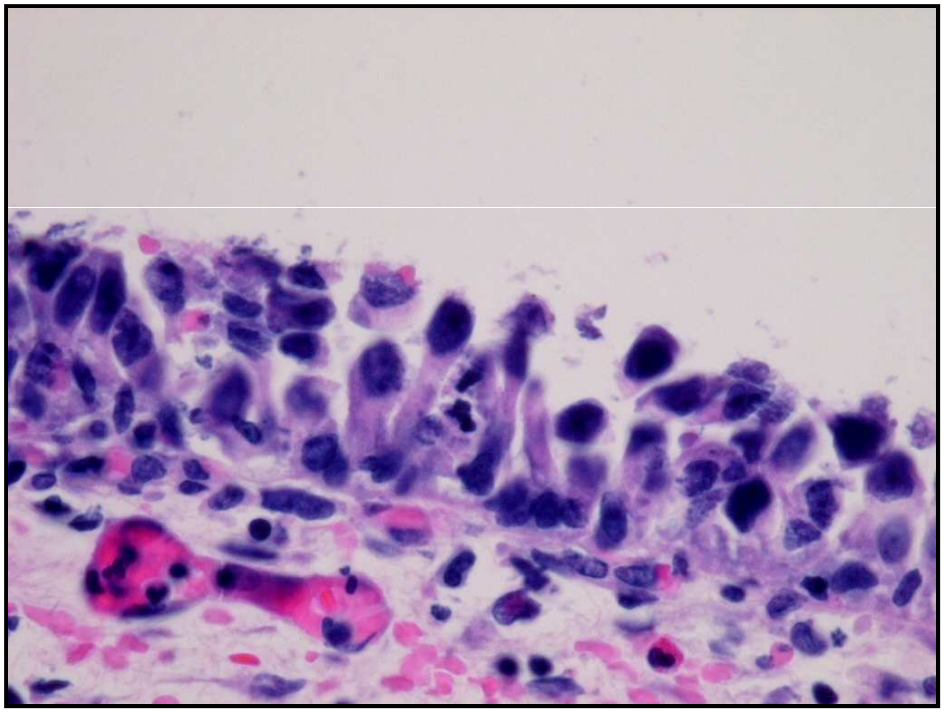


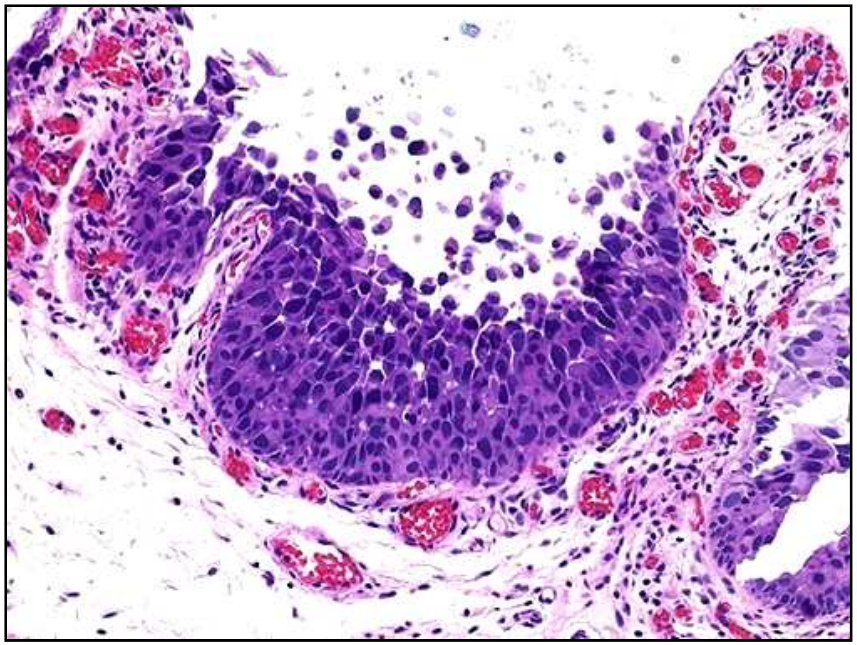


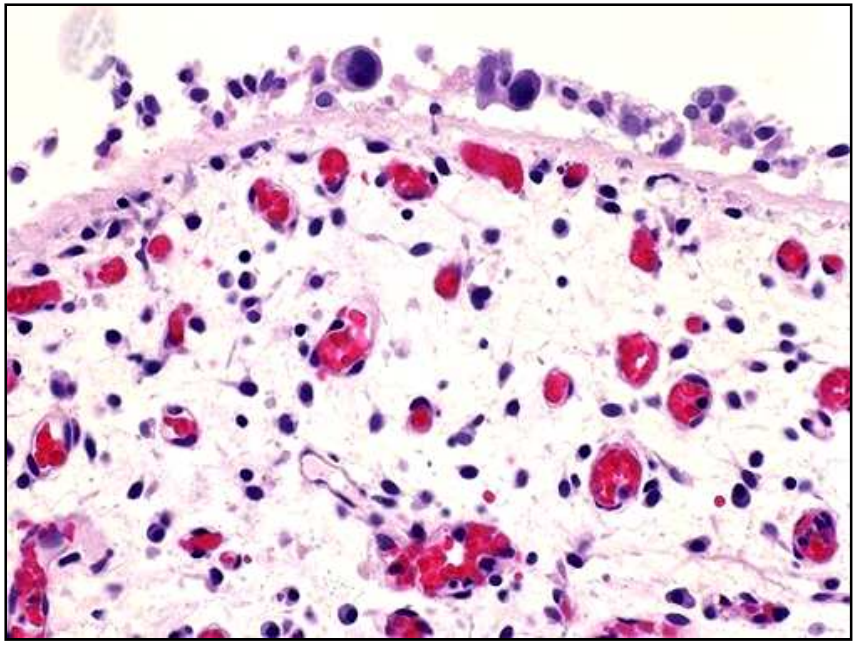




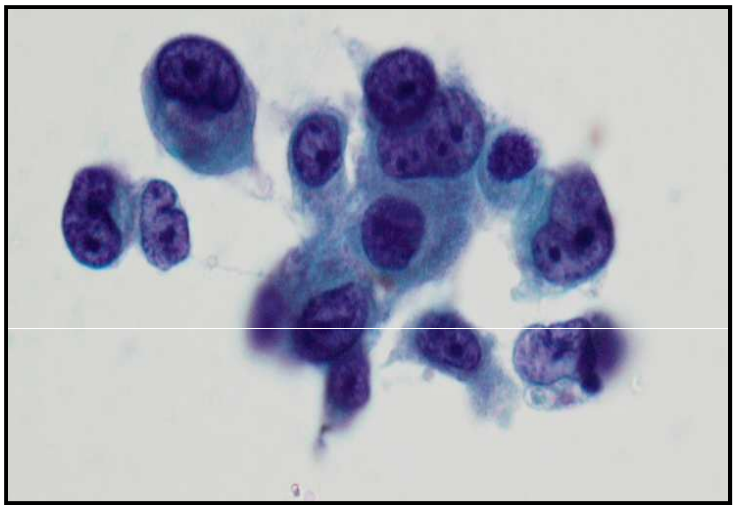
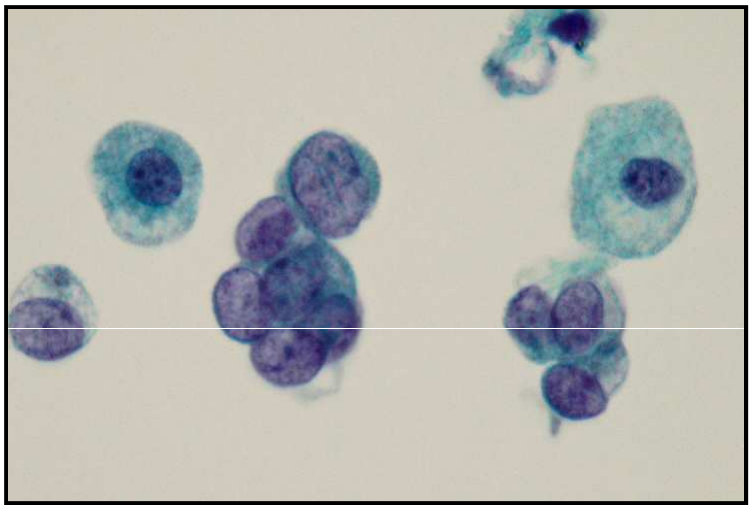
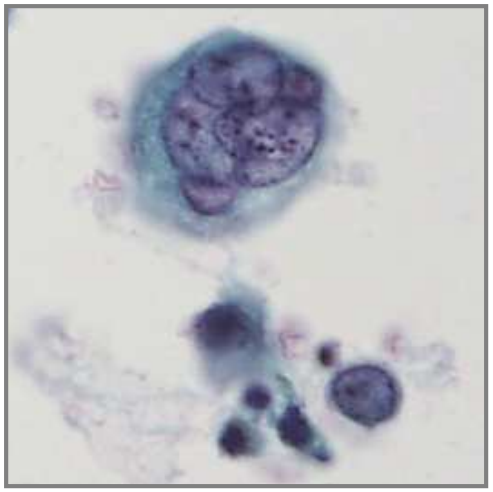
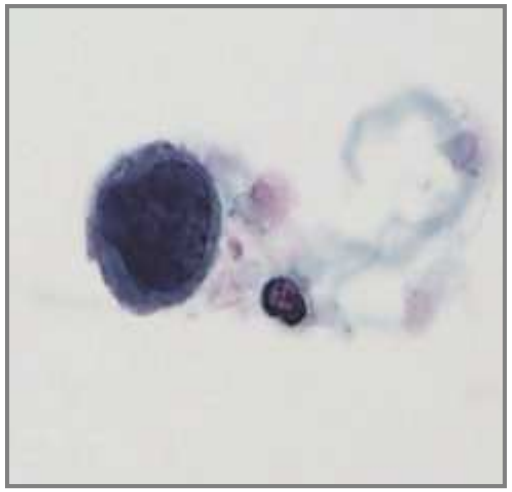
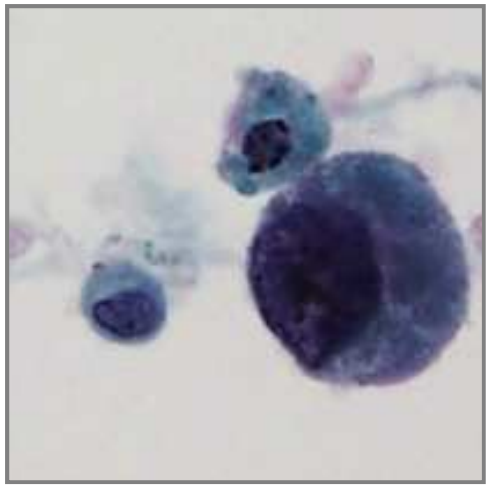
Carcinoma in situ



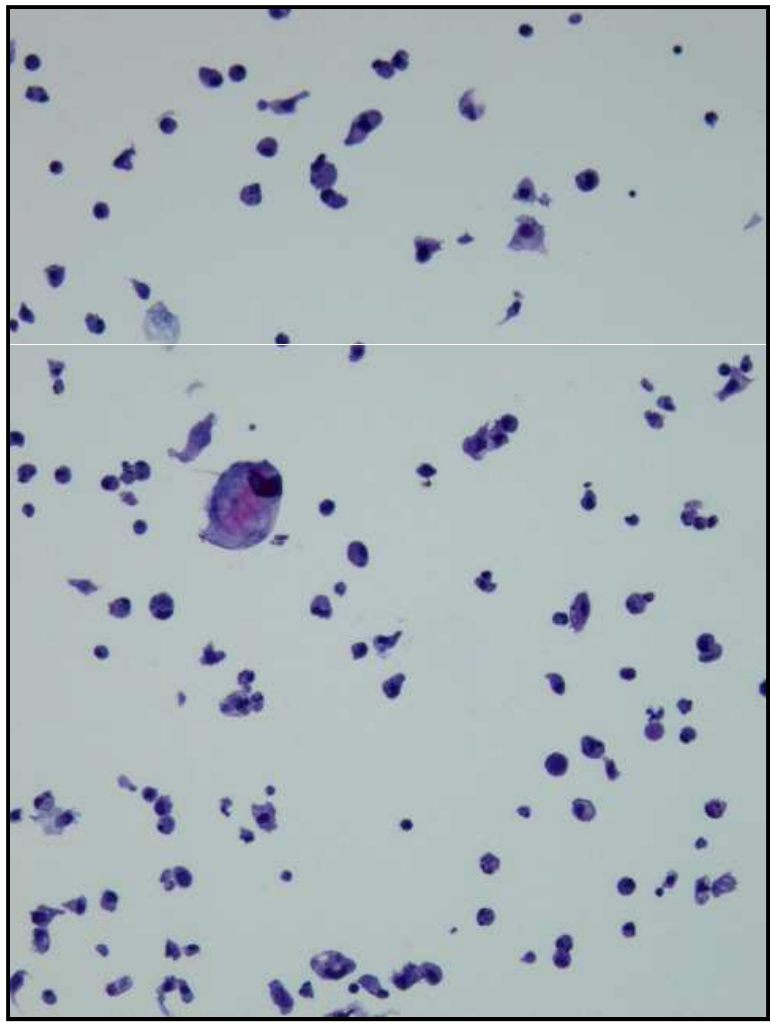


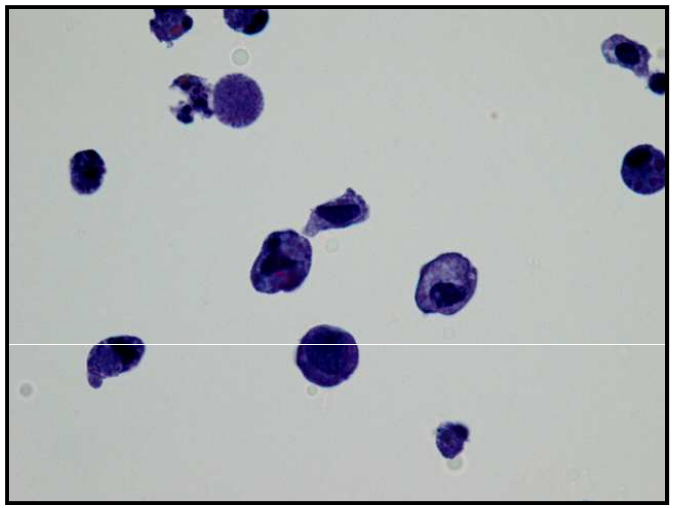


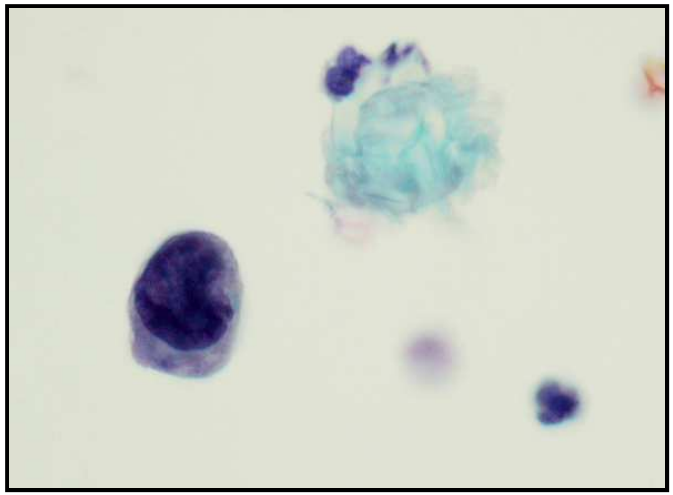
Carcinoma in situ

Voided urine



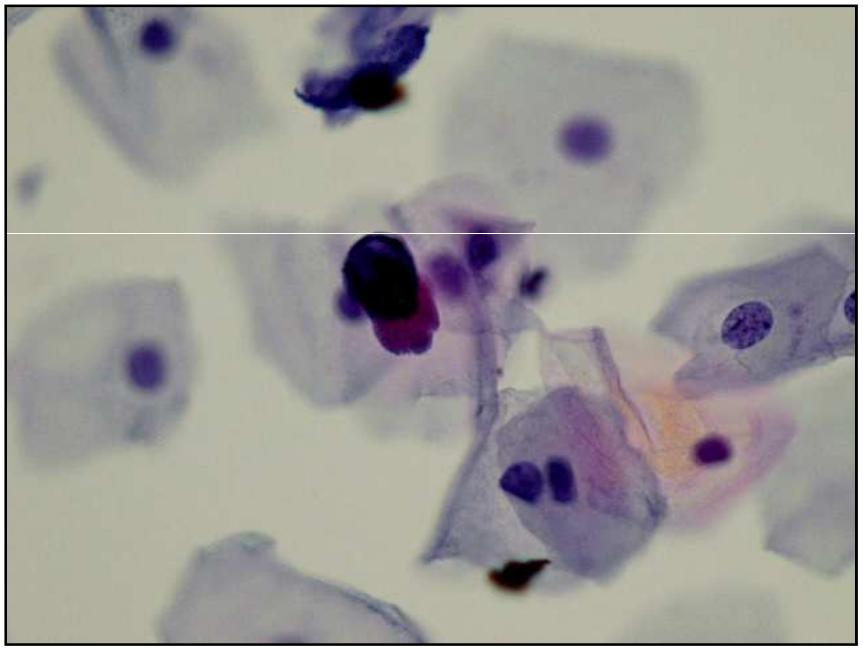


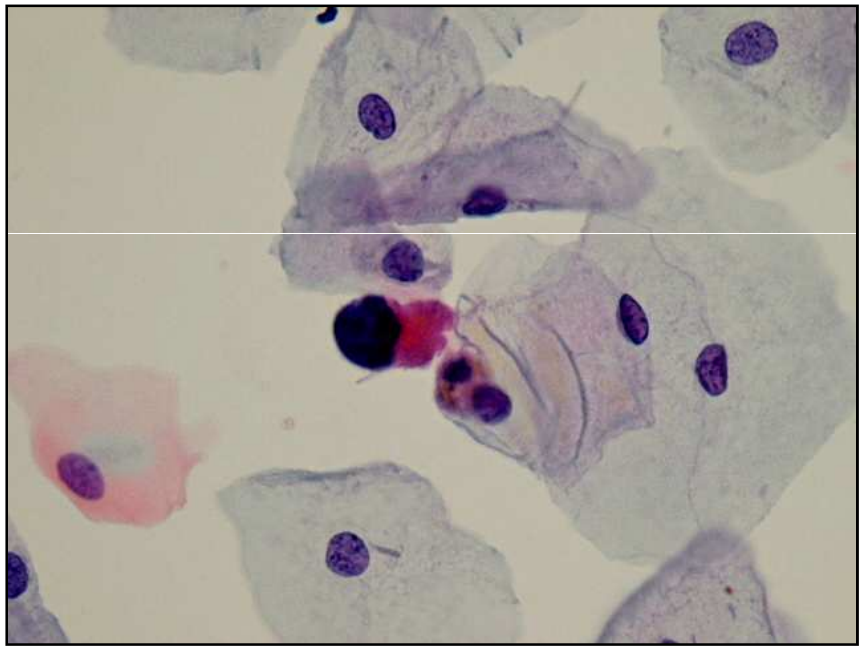


Take home message

- Cellularity – dispersed single cells – in voided urine – think about malignancy
- If the urine is POSITIVE (in general) it is a high grade carcinoma
- We can not asses the stage - carcinoma in situ (Tis) looks the same as papillary HG non-invasive (Ta) or invasive (T1-T3)
- If cyto+ and bx LGUC – urologist will look for CIS

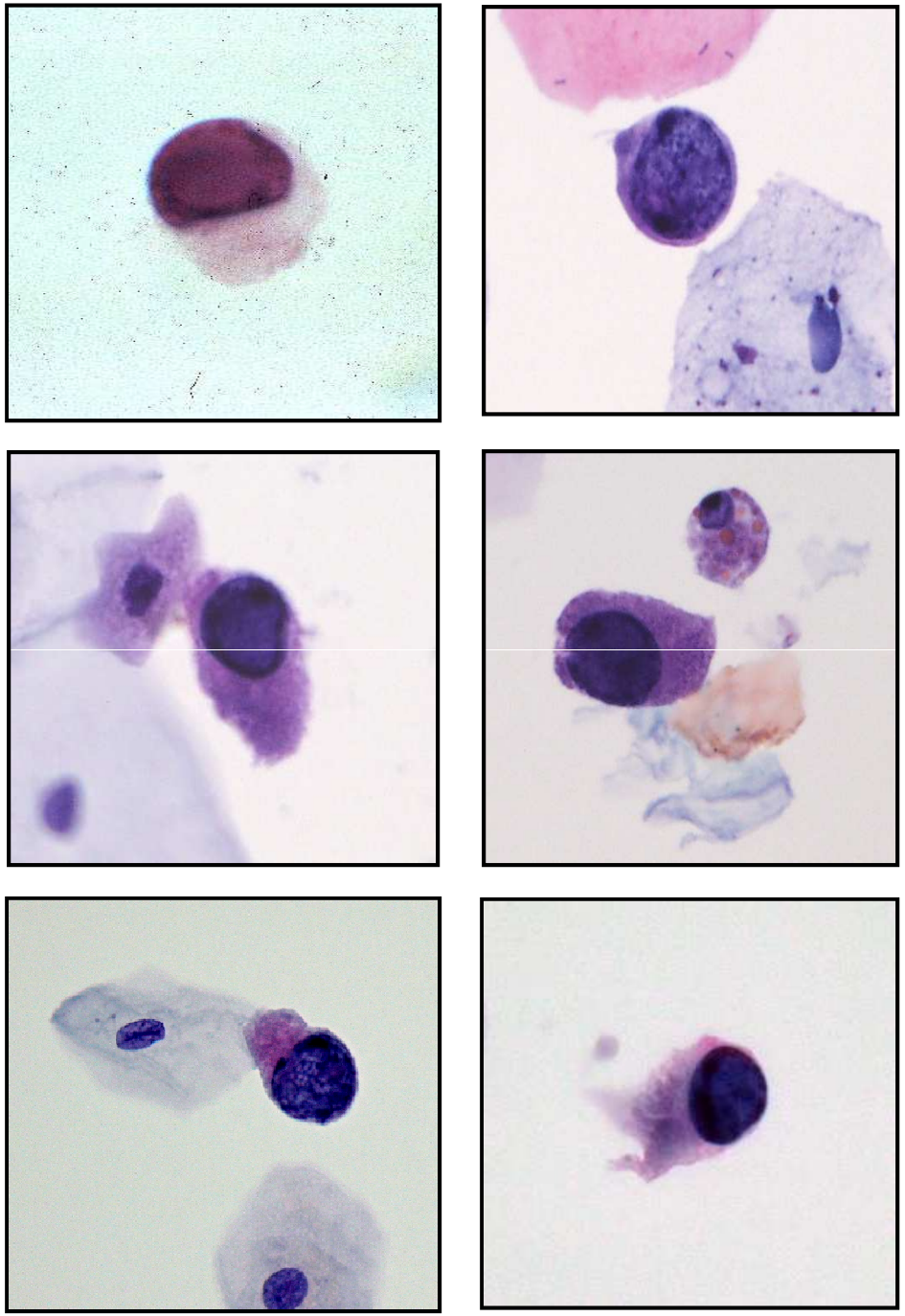
What about previous urines diagnosed as Polyoma?





Human Polyoma Virus

- Small, non-enveloped, double-stranded DNA viruses, BK and JC
- Infection occurs during childhood and is usually subclinical, > 90% of adults are seropositive
- Infection is reactivated in individuals with various degrees of immunological deficits
- Intermittent viruria is demonstrable in 0.3% of healthy adults
- Polyoma virus nephropathy – 3%-4% of renal transplants, loss of graft ~ 50% of cases.
- Cytology - single, large, homogenous, basophilic inclusions occupying most of an enlarged nuclear area (“decoy cell”), also “empty cells” and “comet cells”
- Urothelial cells affected by virus have an abnormal DNA content

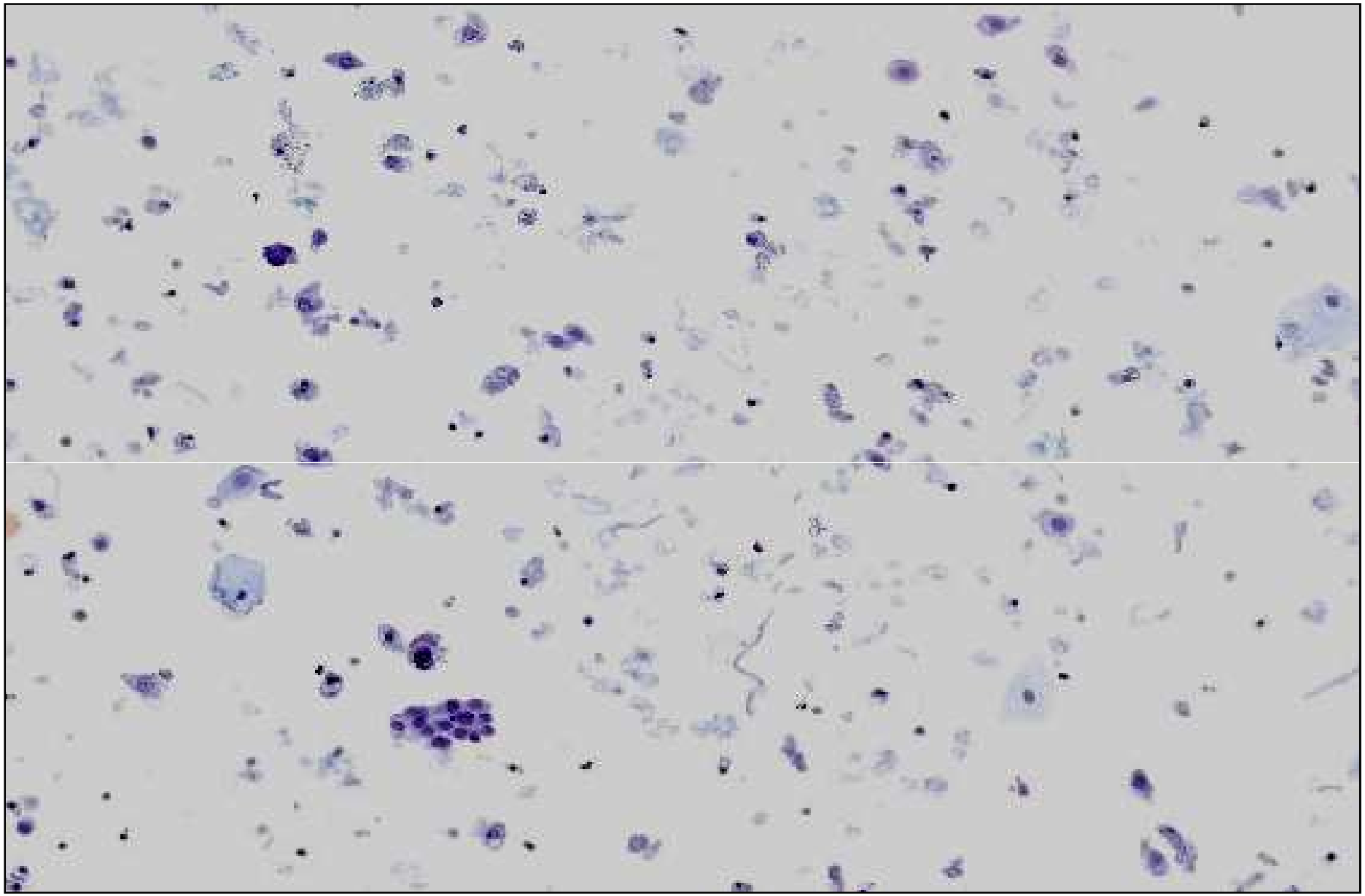


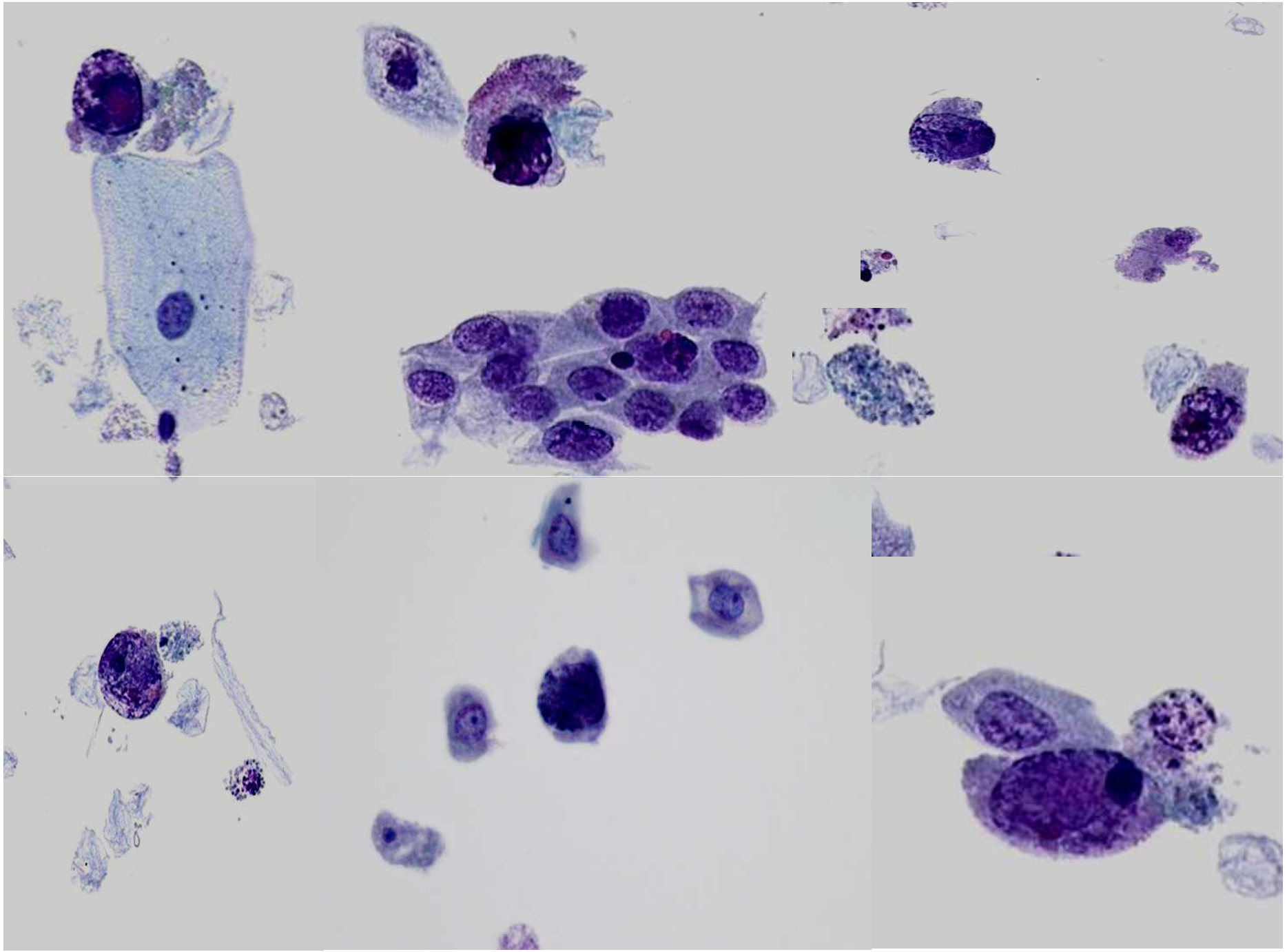
Take home message

- Polyoma – still a significant pitfall
- Irregularity of nuclear membrane – the best discriminatory factor
- You can have A LOT of affected cells
- DNA virus – be ware if you are using DNA based ancillary studies

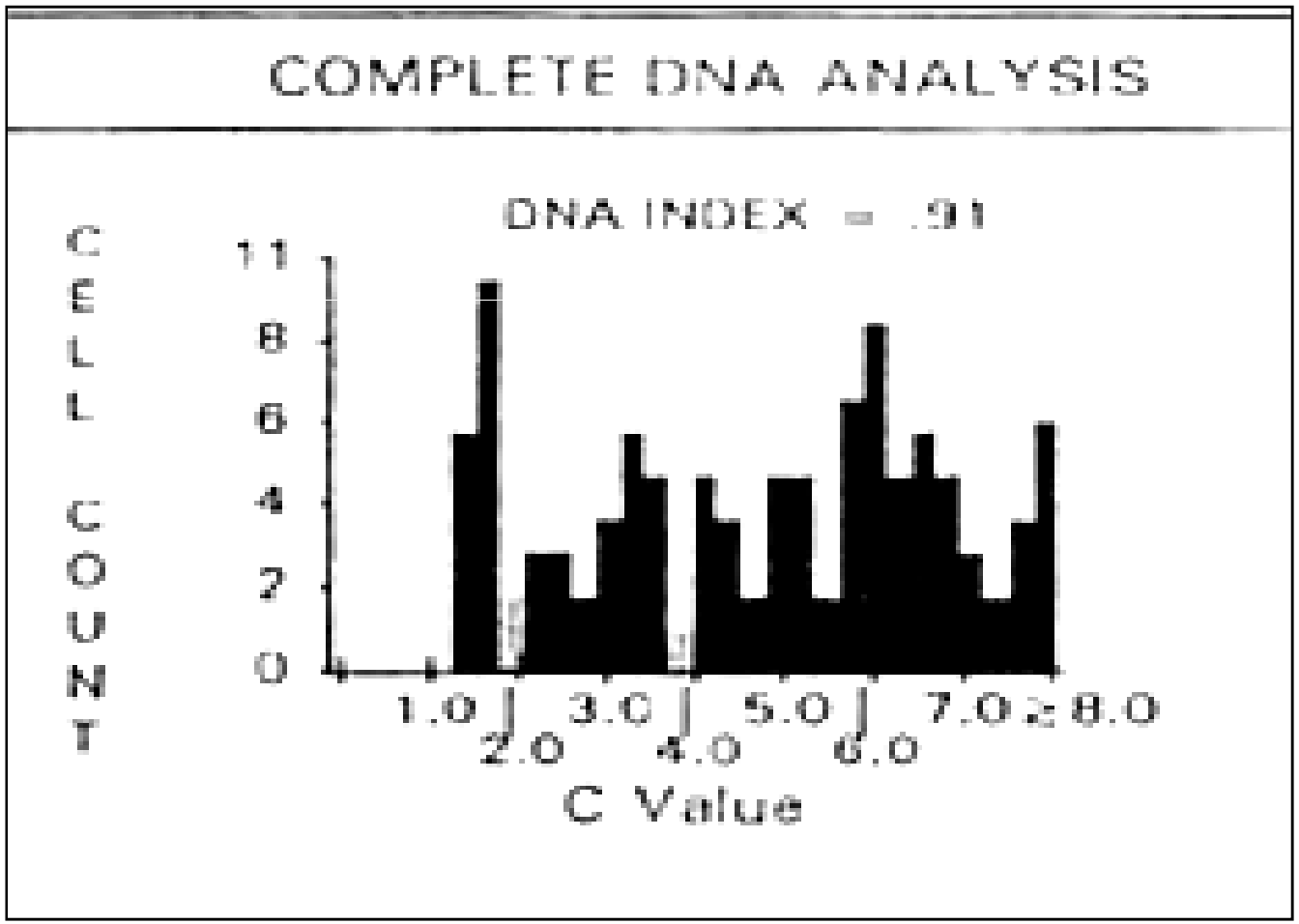
Case 4

- 65 year old man with hematuria
- Voided urine

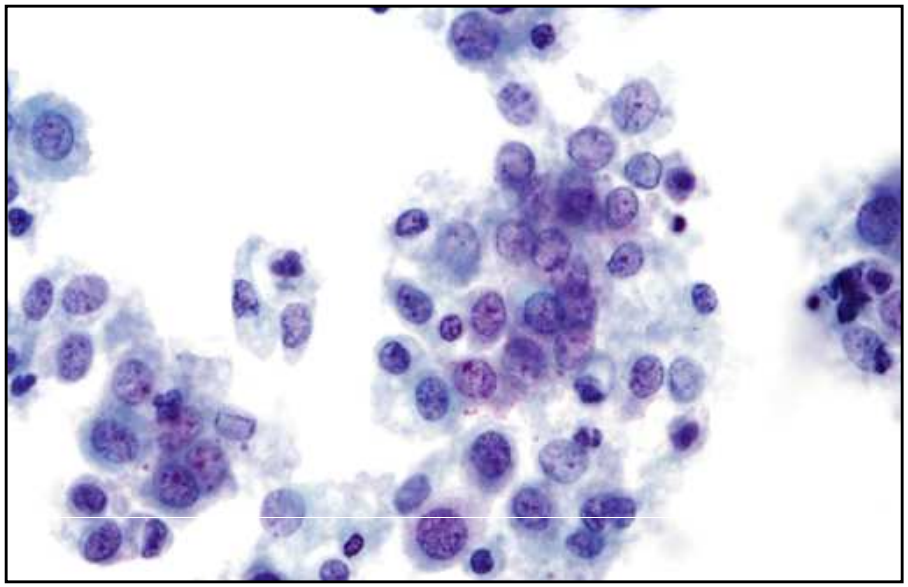


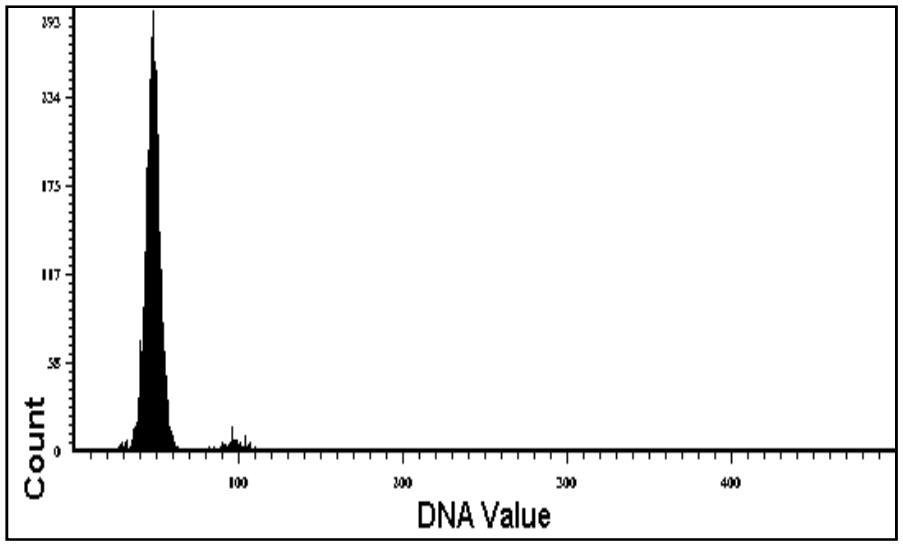


DNA Ploidy - Aneuploid

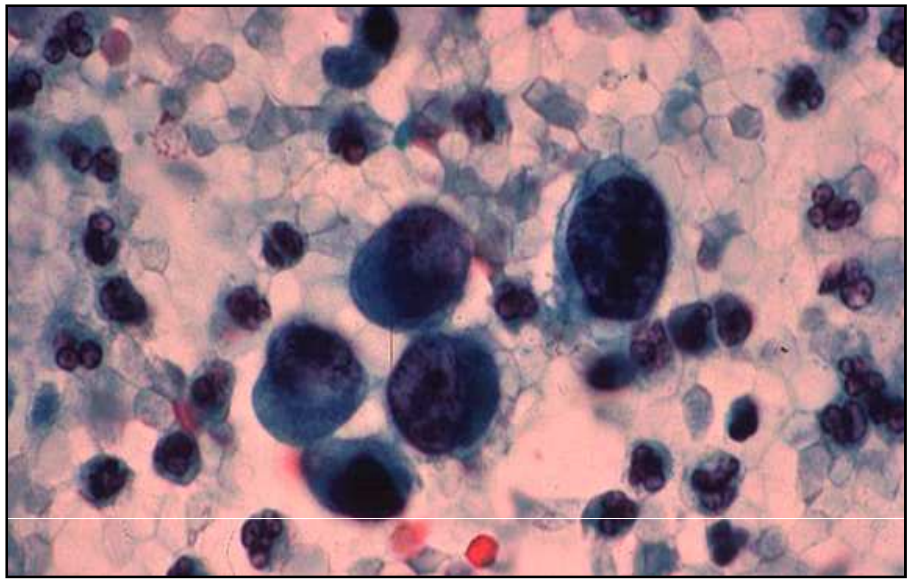


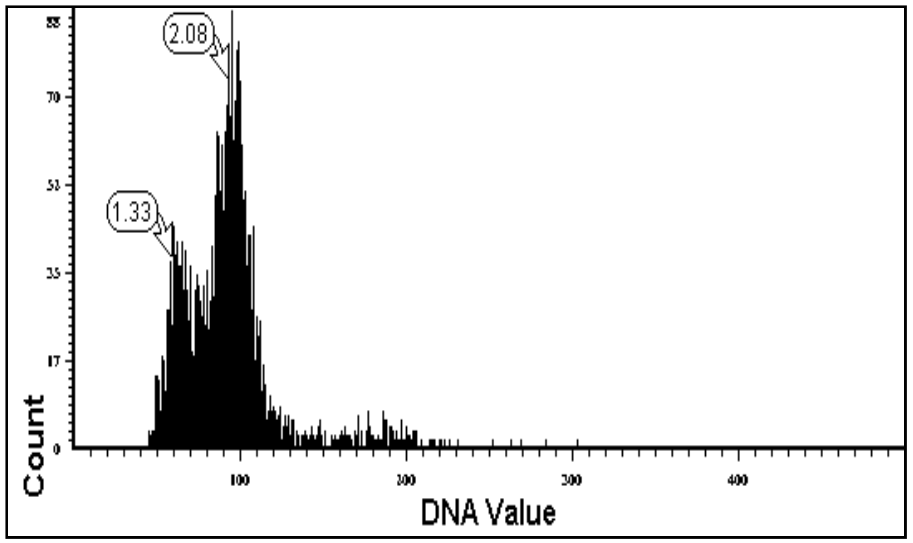
Urothelial carcinoma, low grade, diploid





Urothelial carcinoma, high grade, aneuploid

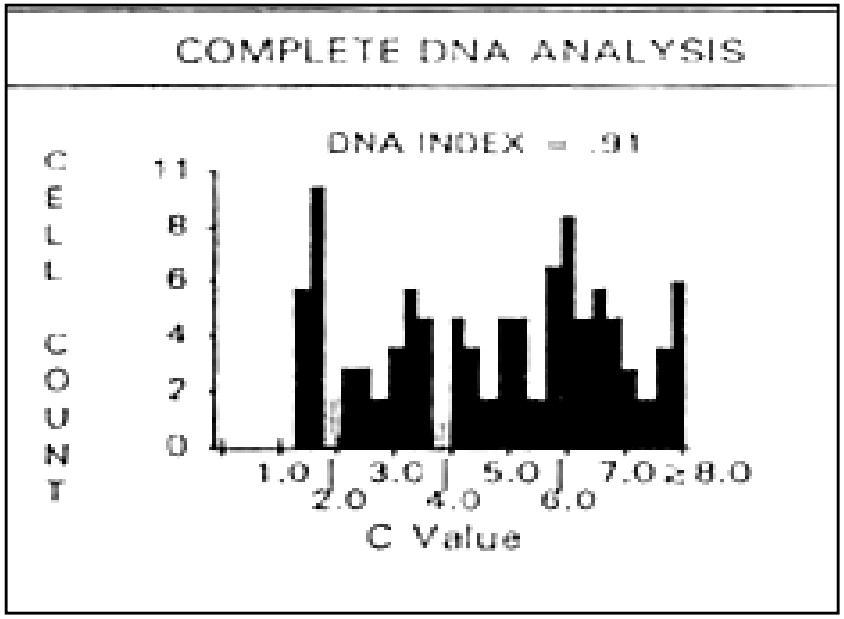


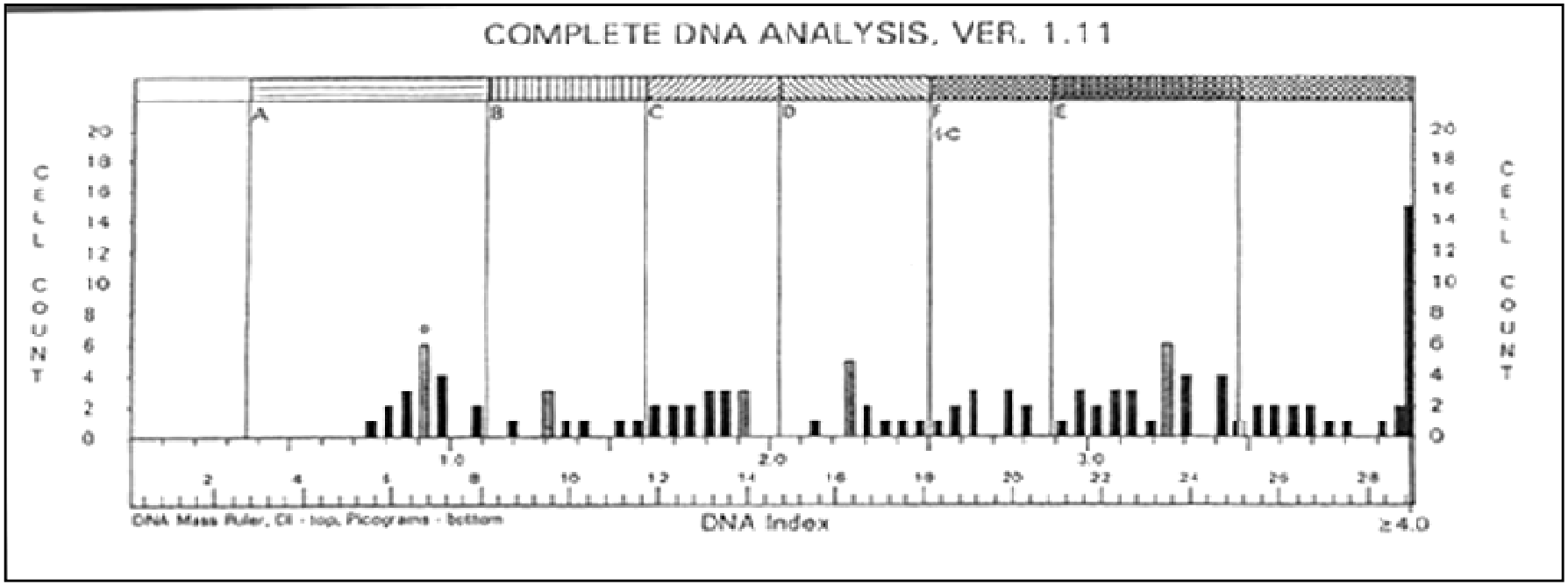


Diagnosis?

- Urothelial carcinoma
- Random biopsies x2
- Cystoscopy x2
- Imaging studies
- Negative
- Patient sued the pathologist

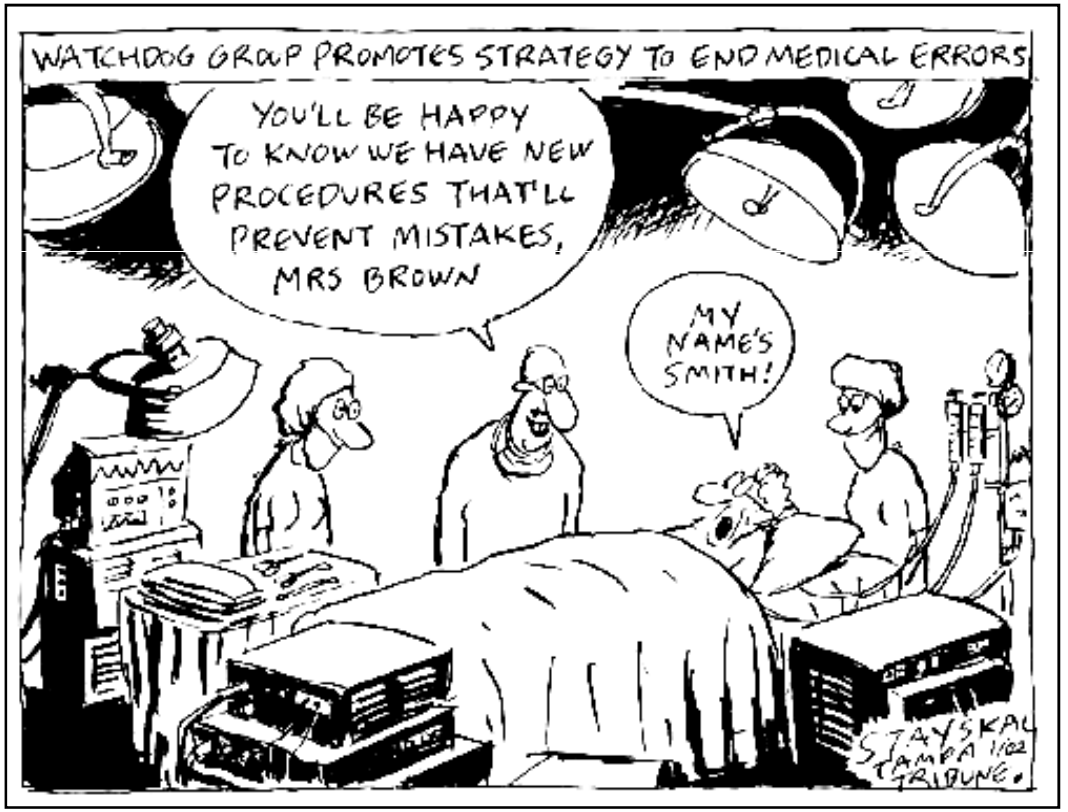
DNA ploidy


COMPLETE DNA ANALYSIS
DNA INDEX = .91
CELL COUNT
0
2
4
6
8
11
1.0
2.0
3.0
4.0
5.0
6.0
7.0
≥8.0
C Value

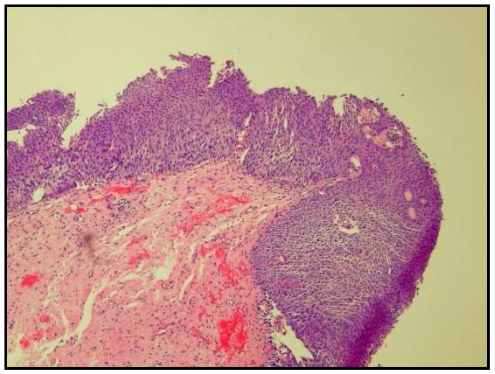

COMPLETE DNA ANALYSIS, VER. 1.11
CELL COUNT
A
B
C
D
E
1C
DNA Index
≥4.0

Why has the error occurred?

- Morphologic similarities
- Unusually high number of affected cells
- Overdependence on ancillary studies



HYPERPLASIA >90%



DNA ploidy by IA, FCM, LSC

9q del

Ta

Ta

RAS

9p del

p16

T1

T2-4

N+/M+

Normal urothelium

RB

p53

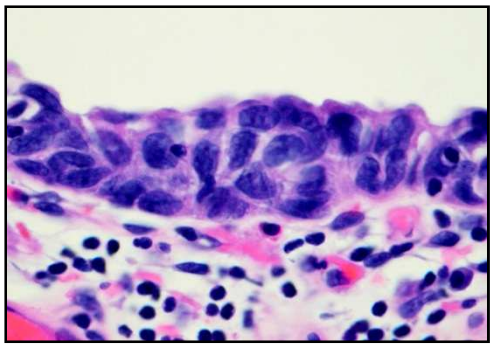
Tis

T1

T2-4

N+/M+

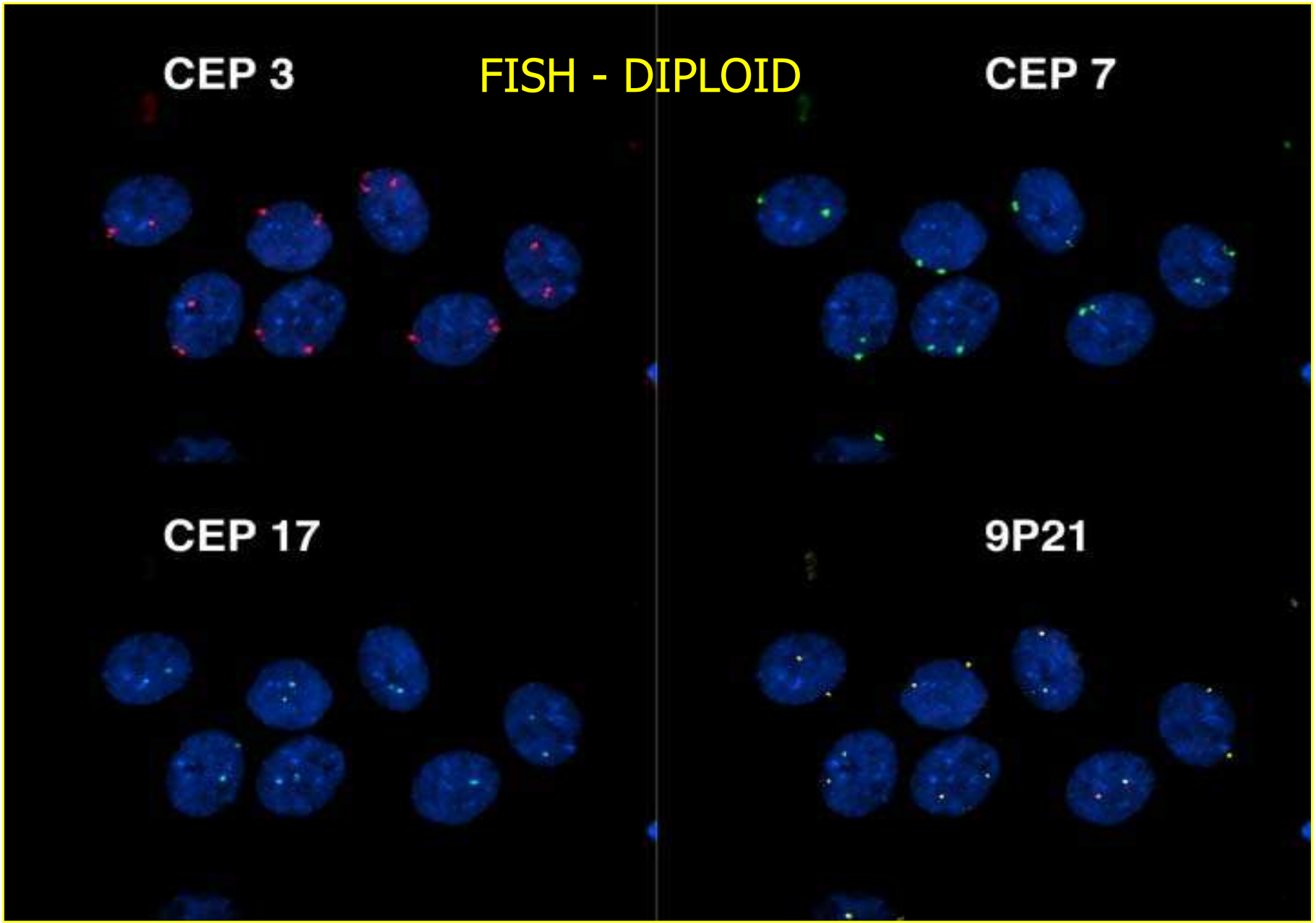
5q, 3p del, 9p del……..



DYSPLASIA ~ 1%

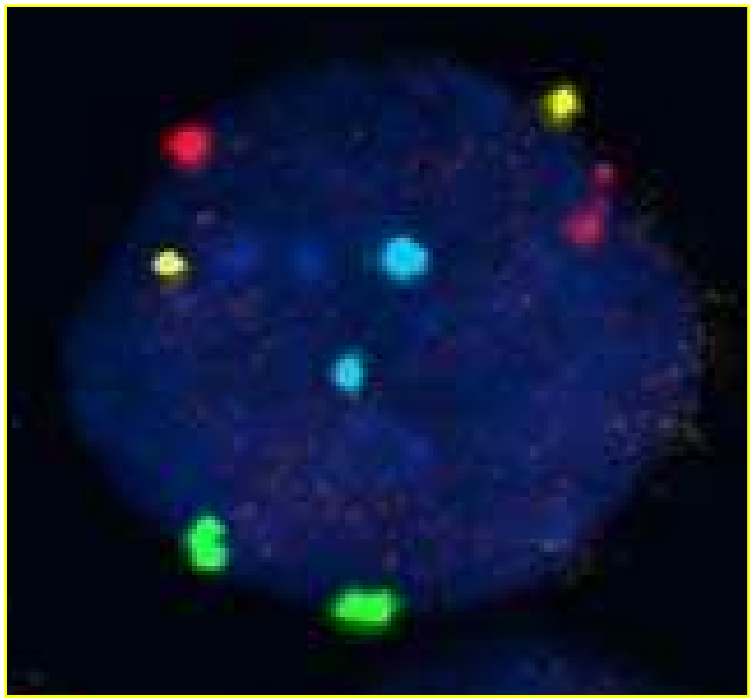
Sokolova et al. J Mol Diagn 2000;2:116

Patient	Tumor stage[8]	Percentage of cells exhibiting tetrasomy with CEP probes or homozygous deletion with 9p21 probe							
		CEP3 2.8%†	CEP7 6.5%	CEP8 7.1%	CEP9 7.1%	CEP11 7.1%	CEP17 6.2%	CEP18 7.0%	LSI 9p21 16.9%‡
D	pT1	ND	39	ND	39	ND	42	ND	13
66	pT3	79	66	7	5	70	84	36	27
69	pTa	5	2	0	1	0	2	0	2
95	pTa	0	0	2	0	2	0	2	2
110	pT1	11	18	6	1	2	10	3	20
171	pT4	1	24	44	0	42	21	2	9
191	pTa	50	17	39	10	27	3	45	5
215	pT1	60	24	2	21	5	38	6	13
219	pT3	53	41	24	44	11	39	14	10
223	pTa	0	0	7	0	5	0	3	43
224	pTIS	ND	81	ND	71	ND	74	ND	70
225	pTIS	20	9	6	4	12	5	5	16
227	pT4	44	69	34	33	14	52	37	1
228	*	53	29	34	13	2	34	32	3
229	pT3	43	35	8	20	47	3	5	4
230	pTa	44	32	9	39	8	38	13	8
234	pTa	3	9	2	9	2	11	3	3
235	**	10	1	1	0	1	9	1	1
236	pTIS	54	49	35	17	34	50	21	62
239	***	0	0	4	0	4	0	3	20
240	pT3	0	13	32	0	23	5	18	1
Sensitivity of probe		**14/19 (73.7%)**	**16/21 (76.2%)**	**11/19 (57.9%)**	**11/21 (52.4%)**	**10/19 (52.6%)**	**13/21 (61.9%)**	**8/19 (42.1%)**	**6/21 (28.6%)**


FISH - DIPLOID
CEP 3
CEP 7
CEP 17
9P21

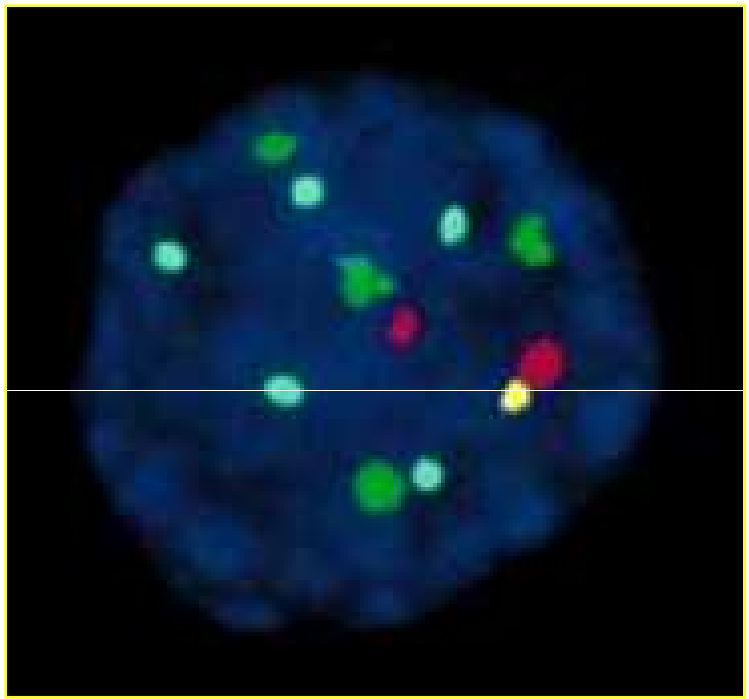
FISH - after UroVysion probe hybridization

FOUR COMBINED PROBES



DIPLOID

- 2 copies of chrom 3 (red)
- 2 copies of chrom 7 (green)
- 2 copies of chrom 17 (aqua)
- 2 copies of region 9p21 (gold)



ANEUPLOID

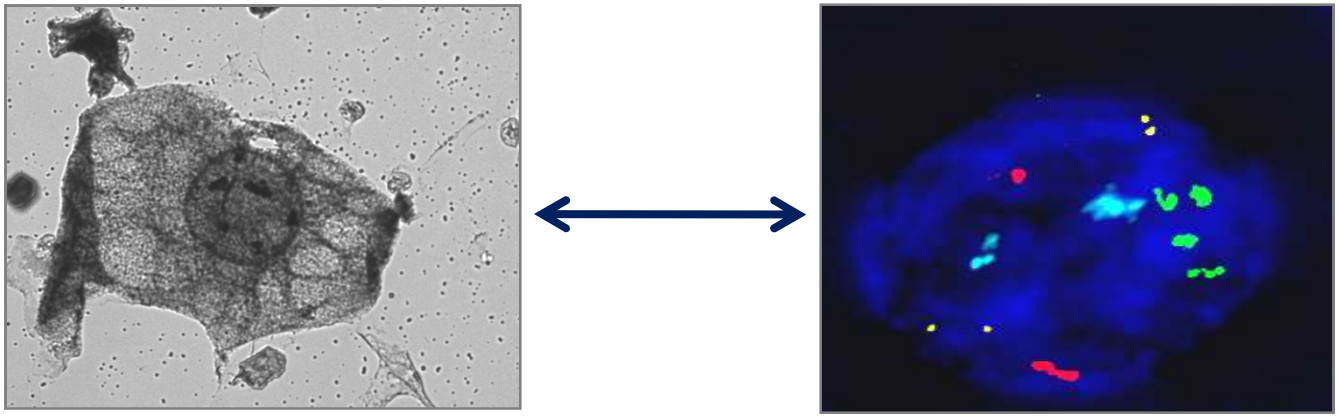
- 2 copies of chrom 3 (red)
- 4 copies of chrom 7 (green)
- 5 copies of chrom 17 (aqua)
- 1 copy of region 9p21 (gold)

UroVision – Review of the Literature

Author	Cytology	FISH
Haling et al.	58%	81%
Fredrich et al.		69%
Mian et al.	45%	96%
Skacel et al.		85%
Dalquen et al.	24%	73%
Placer et al.	64%	80%
Sarosdy et al.	26%	71%
Haling KC		81%

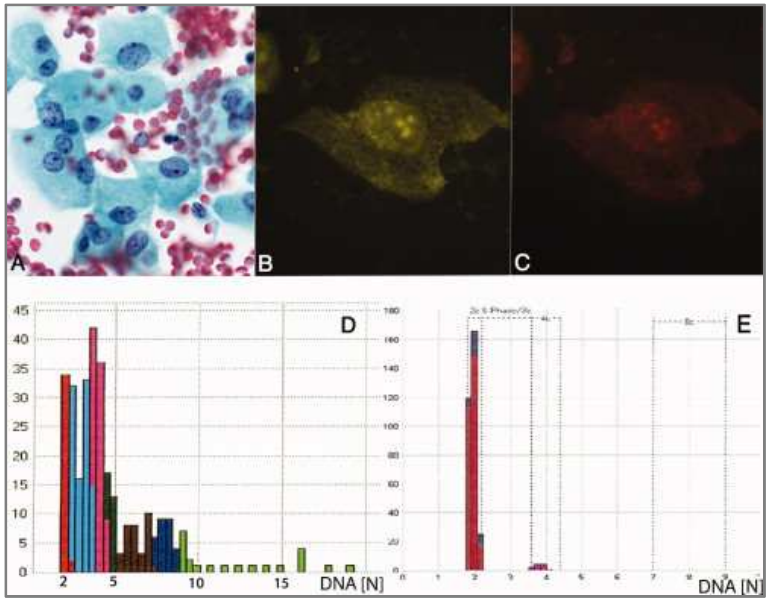
Multicolor fish analysis of instrumented urine samples containing a high proportion of umbrella cells

Wojcik et al. Mod Pathol 2002



Evaluation of chromosomal aberrations in patients with benign conditions and reactive changes in urinary cytology

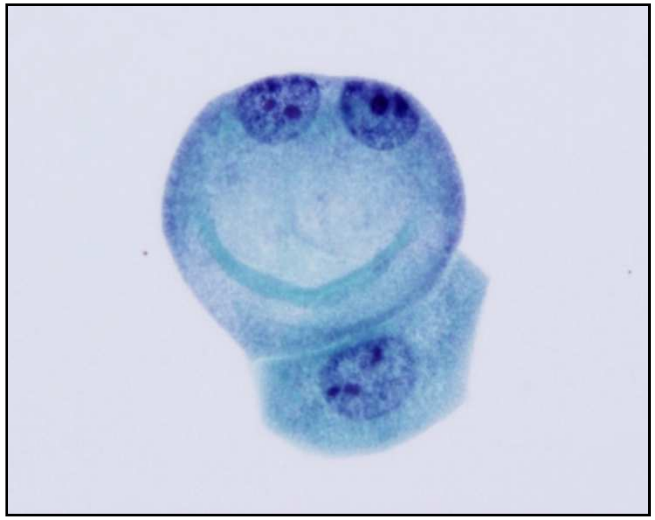
Tapia et al. Cancer Cytopathol 2011



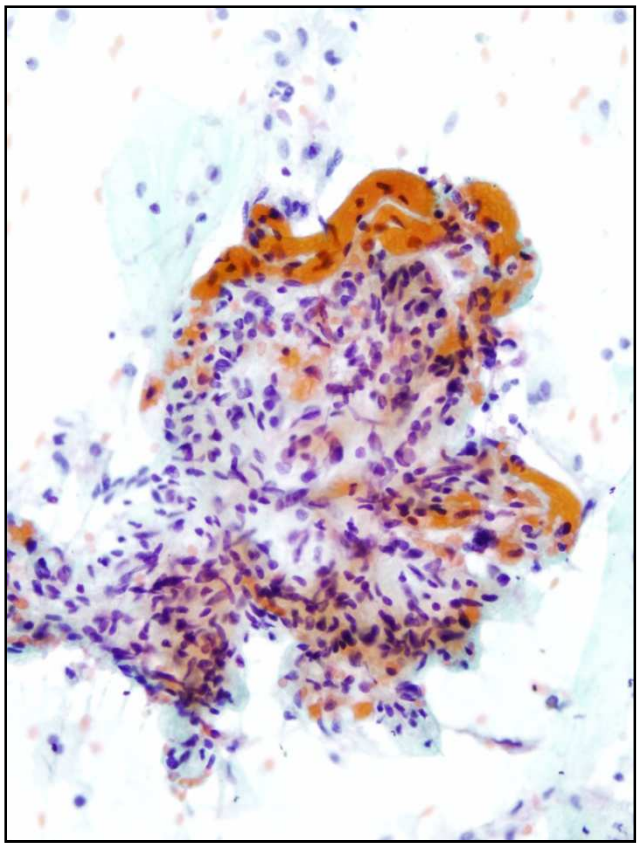
Cancer Cytopathology
pages n/a-n/a, 5 JUL 2011 DOI: 10.1002/cncy.20171
http://onlinelibrary.wiley.com/doi/10.1002/cncy.20171/full#fig2

Final take home message

- Urine cytology is not that bad
- Better miss LG UC than overcall
- We can not be perfect all the time
- Look for a high grade – this one is clinically significant



Understanding Genitourinary System Cytology



Part II: Renal FNA

Güliz Akdas Barkan, M.D., FIAC
Loyola University School of Medicine
Department of Pathology

Renal FNA Cytology Outline

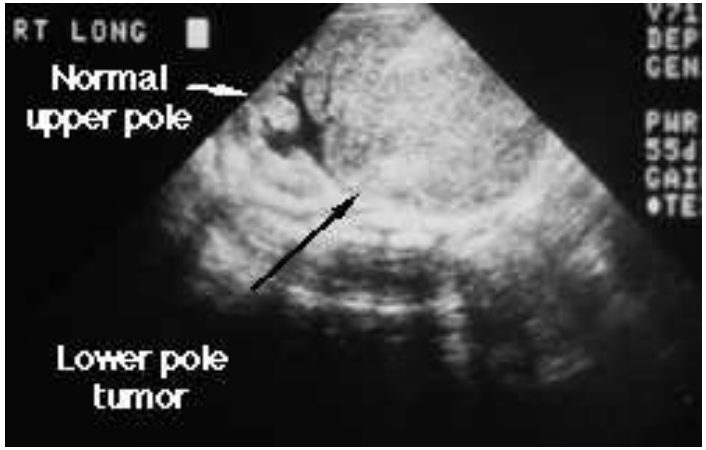
- Indications
- FNA techniques, specimen preparation
- Normal kidney cytology
- Cases
- Molecular Biology and targeted therapy in RCC

Indications of Renal FNA

1. Patients with presumed malignant lesions who are not candidates for resection
2. To decide the approach of surgery especially in smaller masses and masses located close to the renal pelvis.
3. In cases where a non-surgical treatment methods (i.e. minimally invasive methods such as cryotherapy, or radiotherapy) are preferred
4. In cases where preoperative/neoadjuvant chemotherapy or biological response modifiers (such as immunotherapy) are preferred
5. Radiologically indeterminate lesions

Imaging Techniques

- Ultrasonography



- Computed Tomography

Does Renal FNA Have Any Complications?

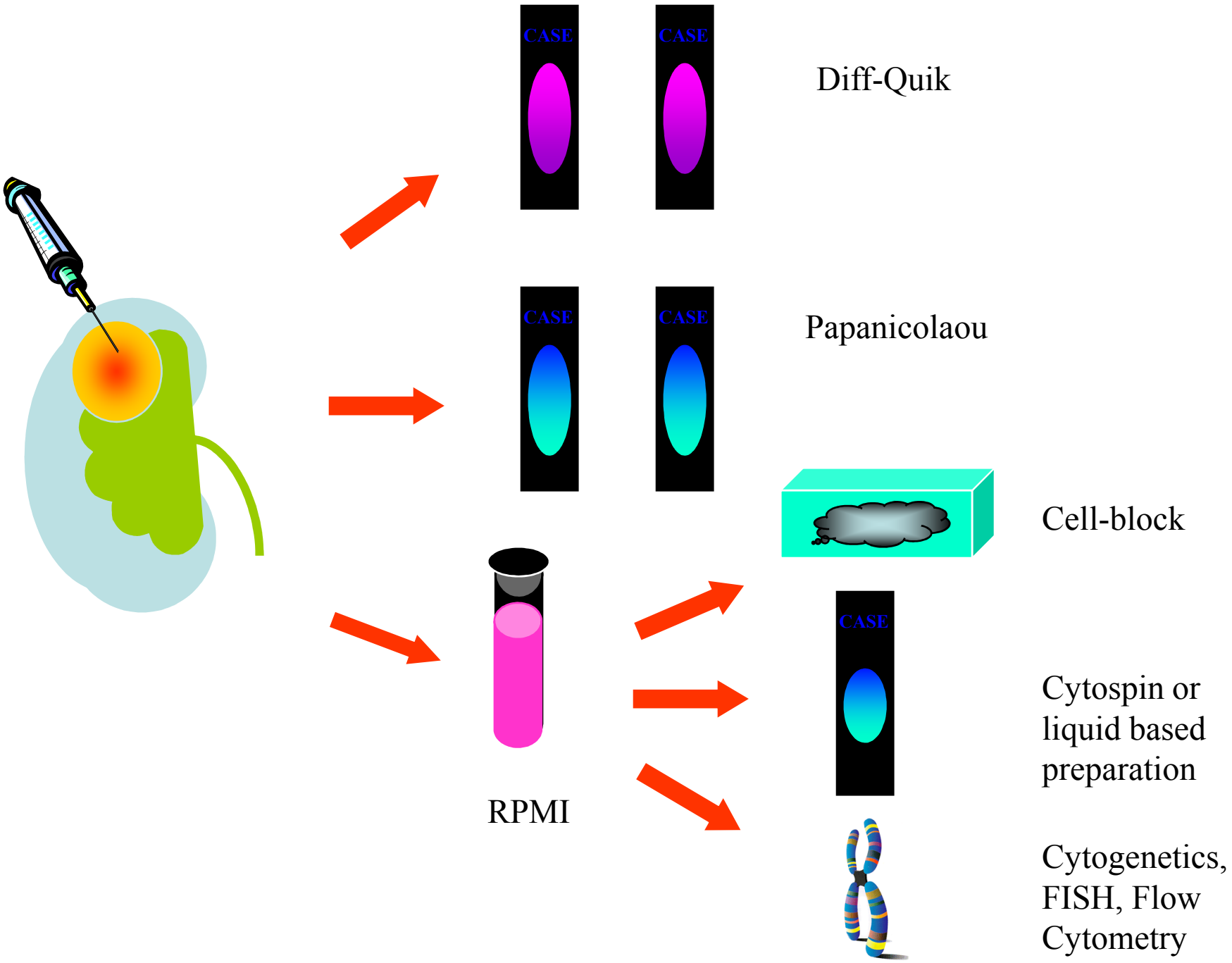
Rare

- Perirenal hemorrhage
- Pneumothorax
- Infection
- A-V fistula
- Urinoma

Very Rare

- Needle- tract seeding

Overall estimated risk for needle tract seeding is less than 0.01%
Herts et al. Semin Urol Oncol 1995
(Reported cases: Gibbons et al: J Urol 1977 Auvert et al: Prog Clin. Bio Res 1982, Kiser et al.:J Urol 1986, Wehle et al.: J Urol 1986,Shenoy et al.: Acta Rad 1991, Abe et al. Br J Urol 1992)


CASE
CASE
Diff-Quik
CASE
CASE
Papanicolaou
Cell-block
RPMI
CASE
Cytospin or
liquid based
preparation
Cytogenetics,
FISH, Flow
Cytometry

Loyola Study: FNA of the kidney: Concordance of cytologic typing/grading with histology in 31 renal masses

31 cases, 40-85 Y, 1.9-14 cm renal mass

28/31 perfect concordance. **3 cases without concordance:**

1. Papillary RCC misdiagnosed as clear cell type on FNA

2. Papillary RCC diagnosed as suspicious on FNA

3. Xanthogranulomatous pyelonephritis misdiagnosed as RCC with necrosis on FNA

Only 4/8 papillary carcinomas were typed (as type 1 or 2) accurately

Low cellularity not associated with tumor size

No. of Cases	Surgical Dx	Cytology Dx (Review)	Concordance
17	RCC, Clear Cell	RCC, Clear Cell	perfect
8	RCC, Papillary	RCC, Papillary (6 cases) RCC, Clear Cell (1 case) suspicious cells seen (1 case)	partial
2	RCC, Chromophobe	Chromophobe ca	perfect
1	Oncocytoma	Oncocytic lesion	perfect
1	Liposarcoma	Sarcoma	perfect
1	Benign cyst	Benign cystic lesion	perfect
1	Xanthogranulomatous Pyelonephritis	RCC with necrosis	none

Masoom et al. Cytopathol 2009 Feb;20(1):50-5

Other Studies & Statistics

Author	Publication	n	Classification	Diag yield	Accuracy	Sensitivity	Specificity
Barkan	J Urol 2009	63	solid/cystic	100%	96%		
Kummerlin	Eur Urol 2008	66	solid/cystic	82%	71-91%	92%	74%
Solano	Diag. Cytopath 2008	31	solid	80%	100%	80%	14%
Neuzillet	J Urol 2004	88	solid<4cm	96%	92%		
Barkan	Mod Path 2003	80	solid	100%	94%		
Brierly	BJU 2000	23	solid < 5cm	84.0%	N/A	64.0%	50.0%
		19	solid >5cm	83.0%	N/A	89.0%	N/A
		7	complex cyst	86.0%	N/A	50.0%	50.0%
Truong	Diag. Cytopath 1999	108	solid/cystic	85.0%	95.6%	N/A	N/A
Wood	J Urol 1999	79	solid	94.0%	94.0%	N/A	N/A

Renal FNA Statistics: Accuracy: 71% to 100%,

Sensitivity: 50-100%,

Specificity: 50-100%.

Diagnostic yield: 40%-95%.

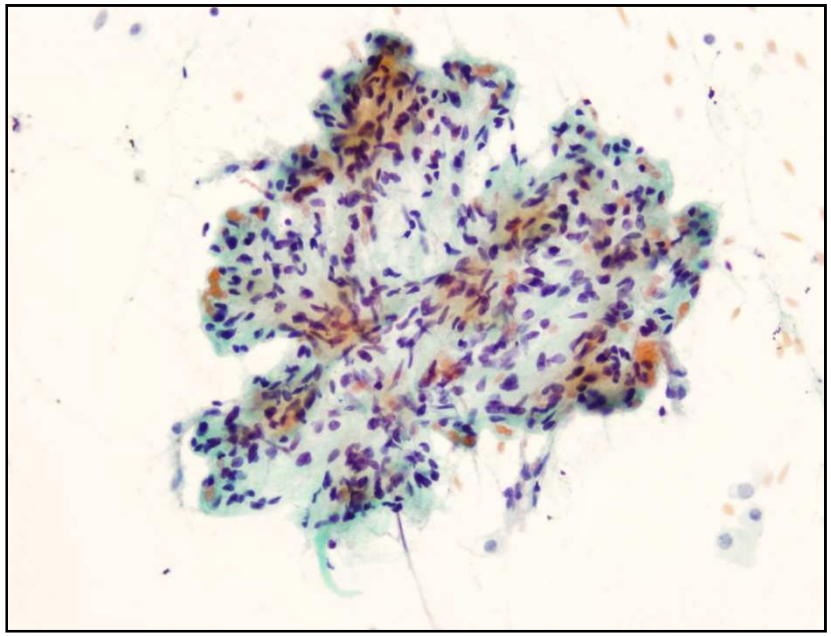
Normal Kidney

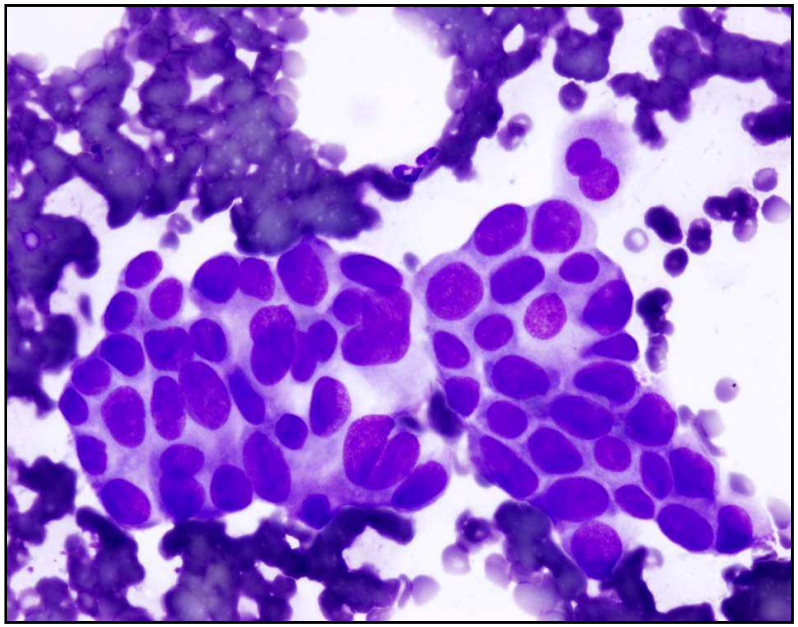
Glomeruli

- Cellular globular structures
- Spindled and round cells
- Prominent capillary loops
- DDx Papillary RCC, AML

Collecting Duct

- Small cells with scant cytoplasm
- Clustering in tight groups
- DDX Adenocarcinoma

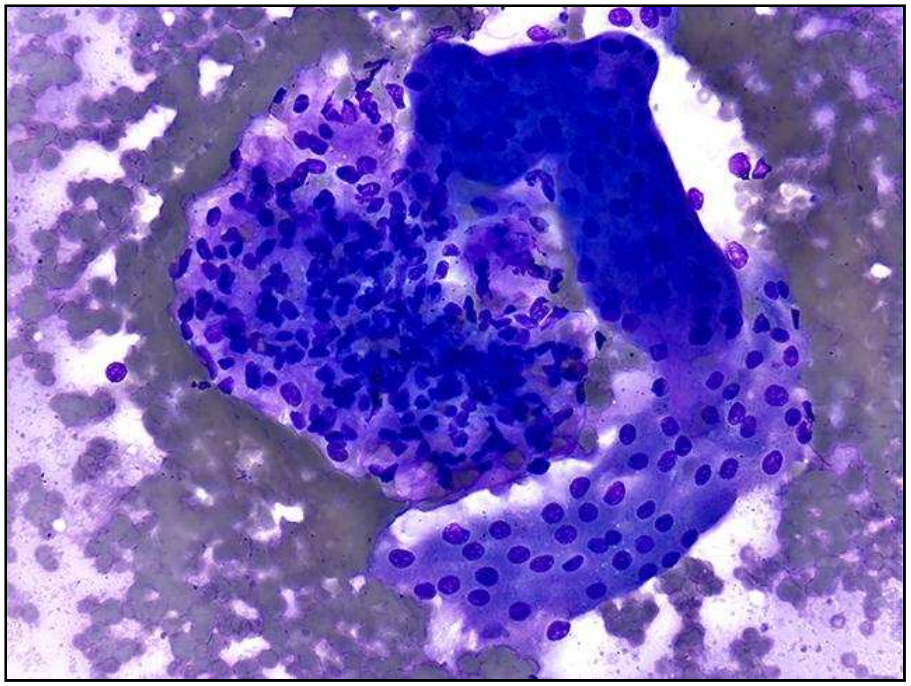




Normal Kidney

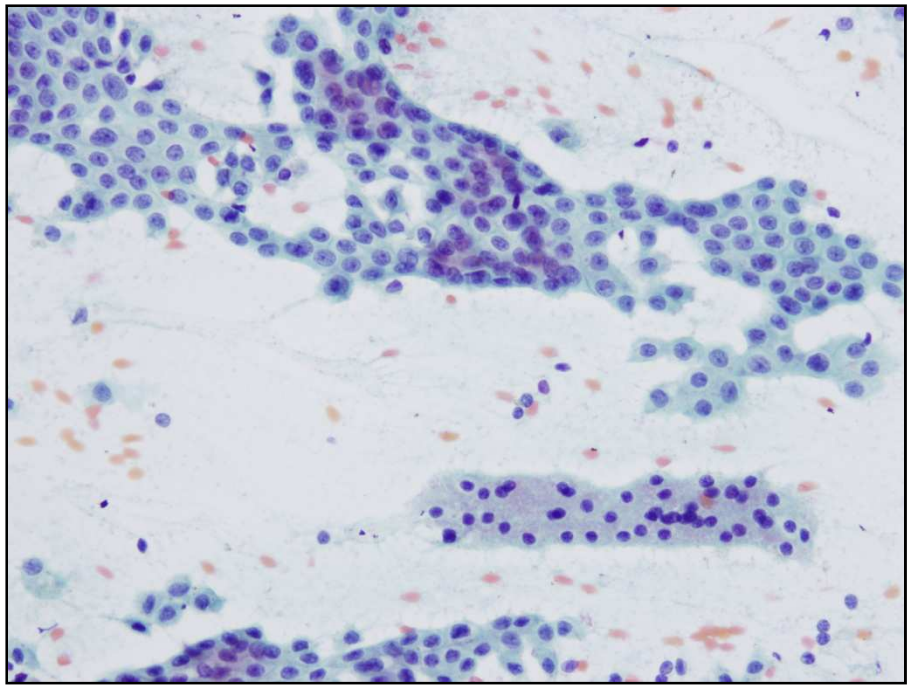
Proximal tubule

- Granular cytoplasm with granules spilling
- Not well-delineated cell borders
- DDx Oncocytoma



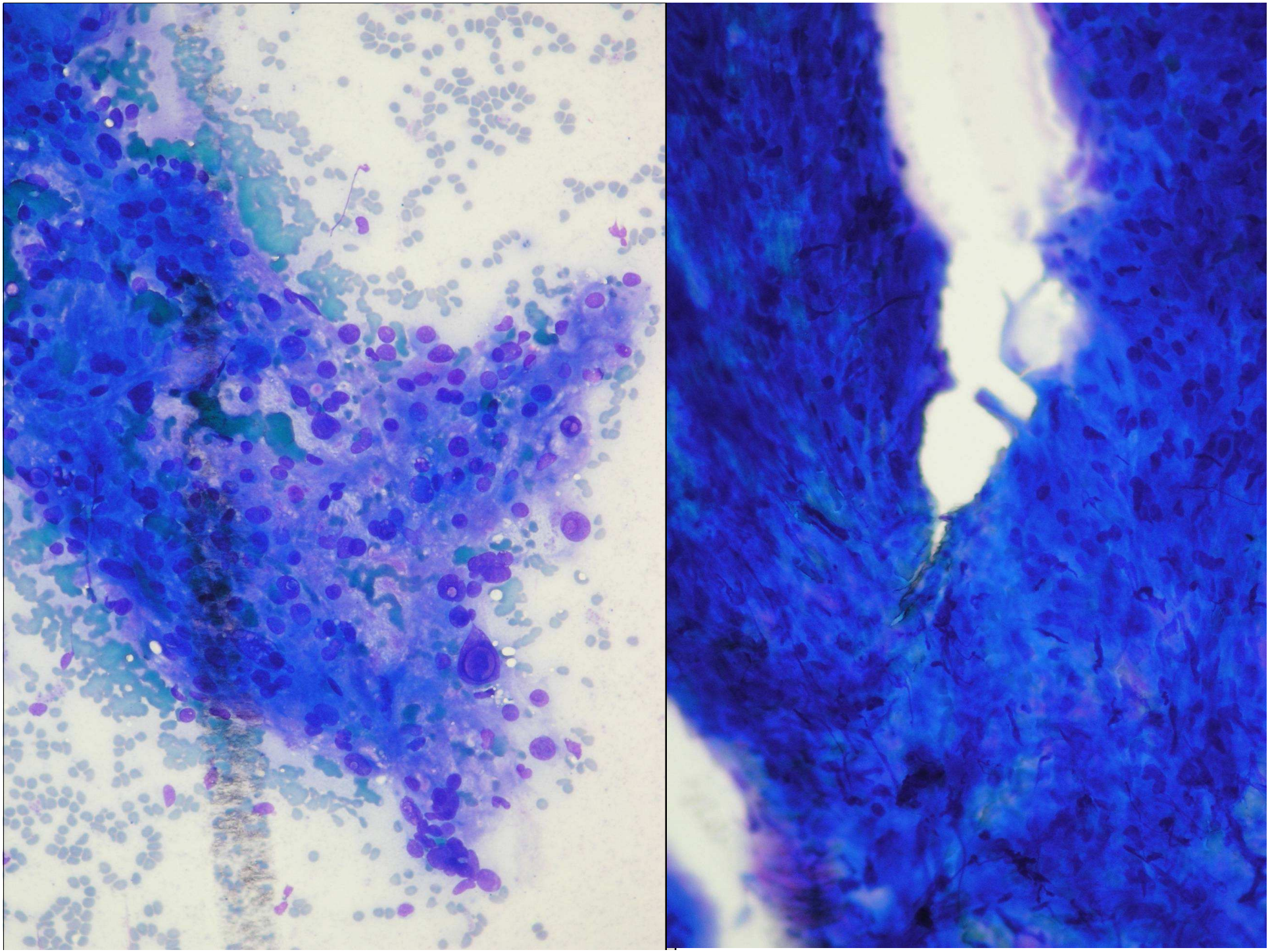
Distal tubule

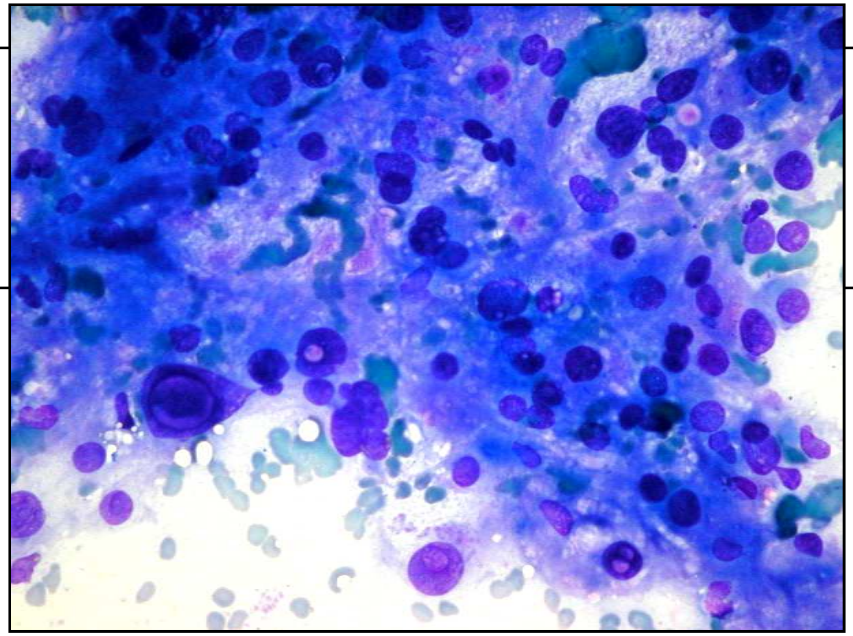
- Clear-granular cytoplasm
- Small cell
- Well-defined cell borders
- DDX Low grade RCC

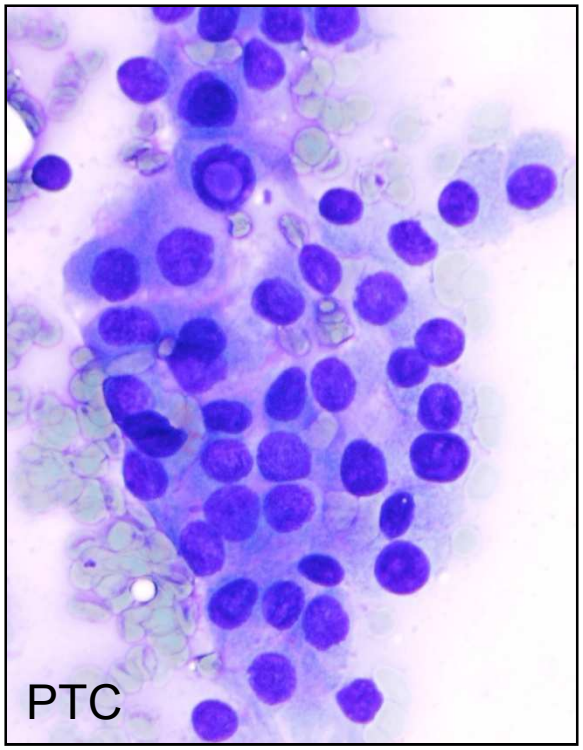


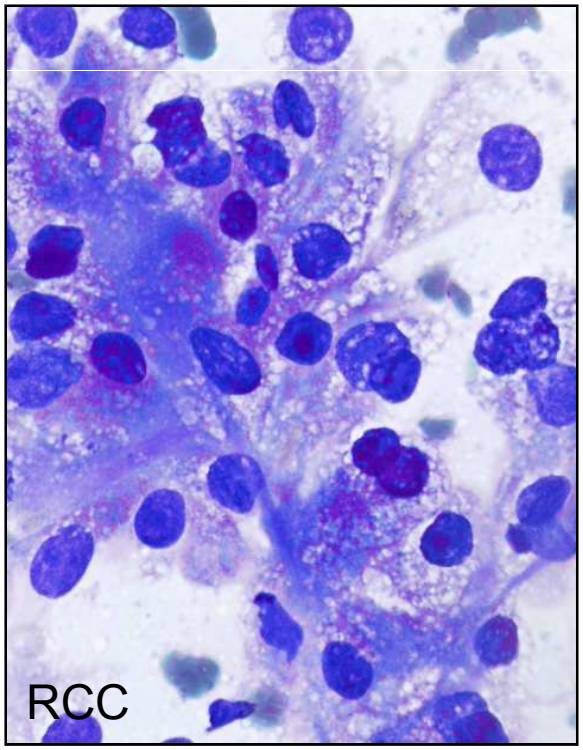
Case 1

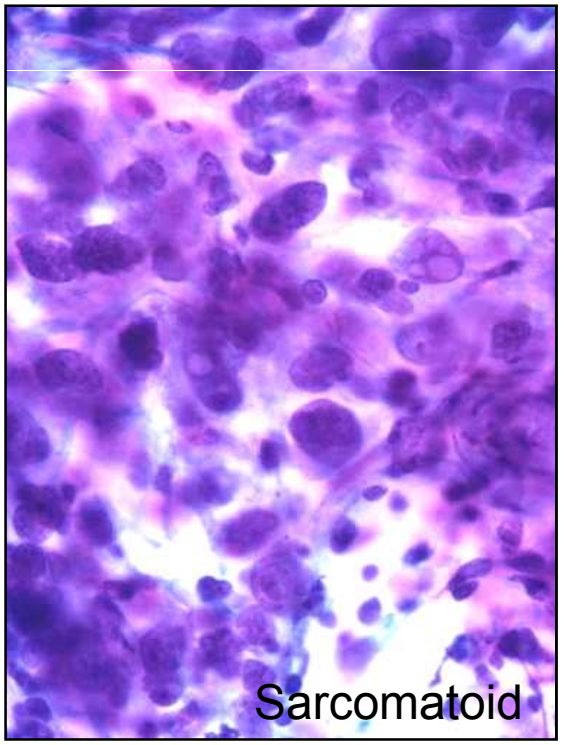
- 28-year-old woman with a recent diagnosis of PTC presented with left flank pain
- Ultrasonography showed a 2.5 cm mass lesion in the upper pole of left kidney
- An US guided FNA was performed

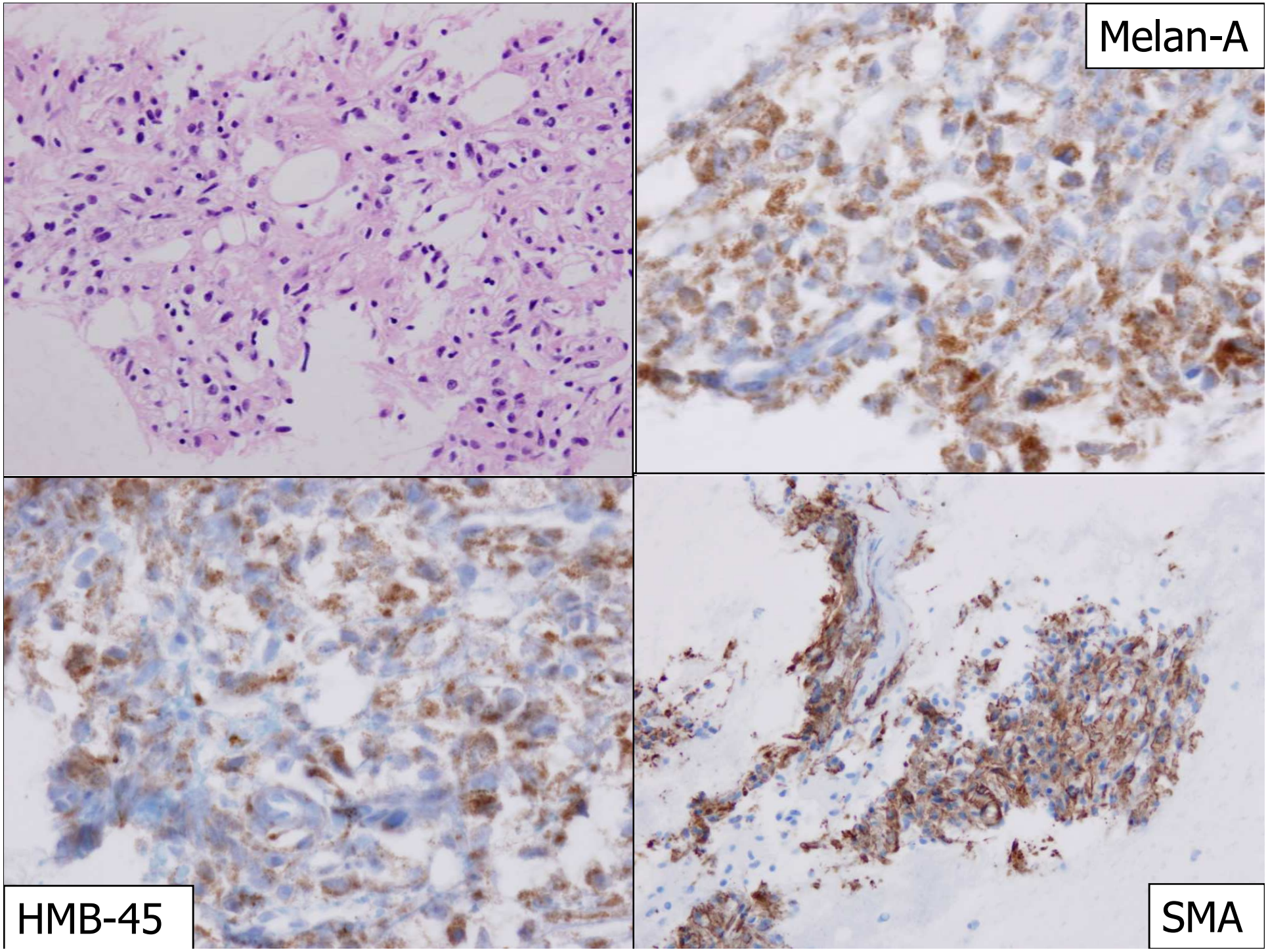





PTC

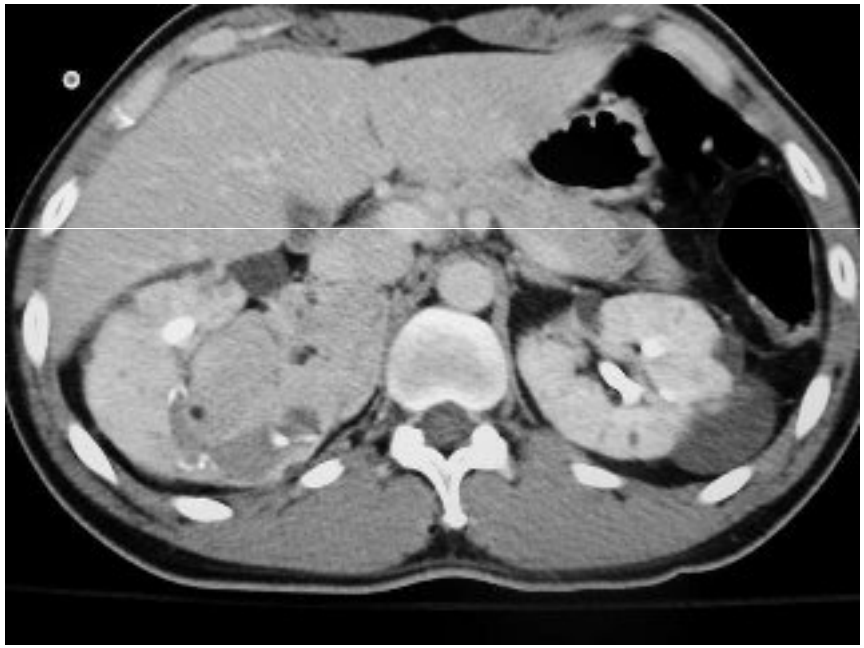

RCC


Sarcomatoid


Melan-A
HMB-45
SMA

Angiomyolipoma

- Rare. 3 components: **spindle cell, epithelioid cells, adipocytic cells, and thick walled blood vessels**
  - US: hypere-echogenic,
  - CT: negative attenuation,
  - MRI (T1):hyperintensity

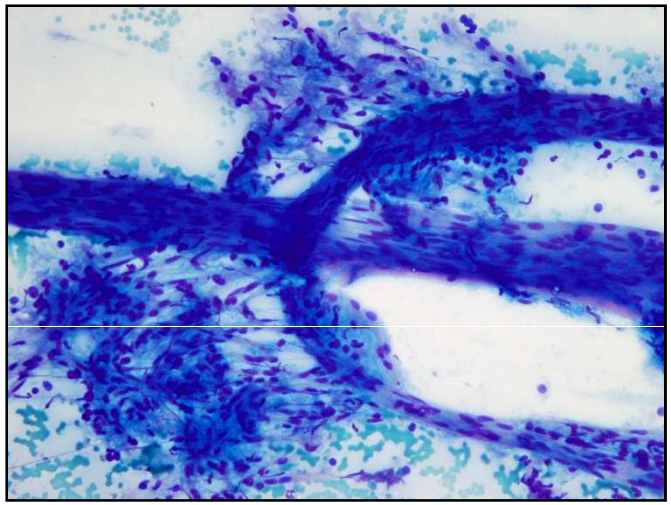


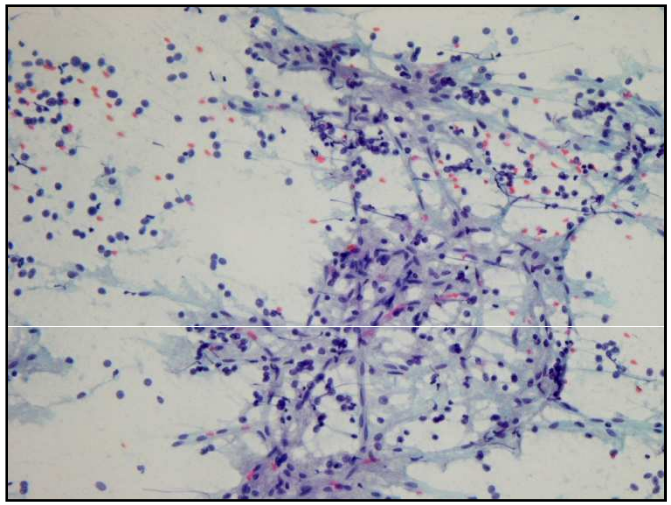
Renal Angimoyoliopma Stone et al. Arch Path Lab Med 2001:125:751-8

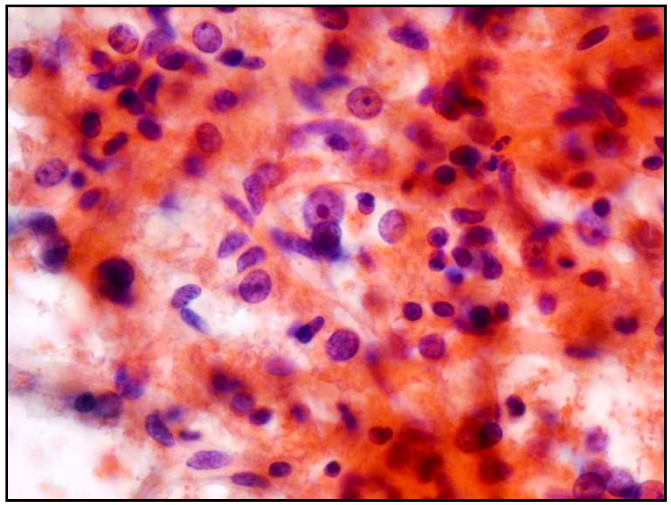
FNA of Renal Angiomyolipoma: Series of 5 cases Crapanzano. Diag Cytopathol 2005; 32:53-7

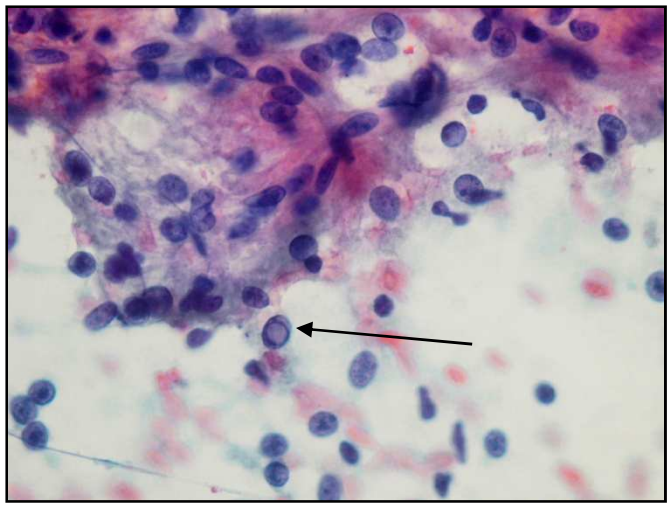
Angiomyolipoma

- Mature adipocytes
- Thick and thin blood vessels
- Spindled and epithelioid smooth muscle cells
- Intranuclear inclusions
- Variable pleomorphism with giant cells





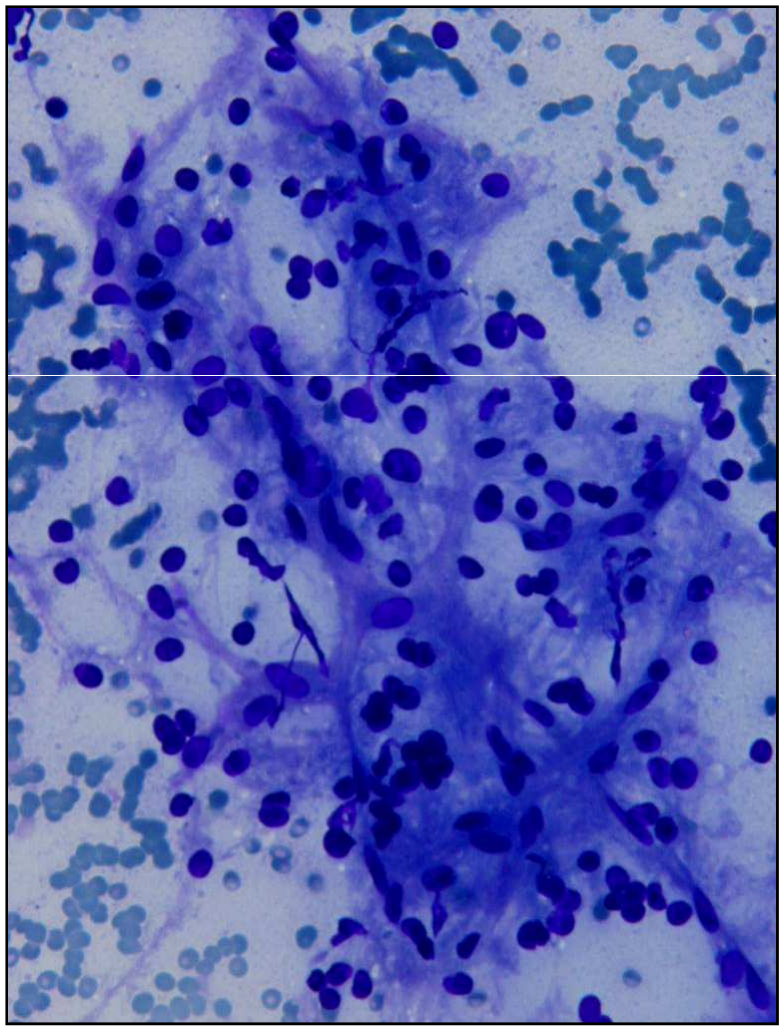


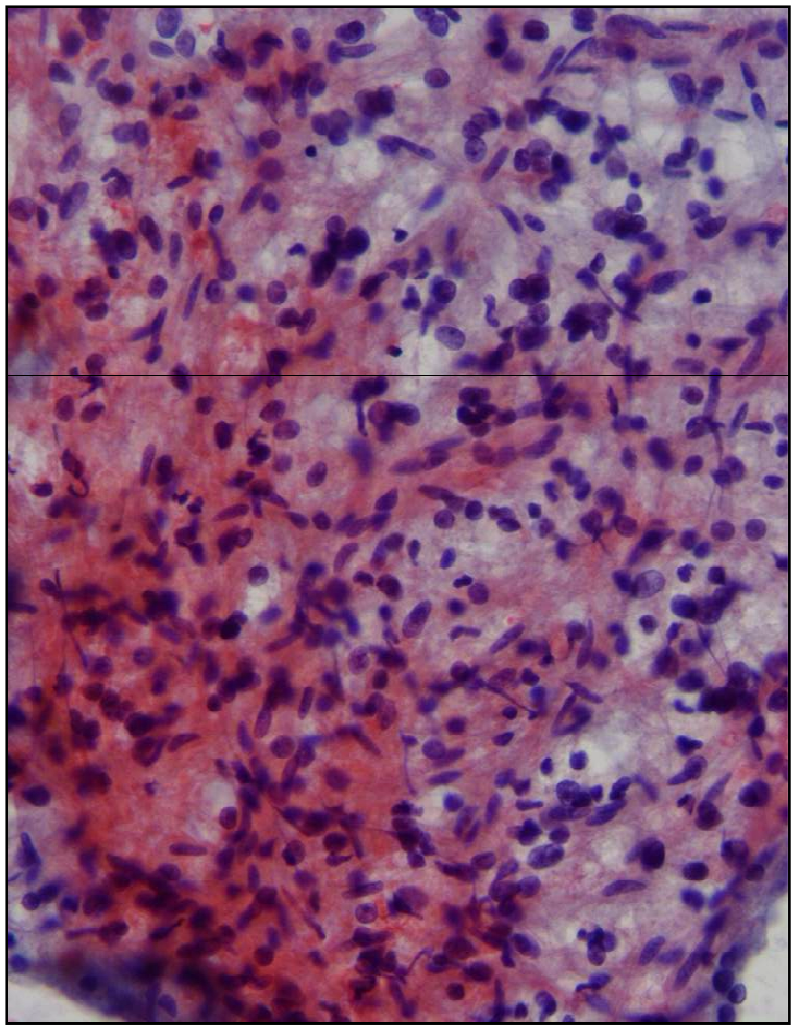


HMB 45

C-kit

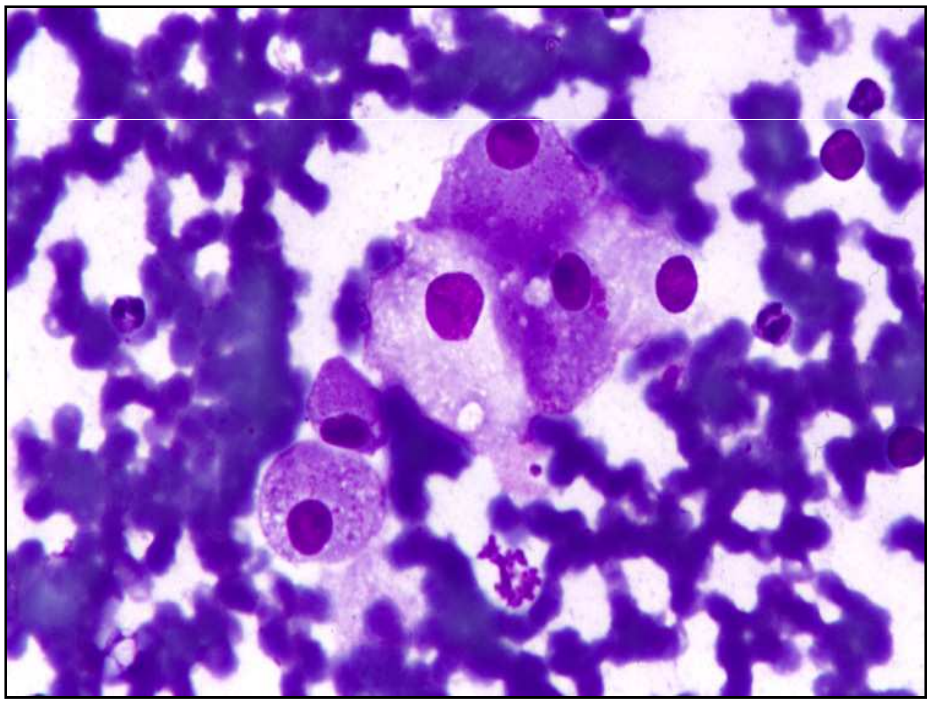
Angiomyolipoma

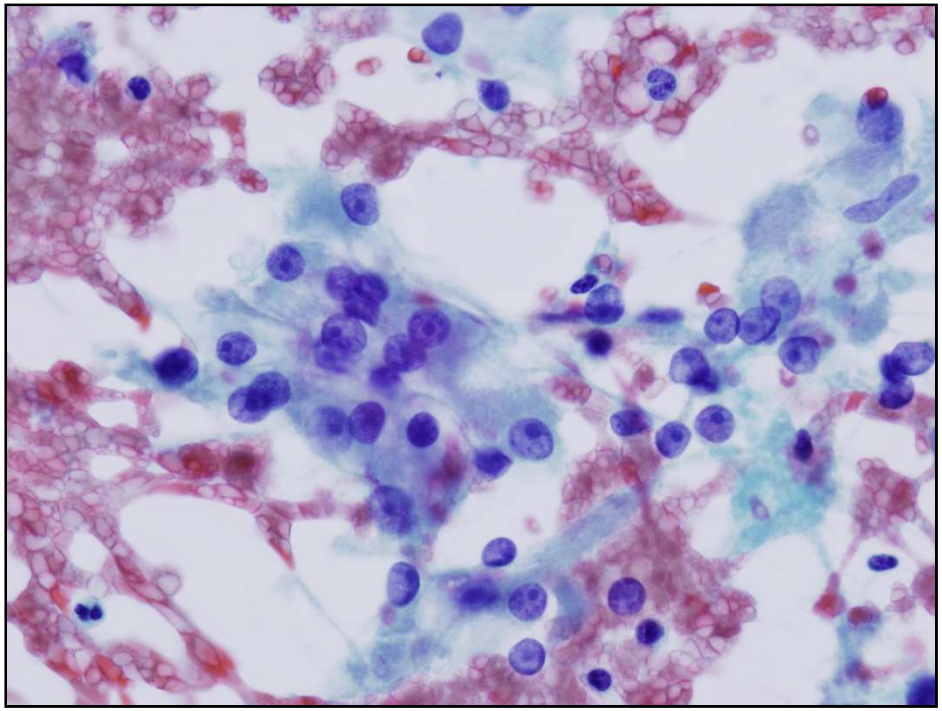




Case 2

57-year-old male with 5.5 cm. cystic mass in the upper pole of the right kidney.





Differential Diagnosis

Benign:

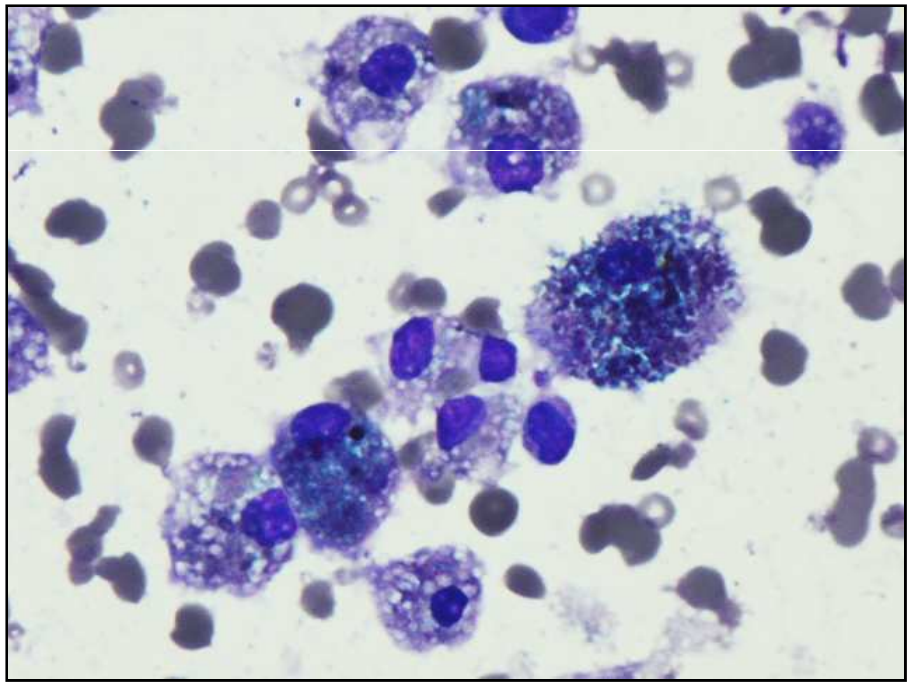
- Macrophages
- Hepatocytes
- Renal tubular epithelium
- Xanthogranulomatous pyelonephritis
- Oncocytoma

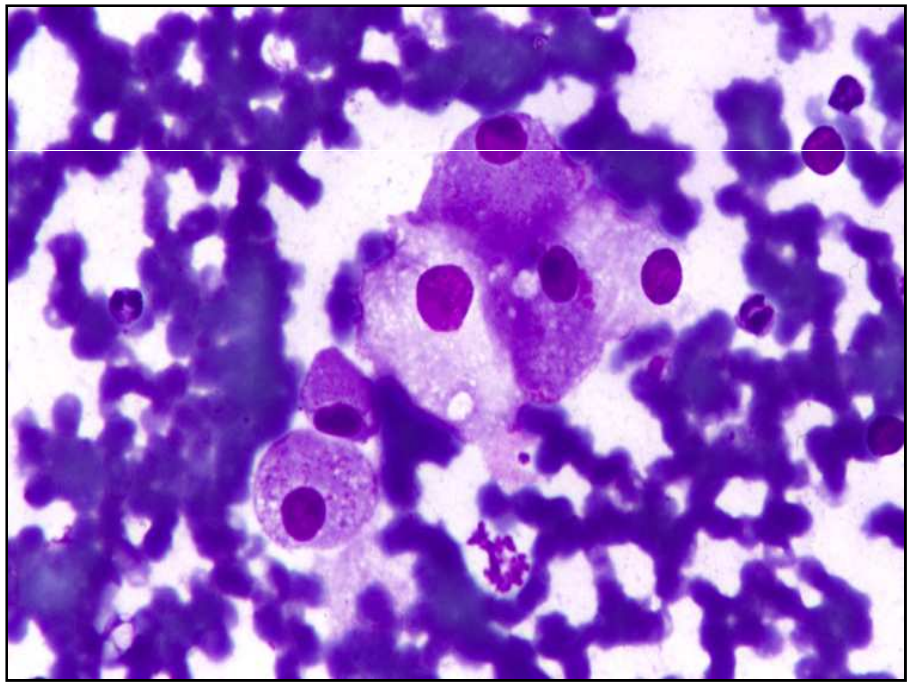
Malignant:

- Renal cell carcinoma, clear cell type
- Renal cell carcinoma, chromophobe type

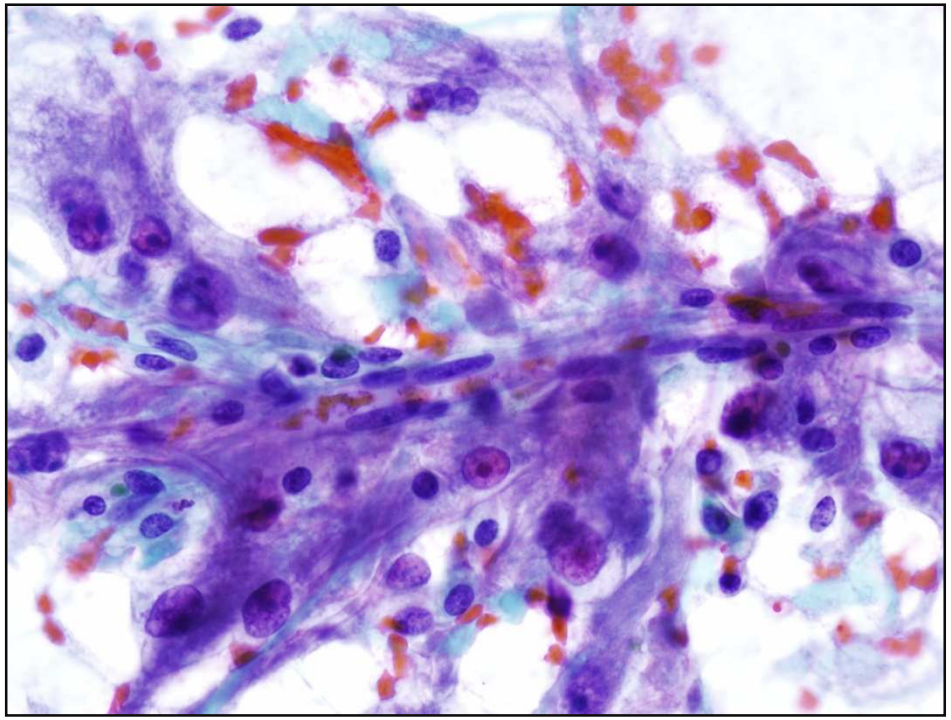
Macrophages

Case 2

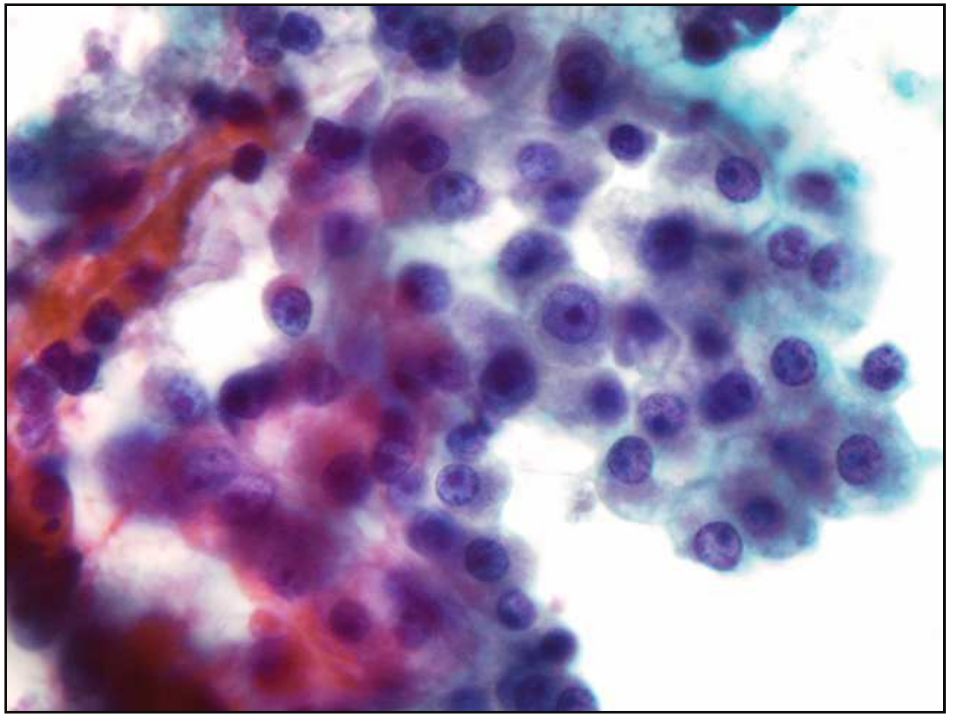




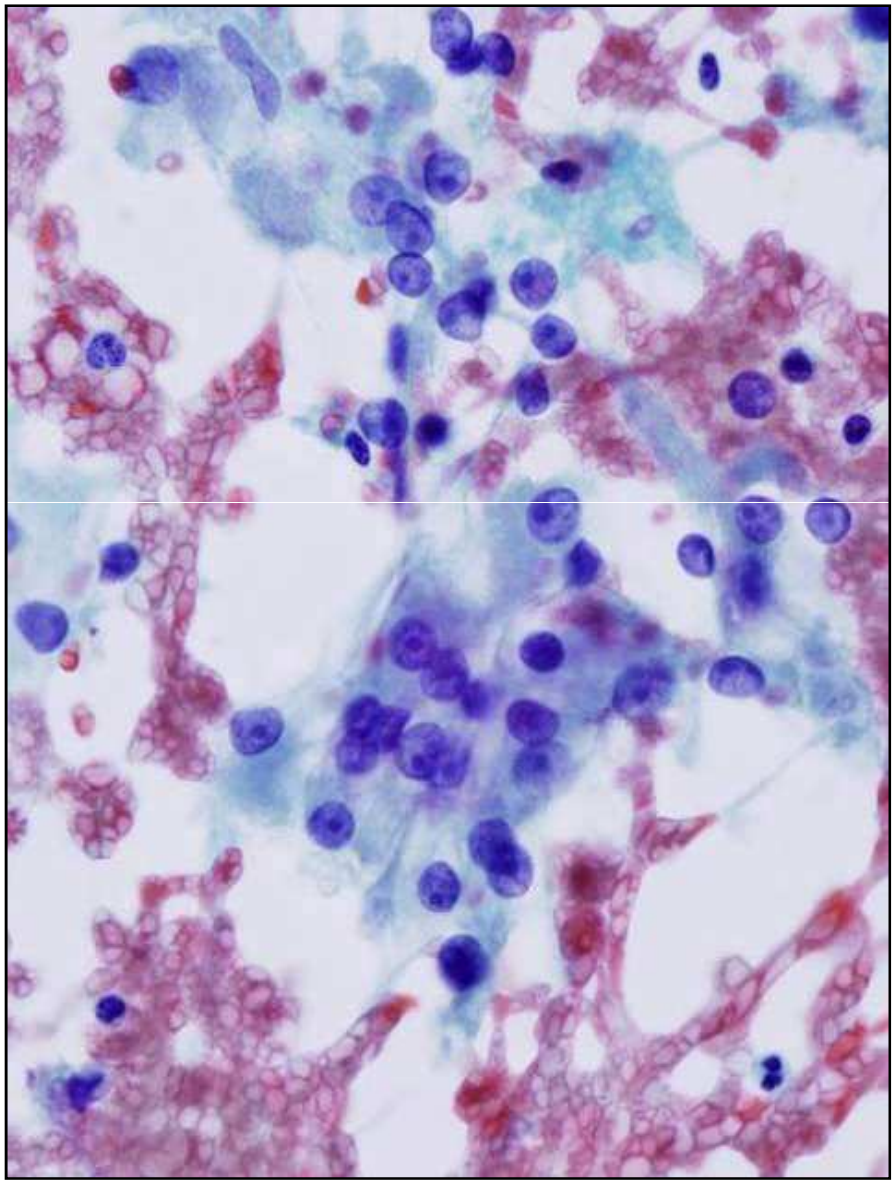
Case 2



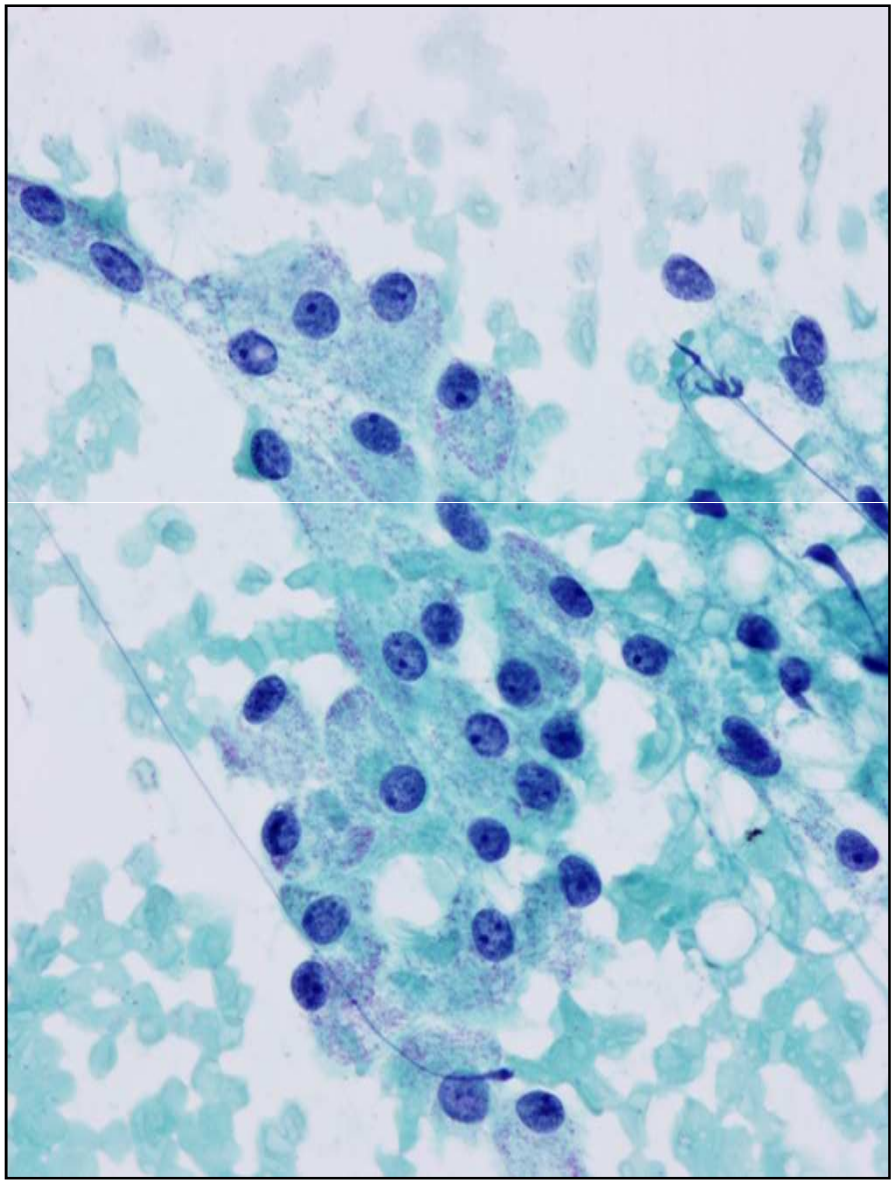
Hepatocytes



Case 2

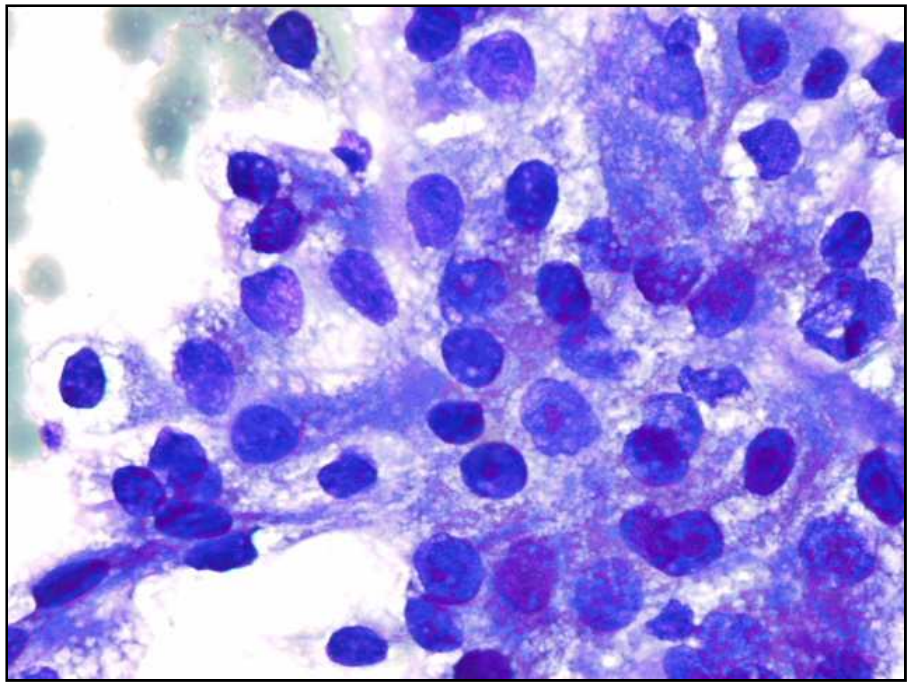


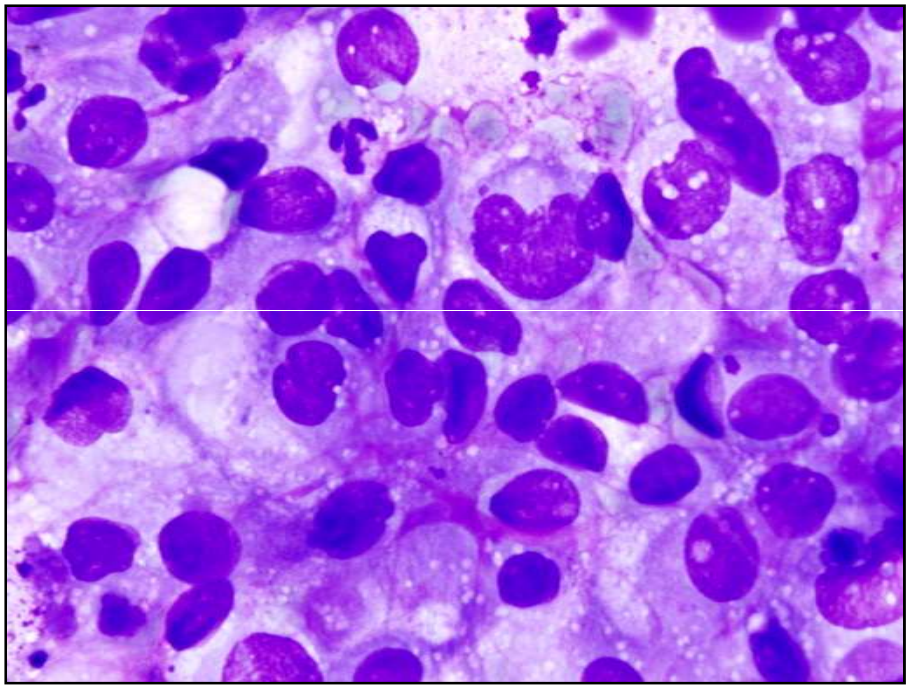
Proximal convoluted tubules



Case 2

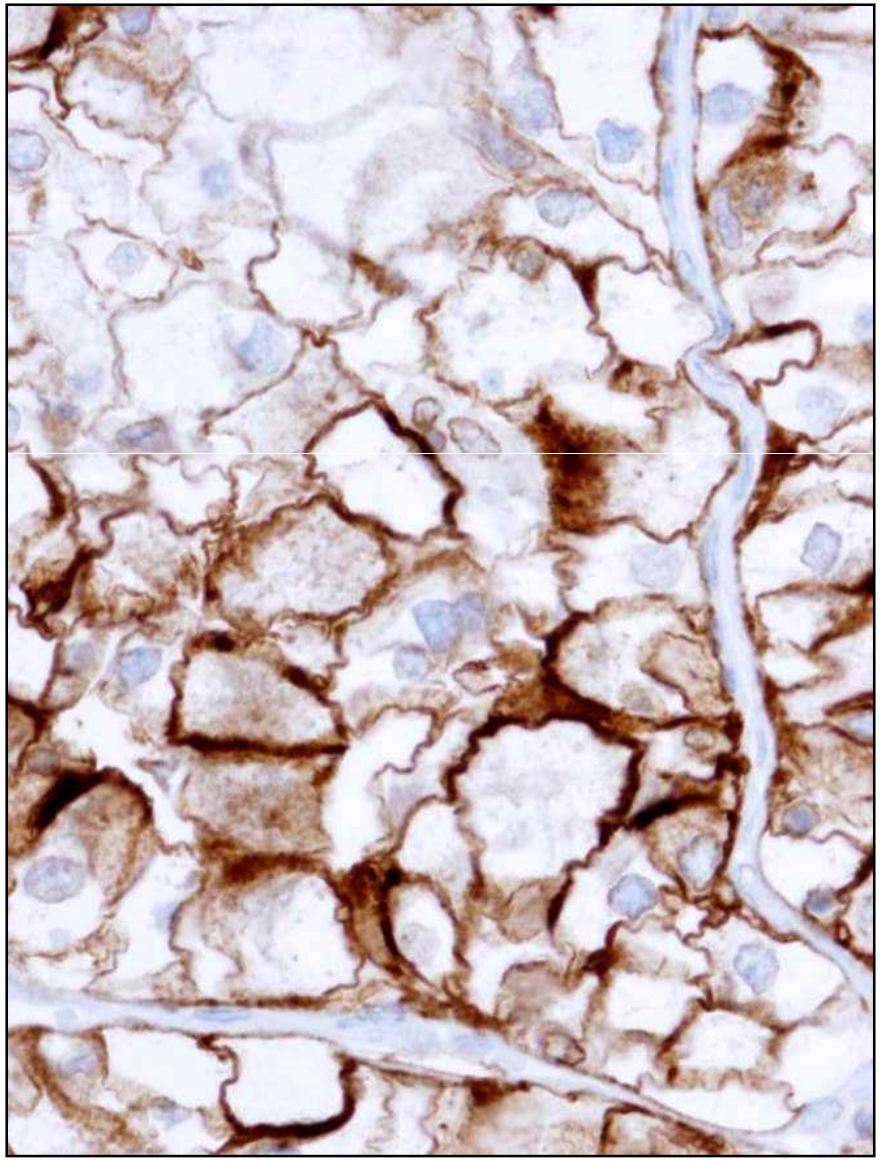
Xanthogranulomatous Pyelonephritis

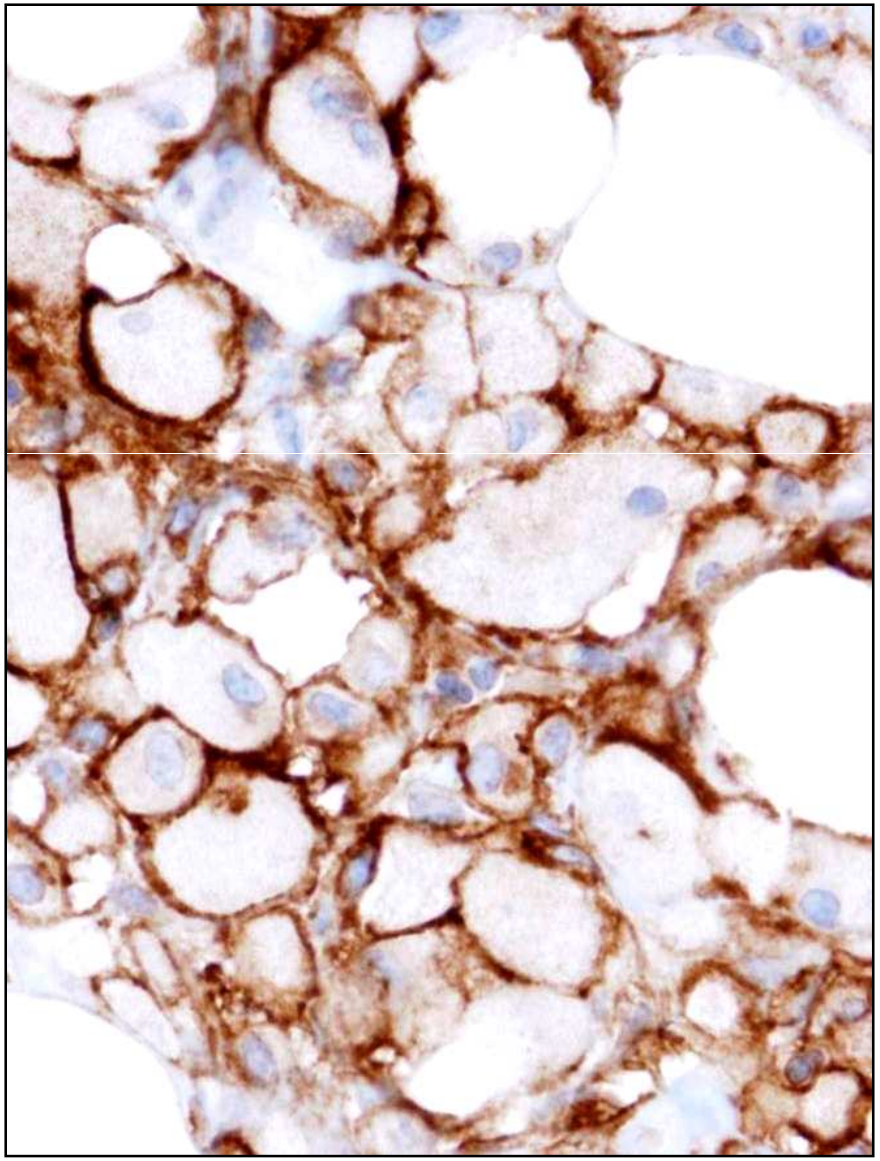




- Inflammatory sequel of chronic suppurative renal infection (Proteus or E.coli)
- Often associated with an obstruction

CD 10 – RCC vs. XGP





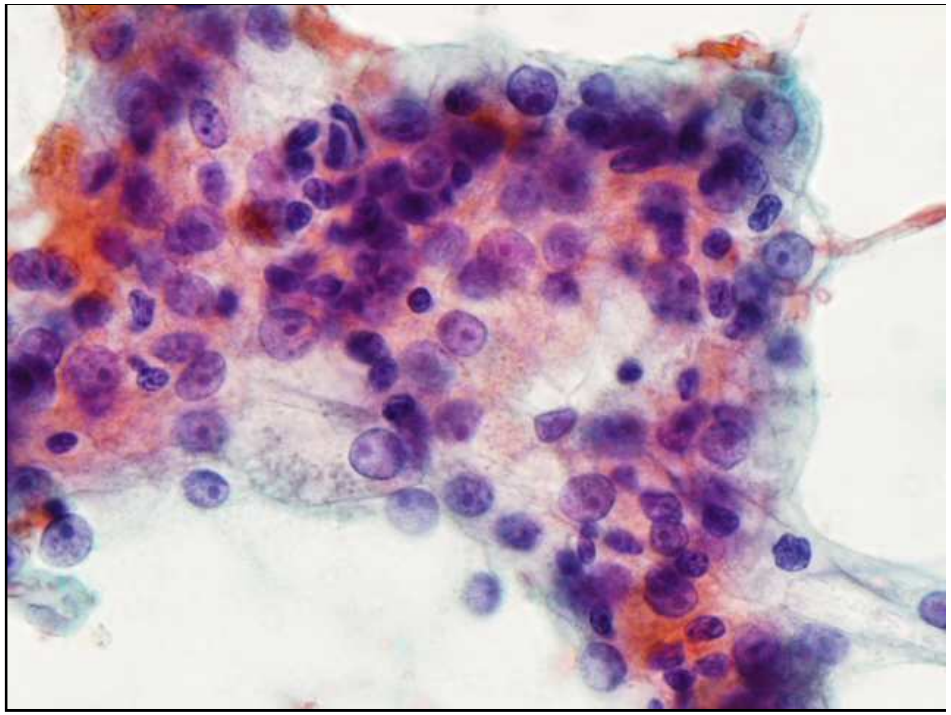
XGP vs. RCC, clear cell type

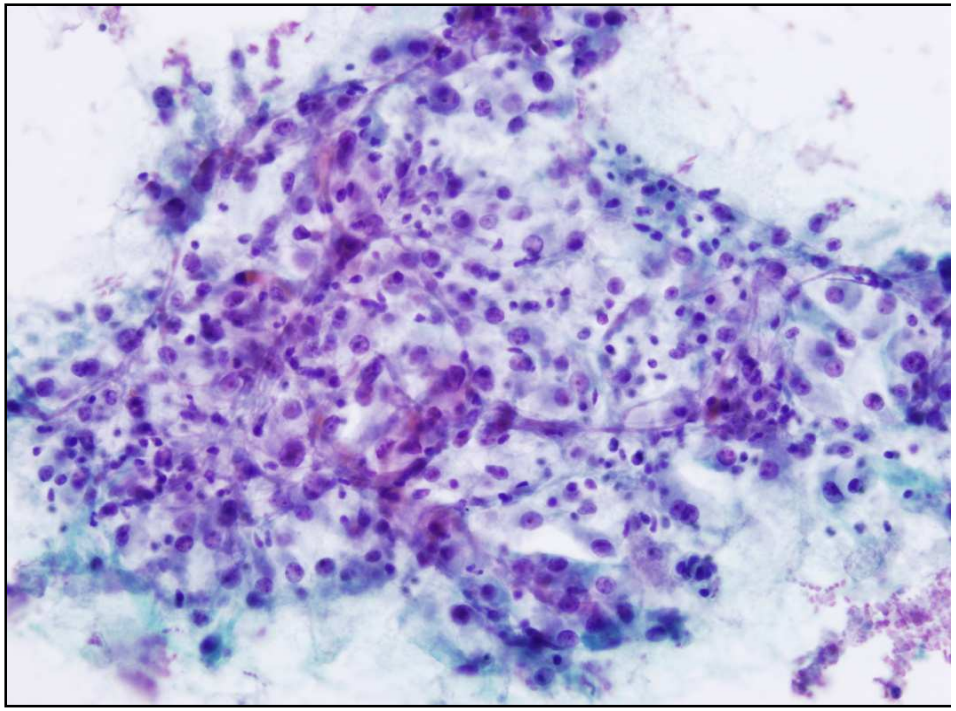
	XGP	RCC, clear cell type
PAS	-	+
Low Mol Wt CK	-	+
EMA	-	+
Vimentin	+	+
CD 10	+	+
CD 68	+	-

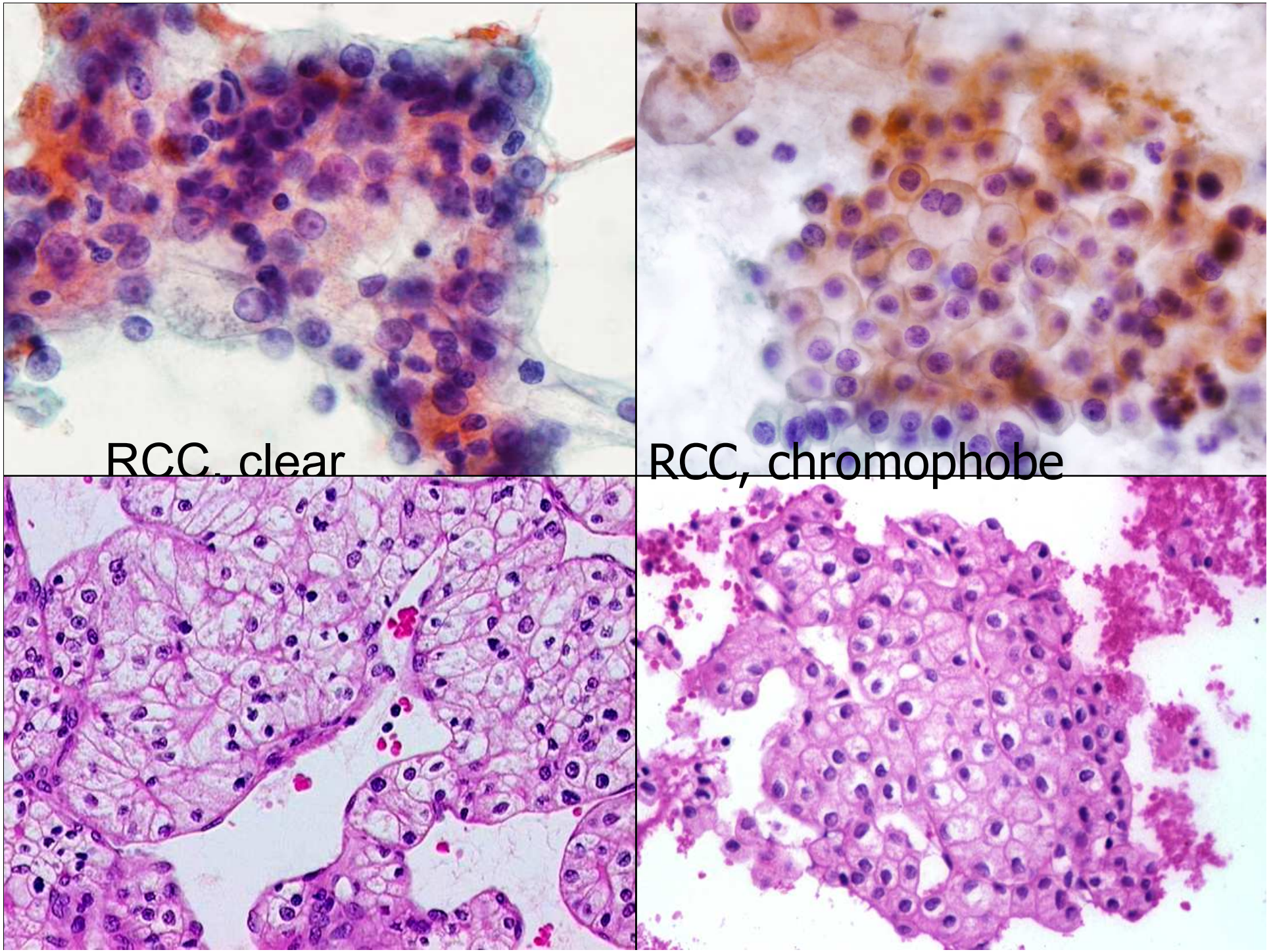
Case 2 Diagnosis:

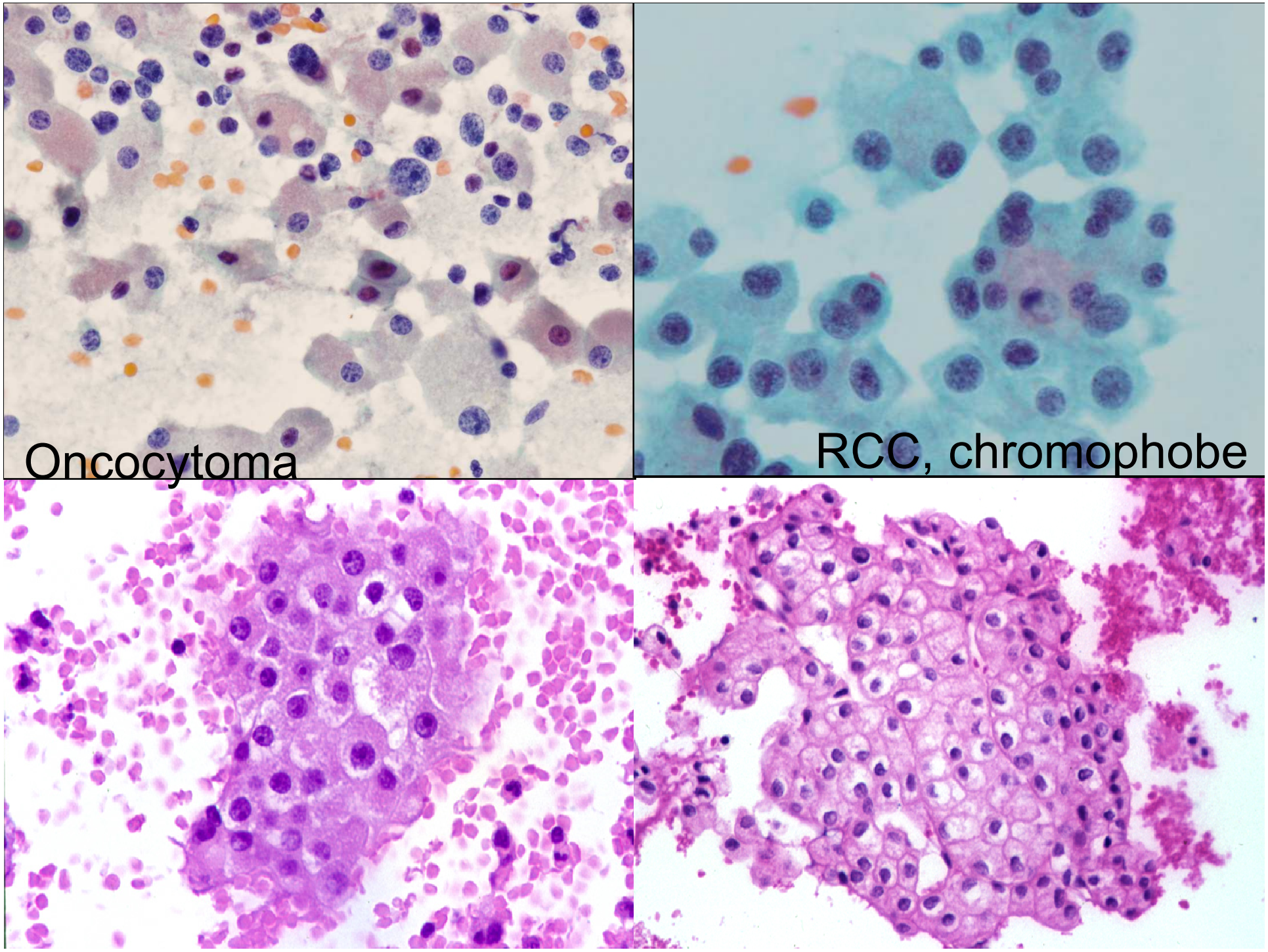
Renal Cell carcinoma, clear cell type

- 70% - 75% of kidney tumors
- Origin: Proximal tubules
- 190,000 new cases/year
- Risk Factors: Smoking, HBP, obesity, phenacetin, acetaminophen use, industrial chemicals, kidney stones, dialysis
- Age:40-60s
- M:F 2:1






RCC, clear
RCC, chromophobe


Oncocytoma
RCC, chromophobe

Chromophobe RCC vs. Oncocytoma

Mazal et.al.Human Path;2005:36;22-8.

212 Renal tumors
102 Clear cell RCC
46 Pap RCC
30 Chrom RCC
3 Collecting Duct Ca
31 Oncocytoma
Stains: Kidney specific cadherin, EMA, Vimentin, CK7, Hale's Colloidal Iron

	Chrom RCC	Onco	Clear RCC	Pap RCC	Coll Duct
ks-cadherin	**96.7%**	**3.2%**	0%	2.2%	0%
CK7	**90%**	**6.5%**	7.8%	76.1%	33%

Kim et al Histopathology. 2009 Apr;54(5):633-5.

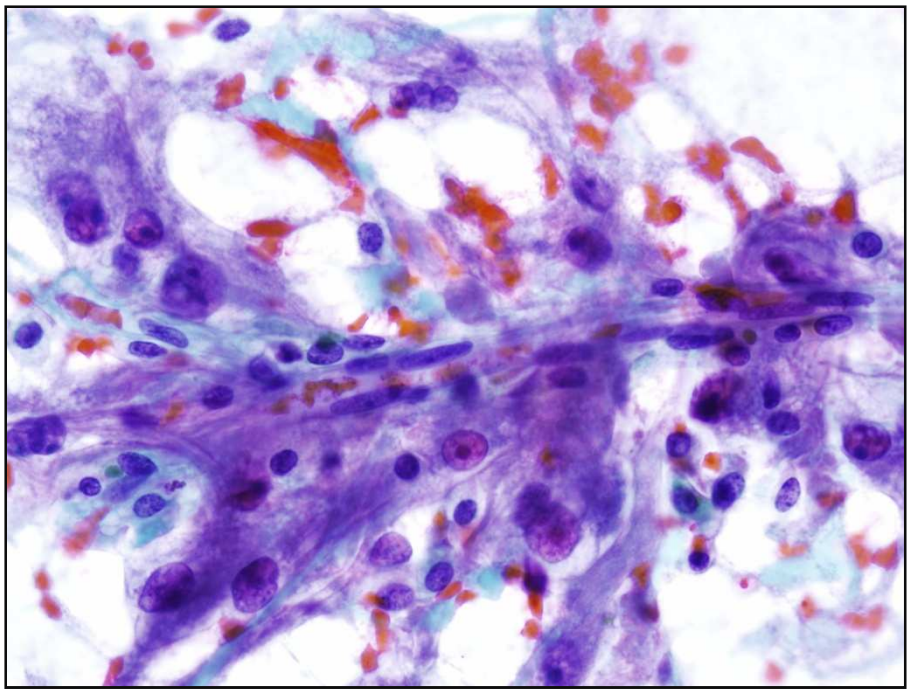
60 Renal tumors
24 Chrom RCC
25 Oncocytoma
11 Hybrid Oncocytic Tumors
Stains: CK7, claudin 8, S100A1

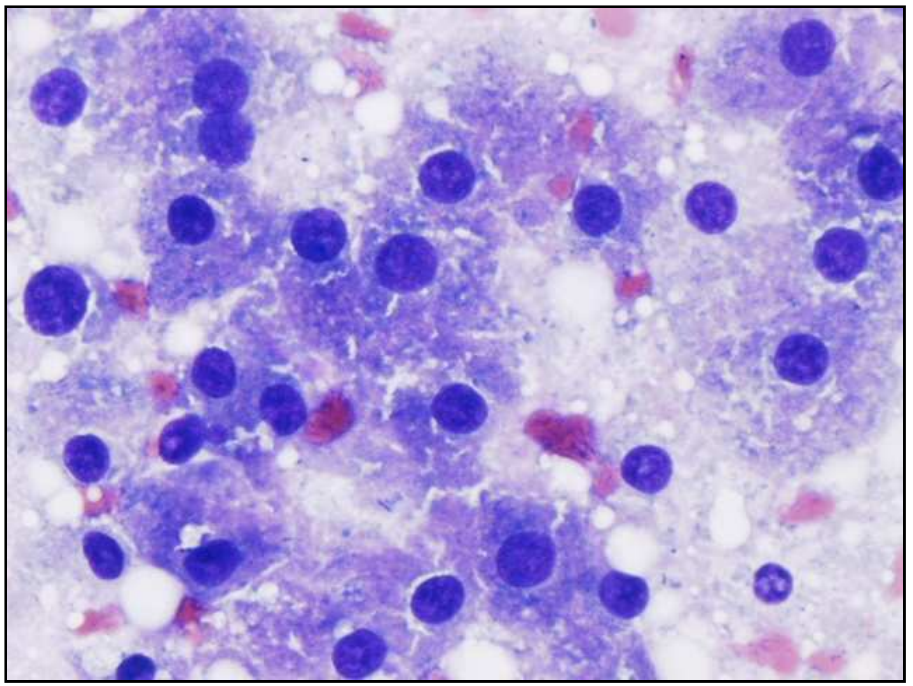
Pattern of immunoreactivity	Classical ChRC	RO	*P*-value
CK7	21/24*	2/25	≤0.01
S100A1	0/24	23/25	≤0.01
Claudin 8, membranous	14/24	0/25	≤0.01
Claudin 8, cytoplasmic	1/24	24/25	≤0.01

*Number of positive cases out of total number of cases.

RCC

Adrenocortical Lesions



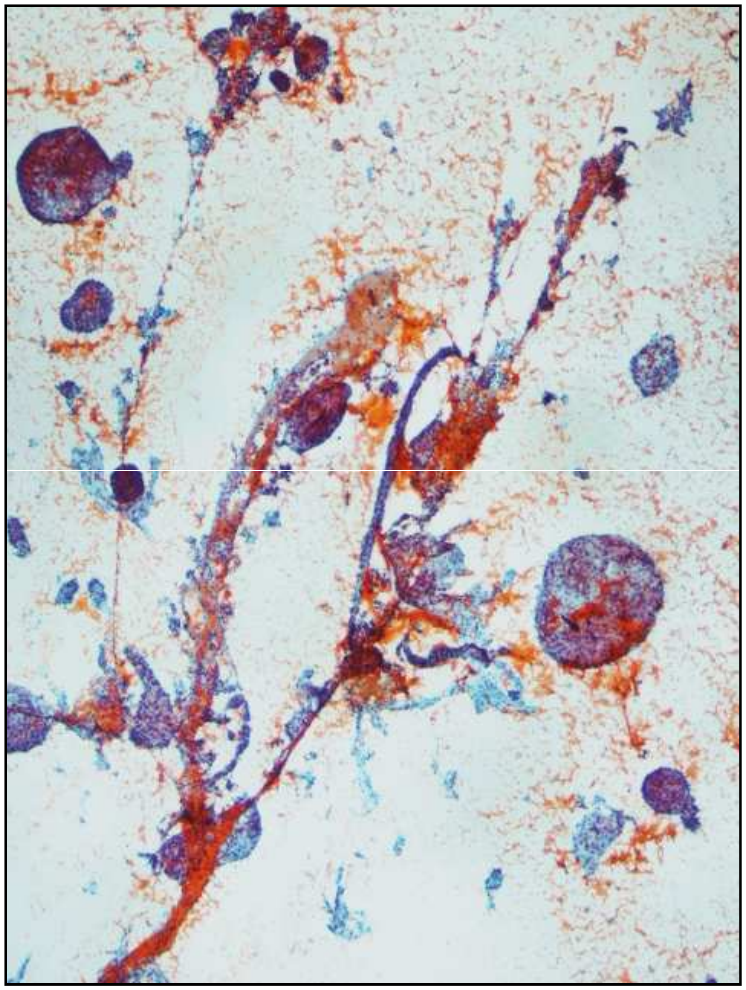


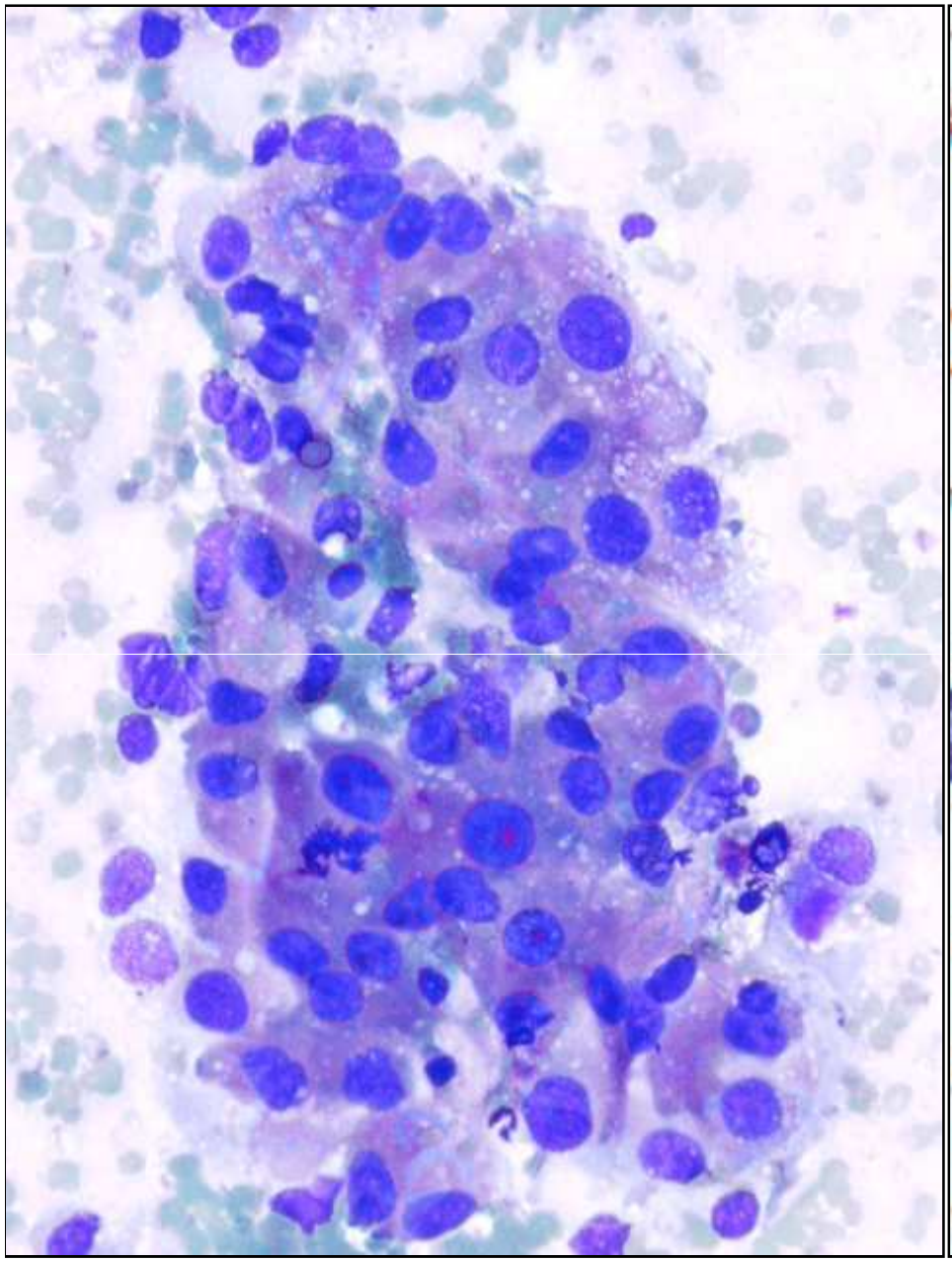
Renal Cell Carcinoma vs. Adrenocortical Lesions

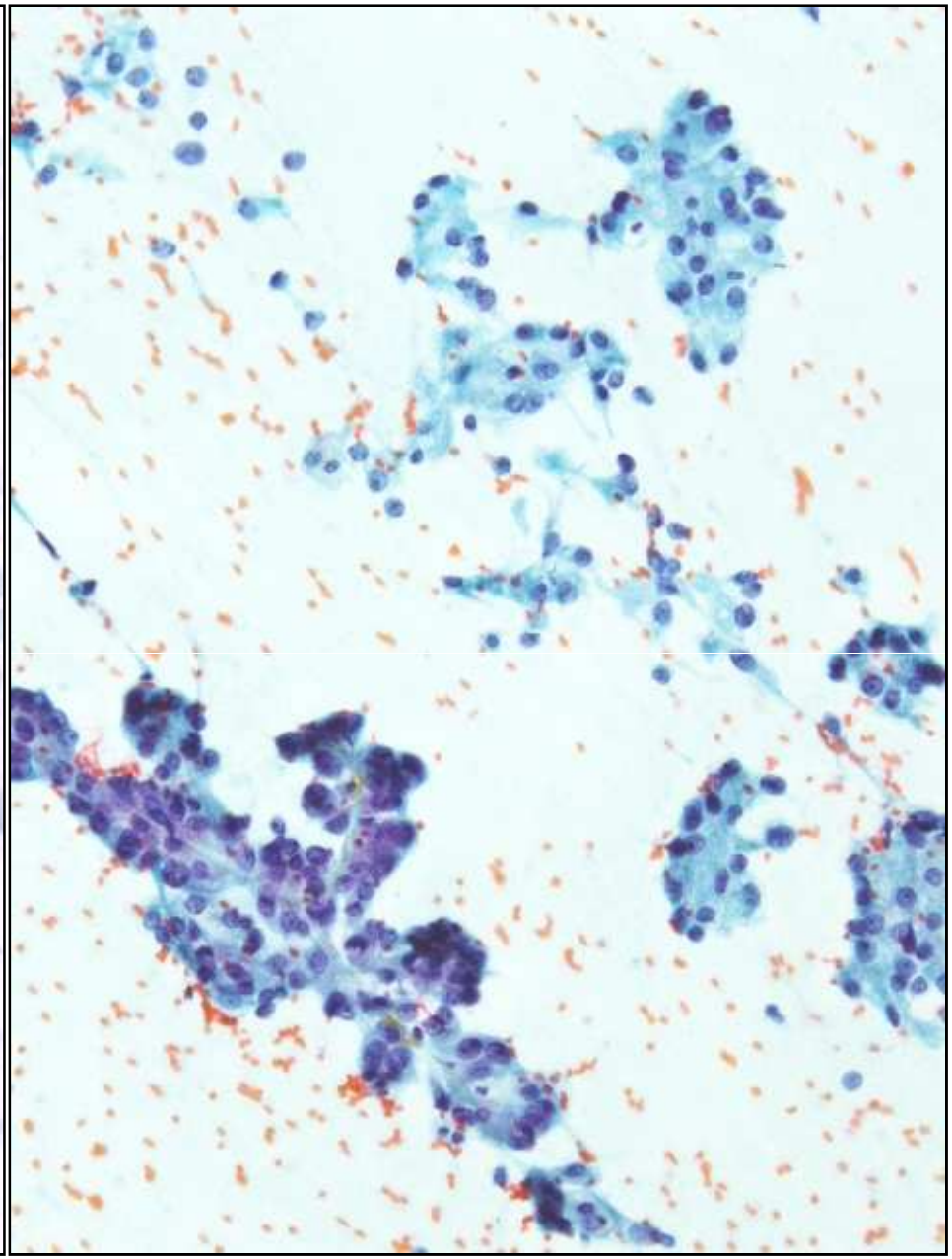
	Kidney	Adrenal
CK7	-	-
CK20	-	-
EMA	+	-
Vimentin	+	+
Inhibin	-	+
Melan A	-	+
Synaptophysin	-	+
Calretinin	-	+
CD 10	+	-

Case 3

- 82-year-old man with diabetes, and severe congestive heart failure presents with hematuria
- 6.0 X 6.1 X 5.3 cm right renal mass
- An ultrasound guided FNA was performed







Differential Diagnosis

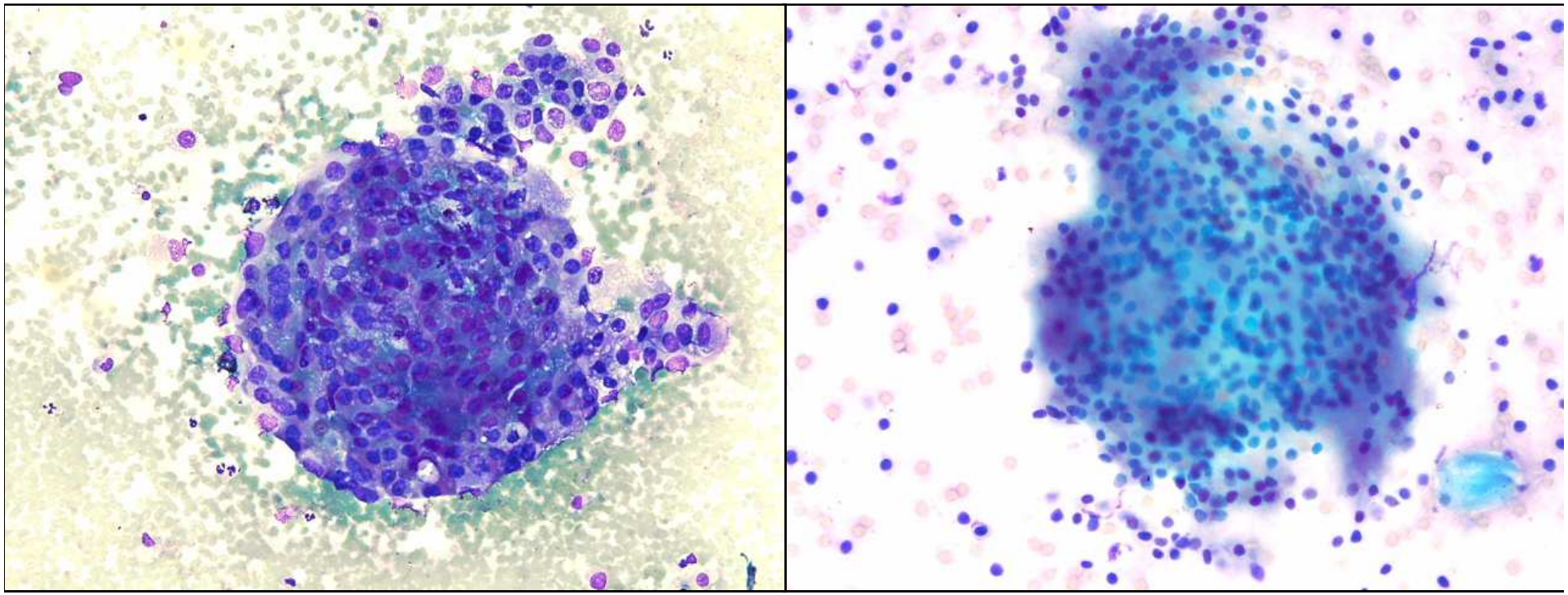
Benign:

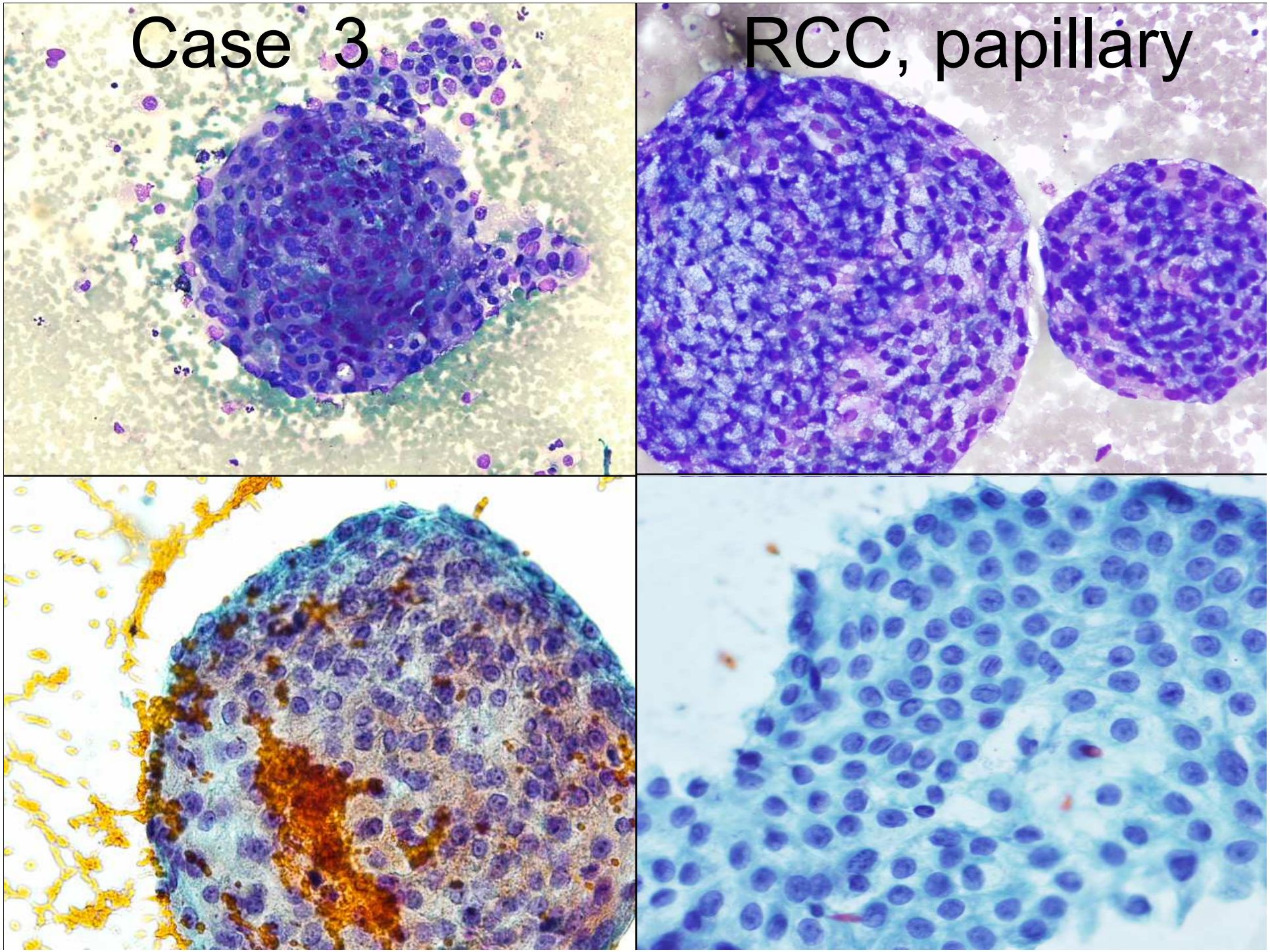
- Normal kidney cells
- Metanephric adenoma

Malignant:

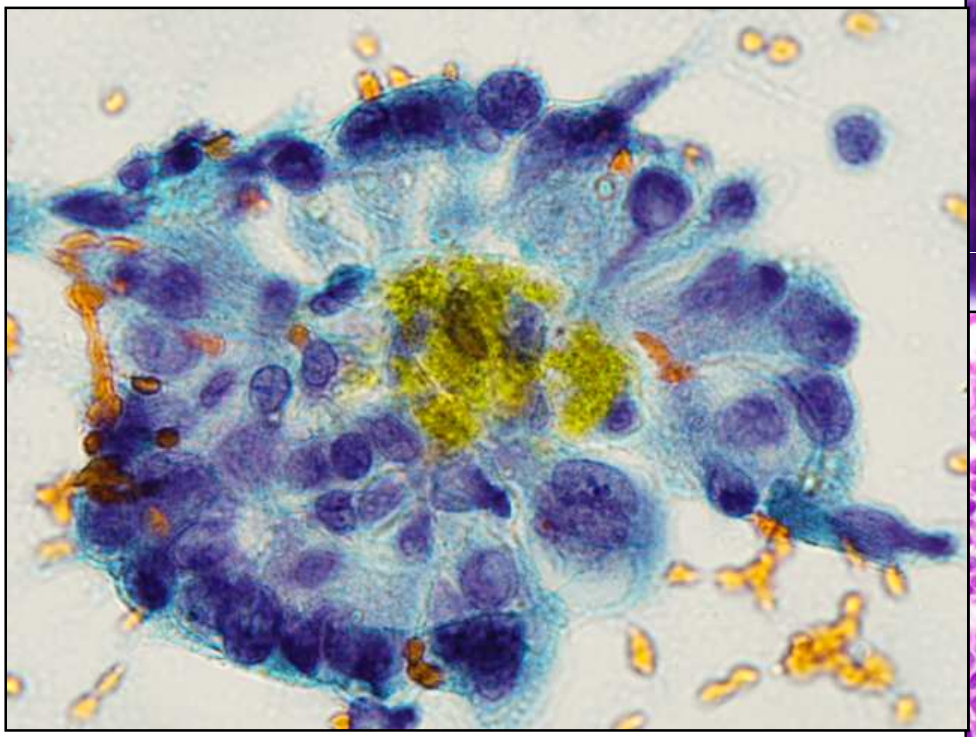
- Renal cell carcinoma, papillary type
- Renal cell carcinoma, clear cell type
- Urothelial carcinoma, low grade
- Metastatic tumor

Case 3 Metanephric Adenoma

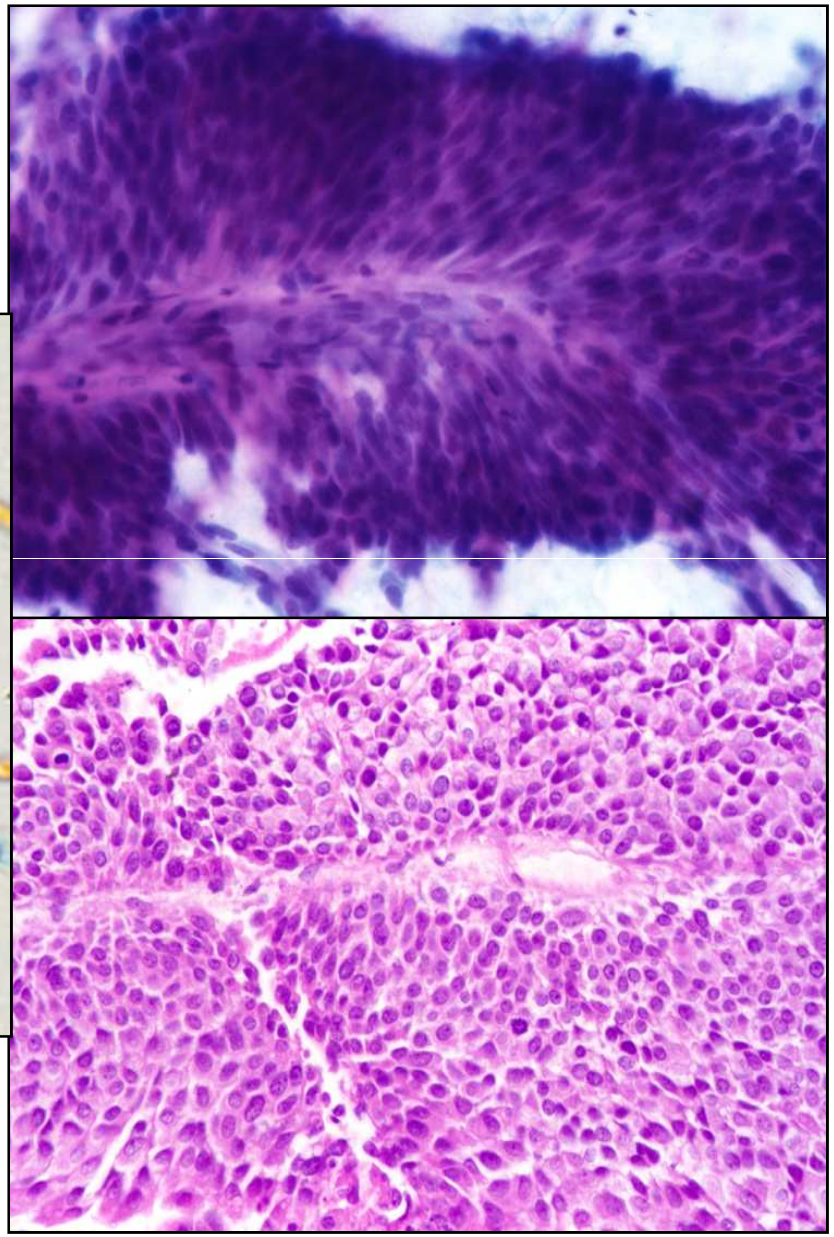



Case 3
RCC, papillary

Case 3

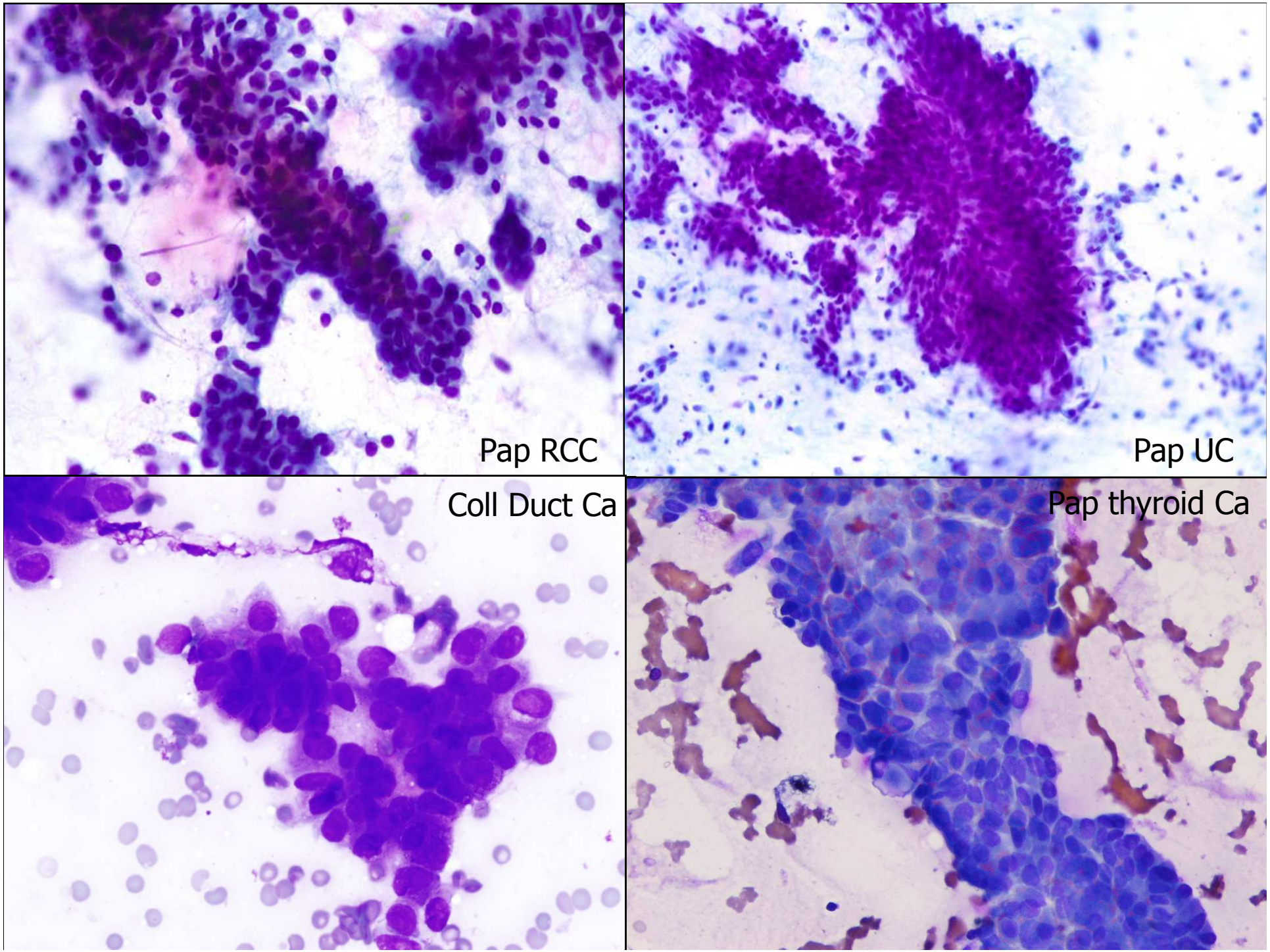


Papillary UC



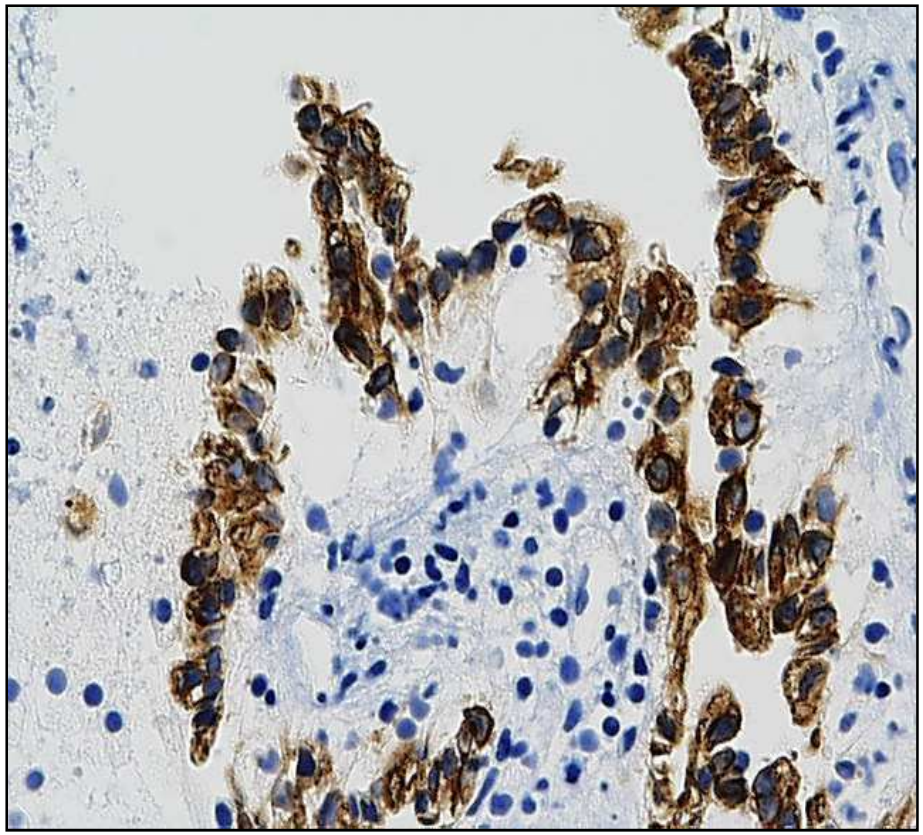
Differential Diagnosis of Papillary Tumors in the Kidney

- Papillary urothelial carcinoma
- Papillary RCC
- Collecting duct carcinoma
- Metastatic tumors


Pap RCC
Pap UC
Coll Duct Ca
Pap thyroid Ca

Papillary RCC Immunohistochemistry

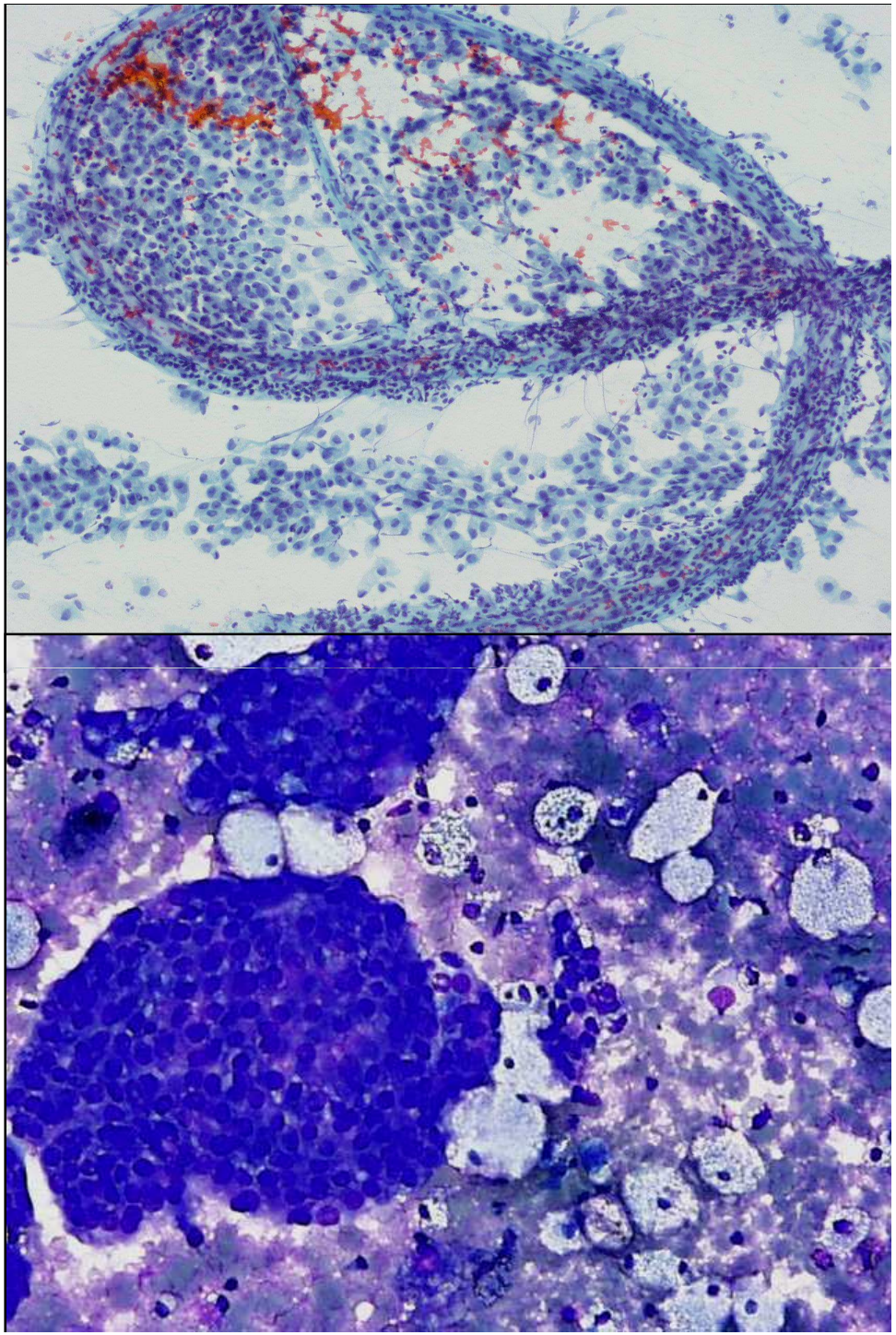
- Like other RCC
  - EMA (+)
  - Low molecular weight cytokeratin (+)
  - Mucin (-)
  - CEA (-)
- Unlike other RCC
  - CK 7 (+)
  - AMACR (+)
- Unlike Collecting Duct Ca
  - High molecular weight cytokeratin (-)



CK 7

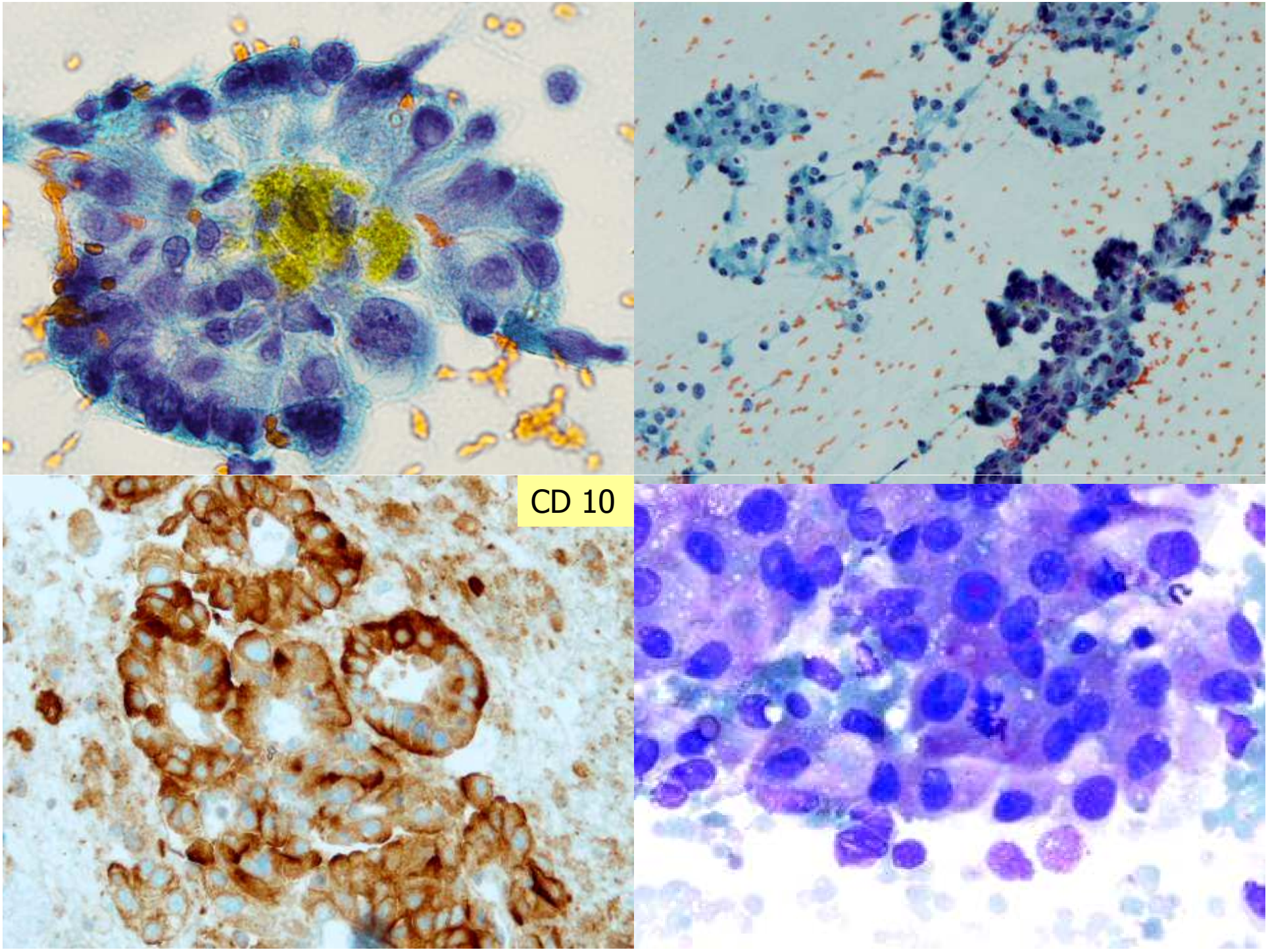
Papillary RCC

- 10% of renal tumors
- Papillary renal tumors are composed of at least 50% of papillary structures
- Renal cortical adenomas are frequently associated with PRCC in the same kidney, suggesting the possibility of transformation from adenoma to carcinoma
- Cytology:
  - Cellular smears
  - Papillary fragments, large cellular balls
  - Foamy histiocytes, psammoma bodies



Back to the case…

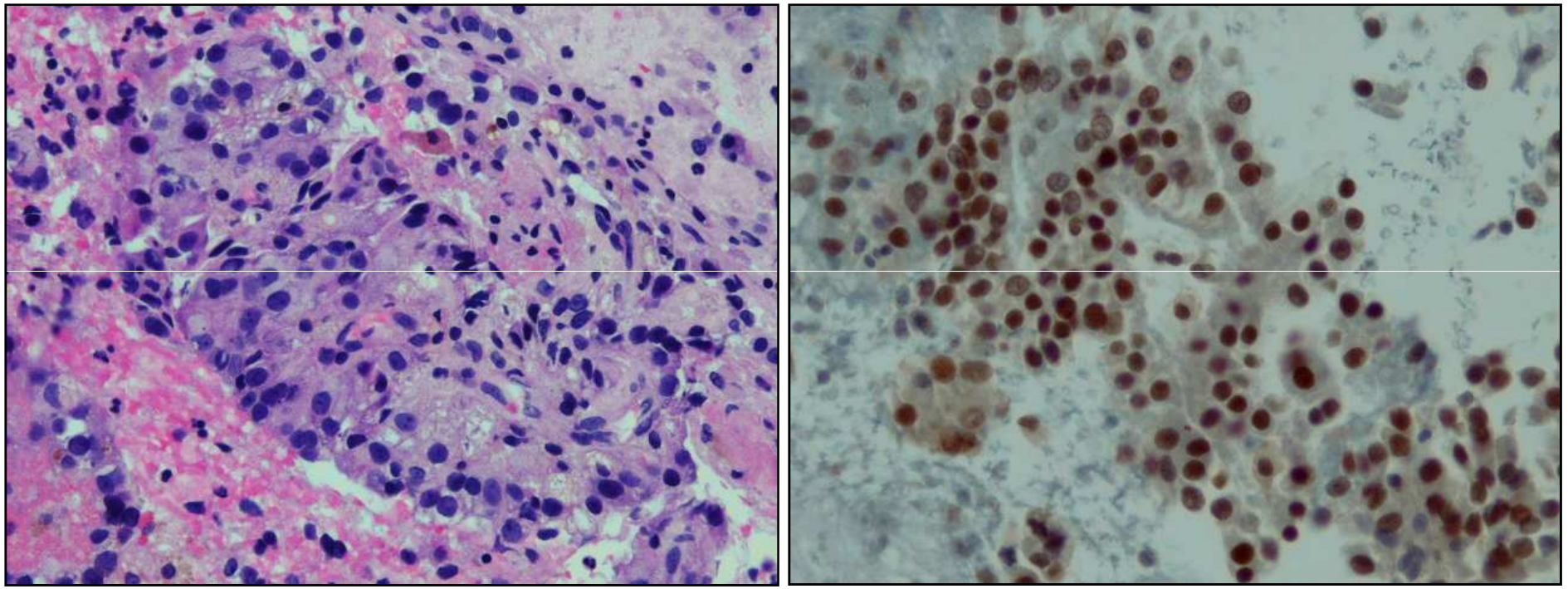
- Is this a Papillary RCC?


CD 10

	CCRCC	PRCC	ChRCC	ONC	UC	CDC
CD10	81–100%	63–100%	± (26%)	± (33%)	-	-
RCC	75–85%	75–96%	± (45%)	-	-	
VIM	+	±	-	±	-	
EMA	+		+	75%		+
CK7	-	+ (type 1)	73–100% (diffuse/strong)	±	+	±
CK20	-	± (type 2)	-	±	±	-
CD15	75%	100%	± (25%)	(63%)	-	
CD117	± (15%)	± (28%)	57–100%	+	-	-
MUC1	84%	72–100% (type 1)	95%		-	
AMACR	25% (focal/weak)	100% (strong)	-	-	±	
LMWCK	+	+		+	+	
HMWCK	-	± (focal)	-	-	+	+
E-cad	5%	0% (type 1)	95–100%	100%		

Adapted from Zhou and Magi GalluzziThe Usefulness of Immunohistochemical Markers in the Differential Diagnosis of Renal Neoplasms**Clinics in Laboratory Medicine** - Volume 25, Issue 2 (June 2005)

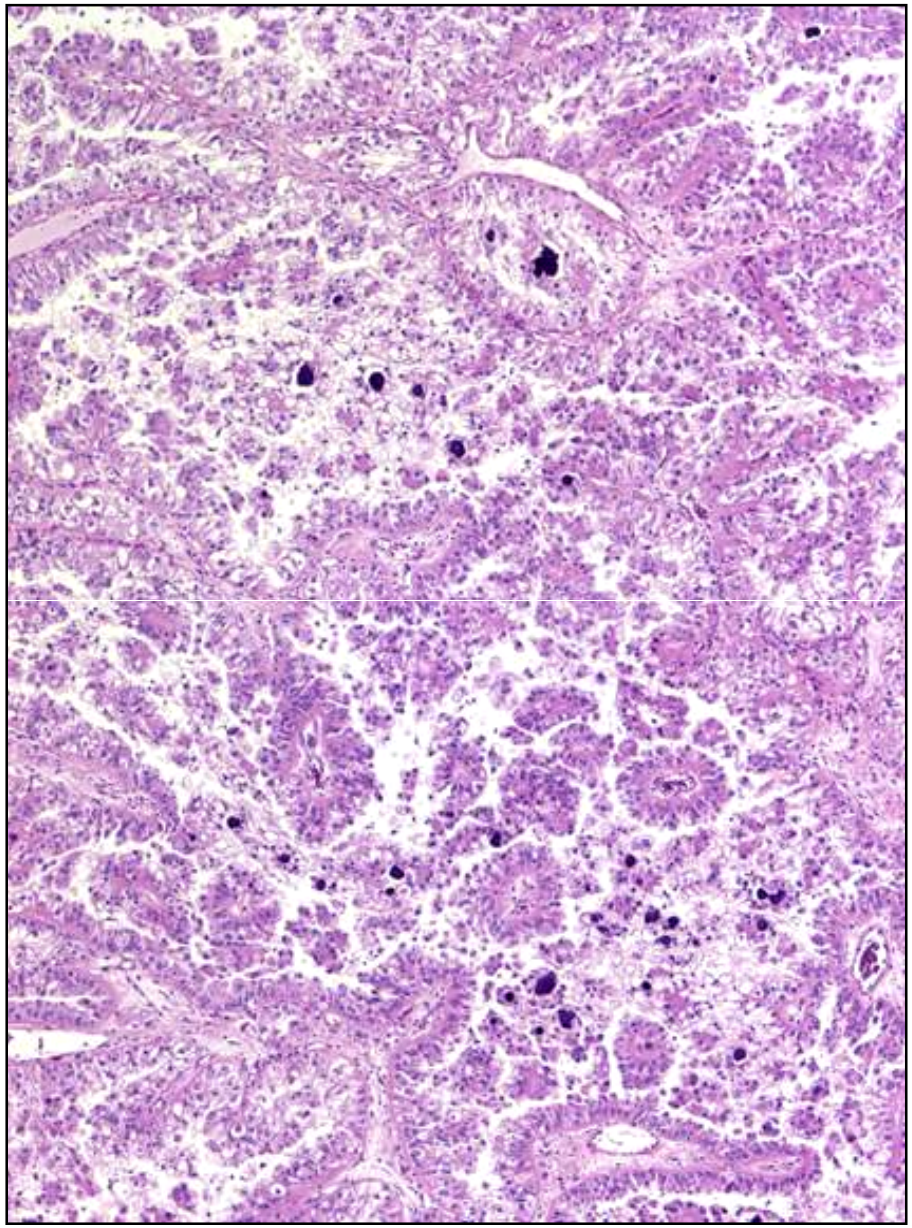
TFE 3 stain - nuclear

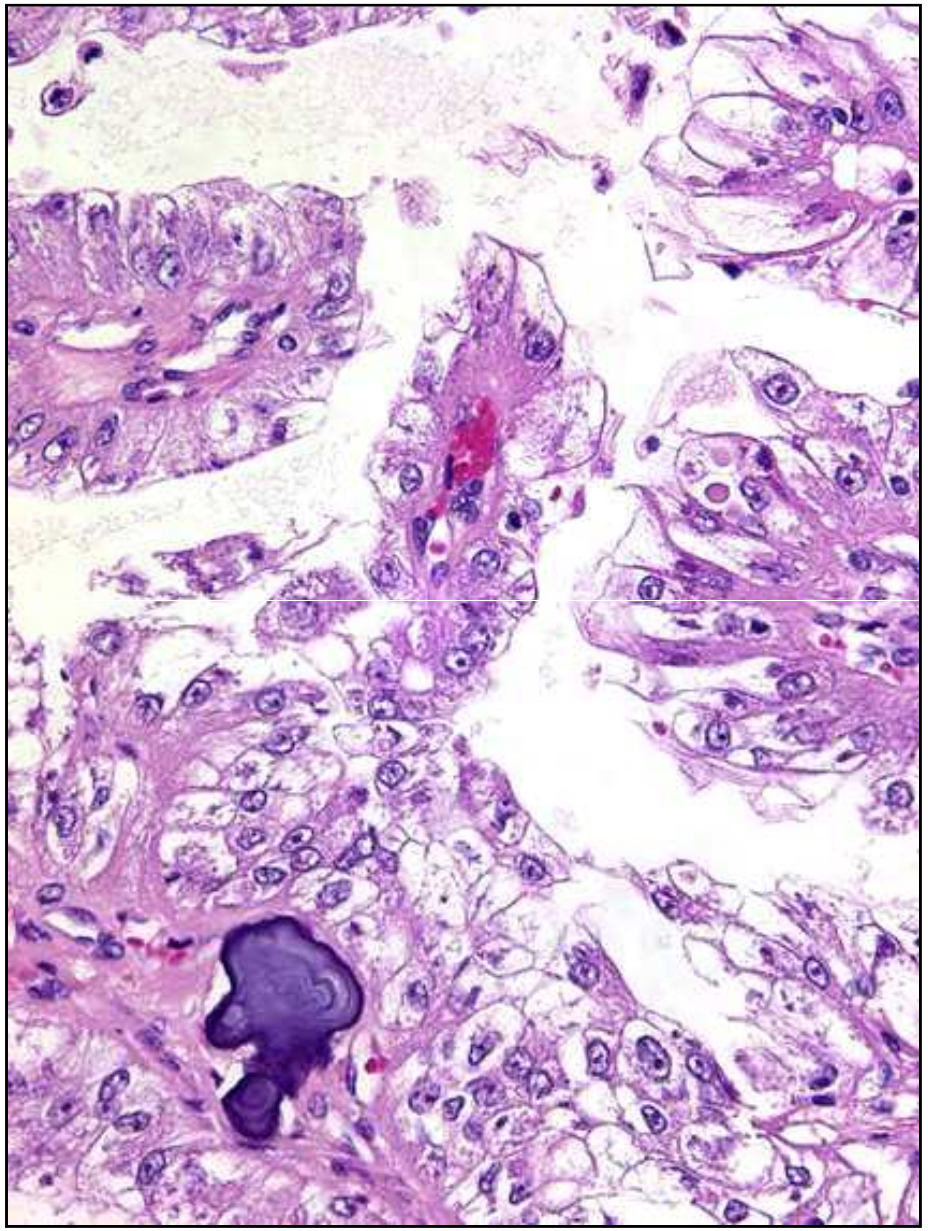


Dx: Xp11 Translocation Carcinoma

Xp11 translocation carcinoma

- Several different translocations involving chr. Xp11.2 resulting in gene fusions involving the *TFE3 gene*
- t(X,17) has features of both RCC and alveolar soft part sarcoma
- Children and young adults
- Present at advance stage, clinical course indolent?
- Histo – papillary architecture + clear cells

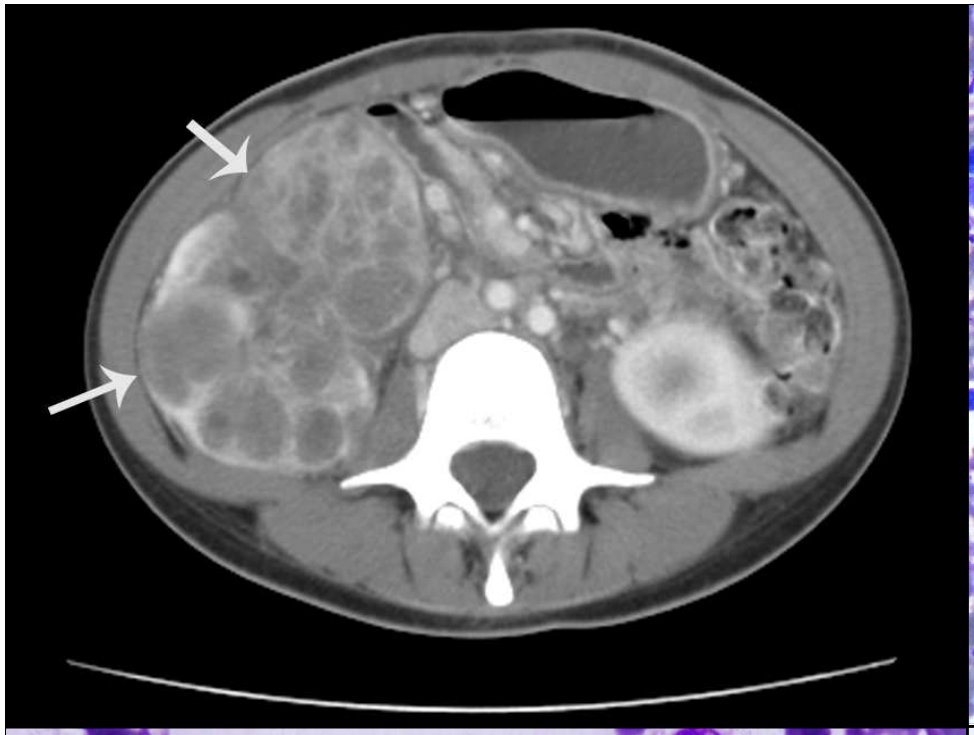


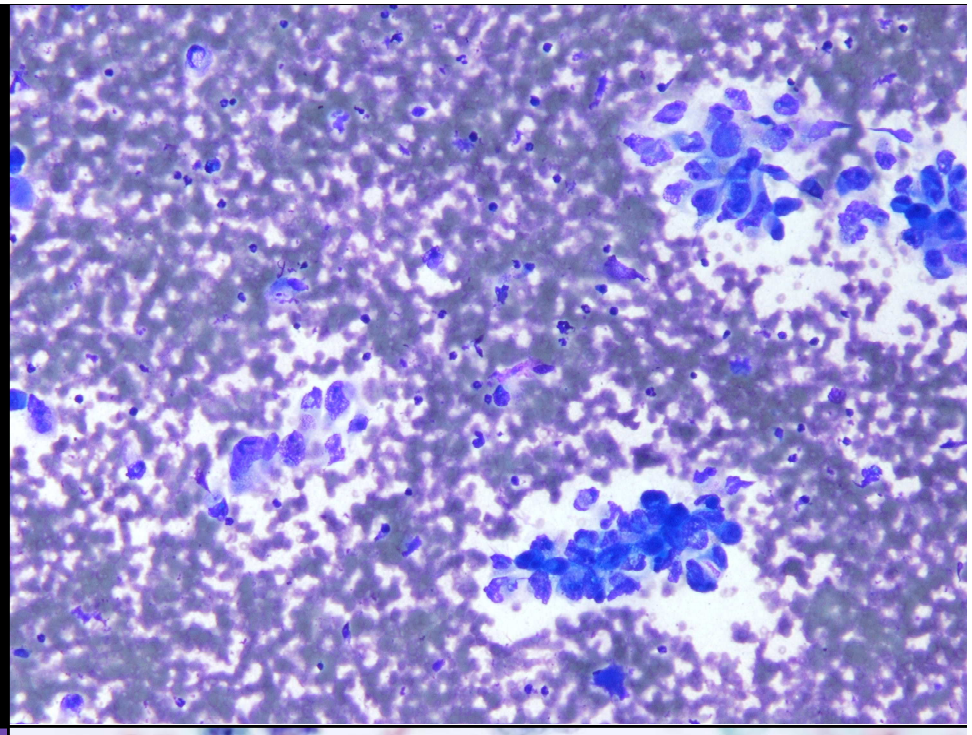


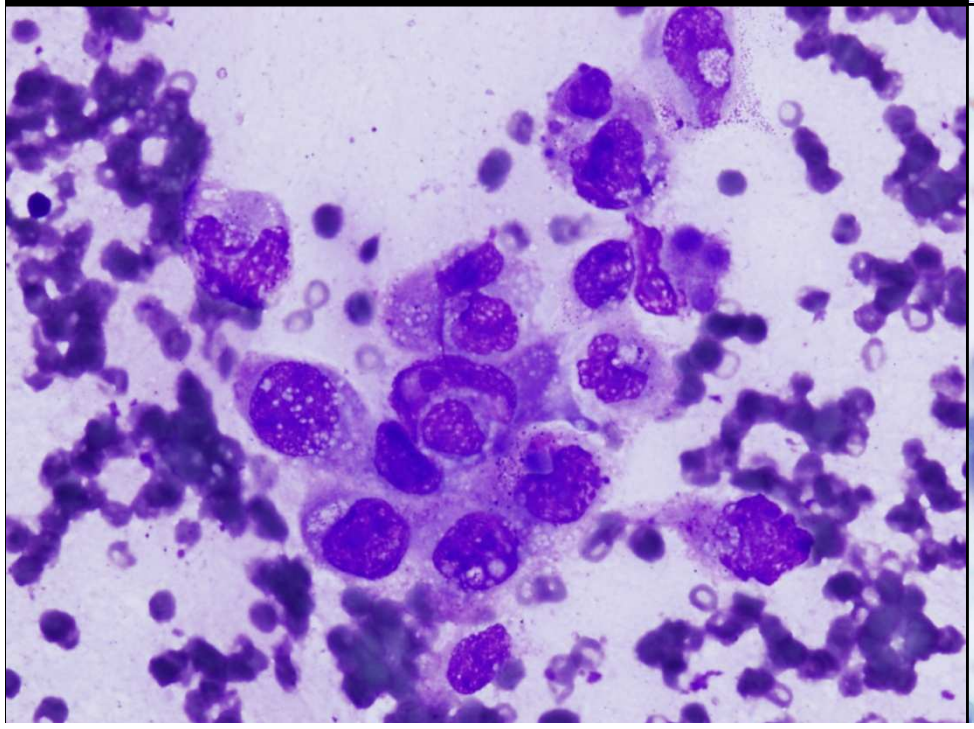
Renal Medullary Carcinoma

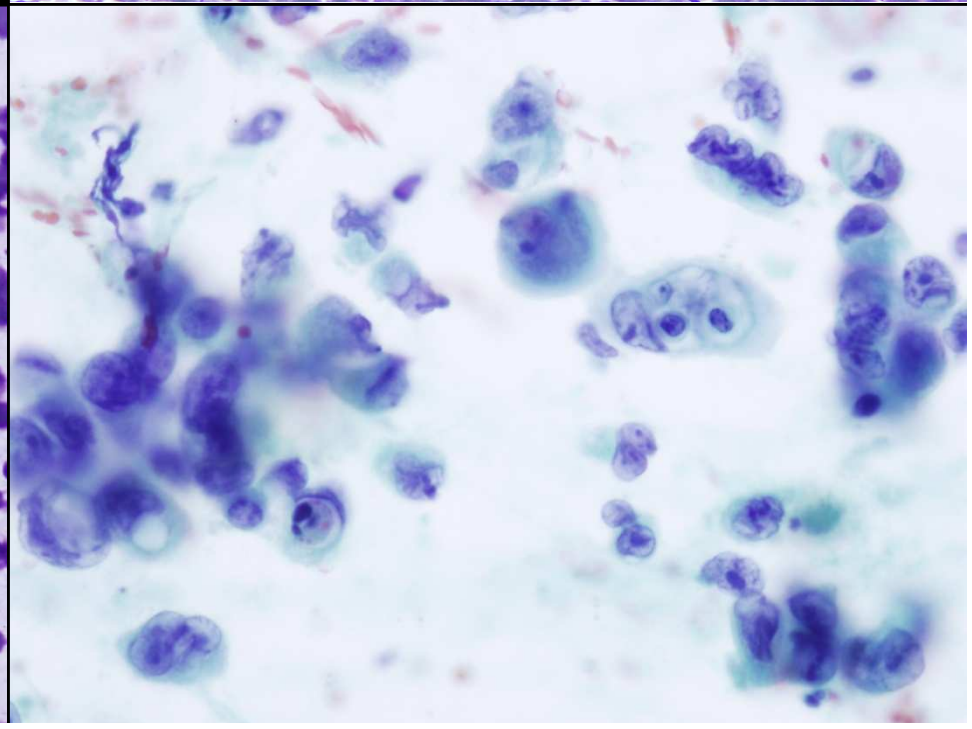
- Young black men
- Sickle cell trait
- Cohesive cellular groups with vacuolated cytoplasm, indented nuclei, irregular membranes, coarse or vesicular chromatin...essentially like a hg ca.

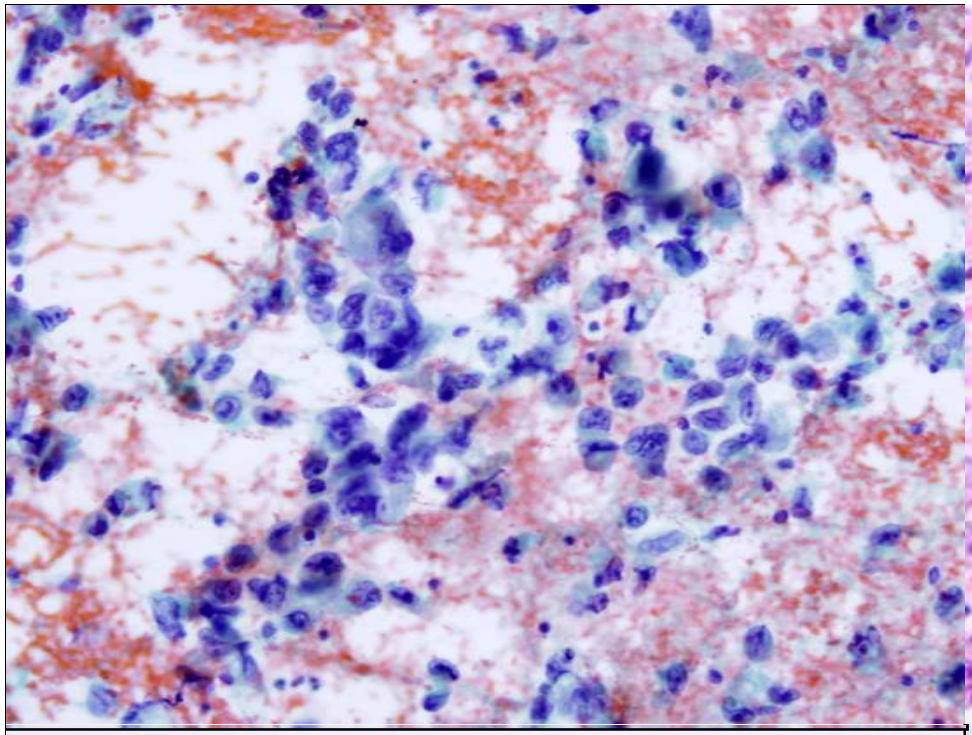
Assad L et al. Cytologic features of Renal Medullary Carcinoma Cancer. 2005 Feb 25;105:28-34.

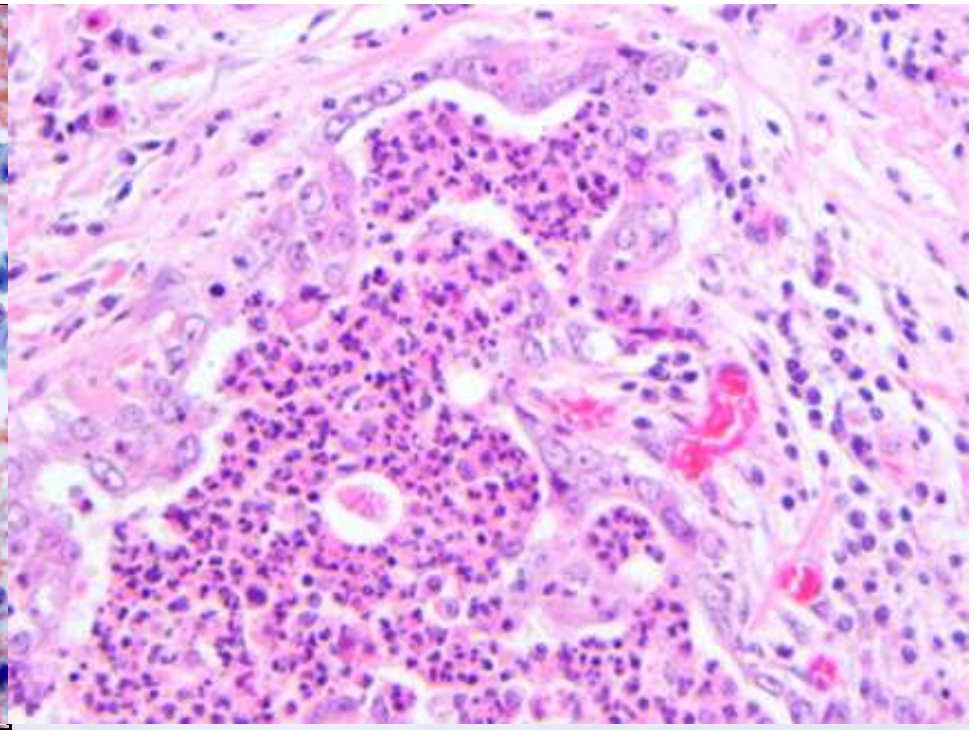


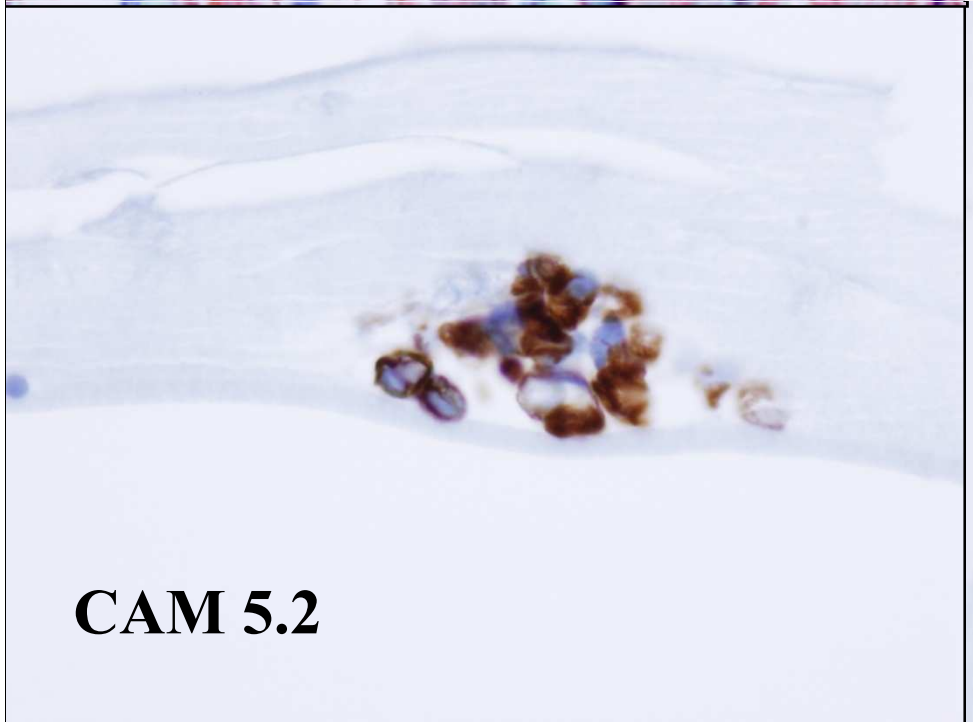




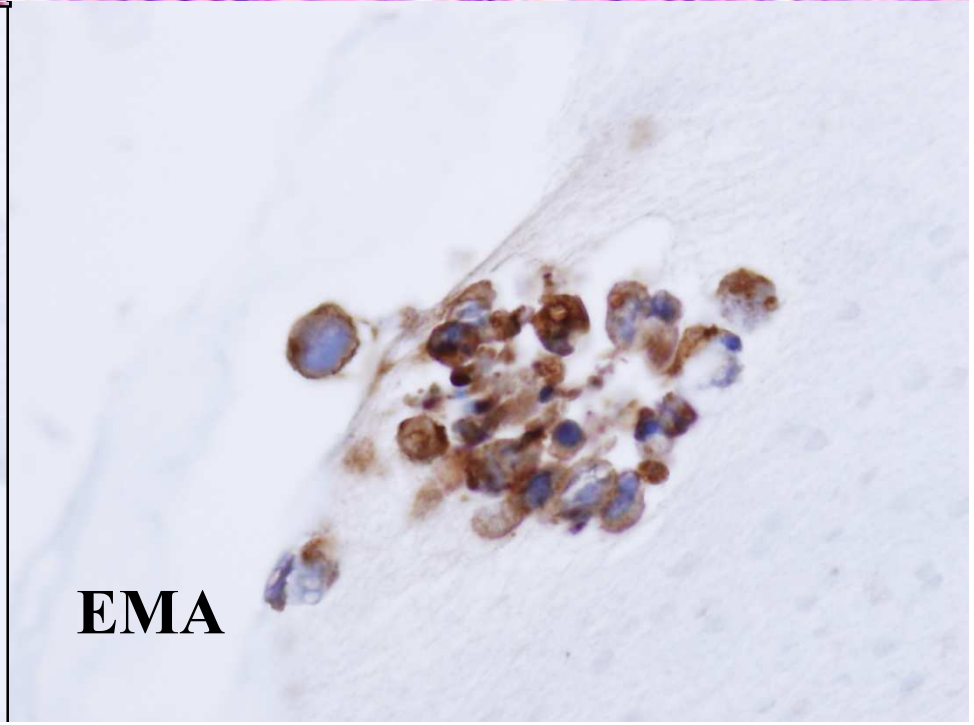








CAM 5.2

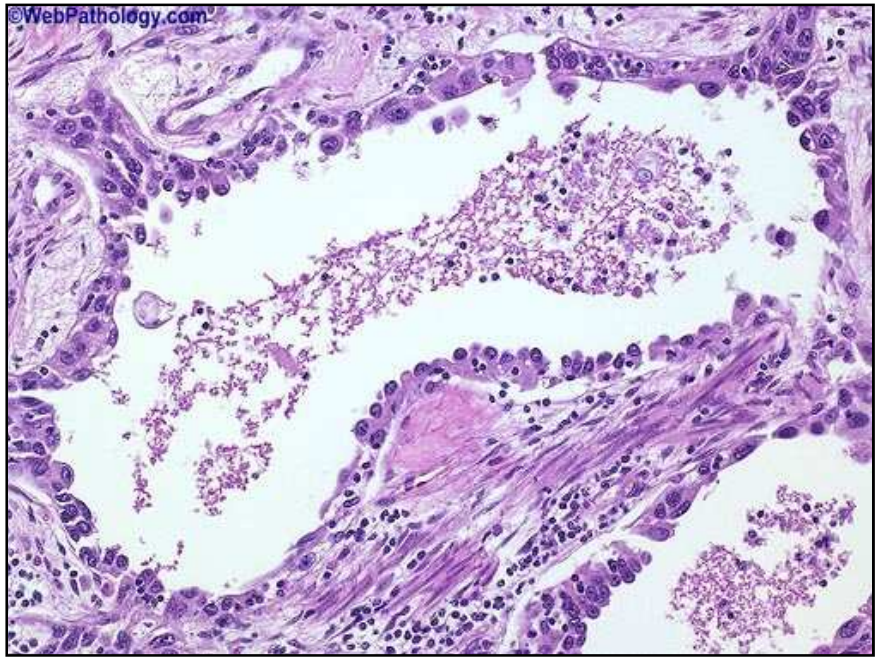


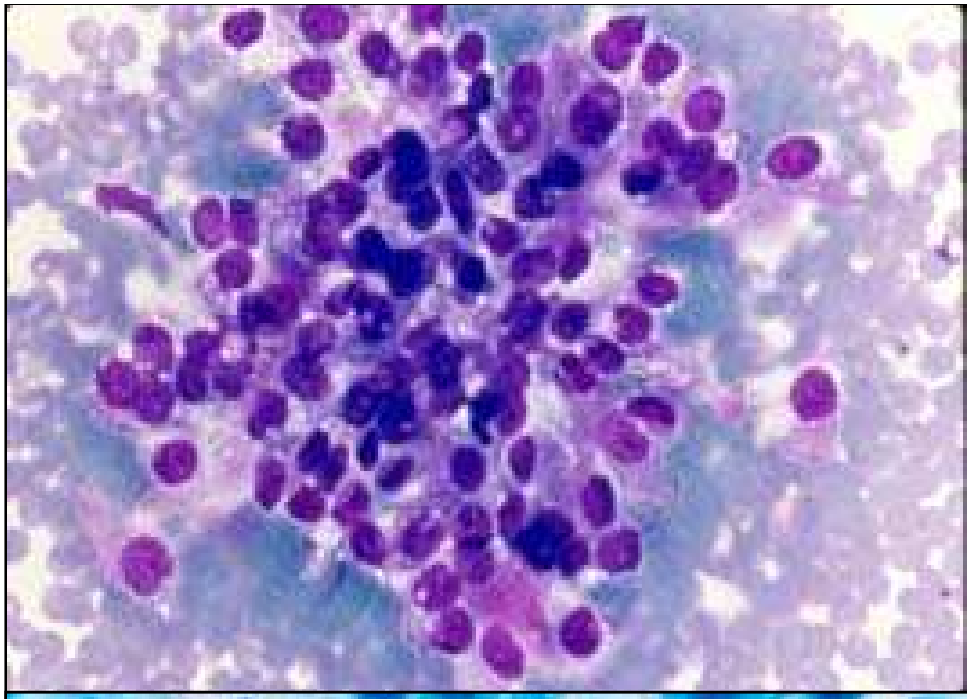
EMA

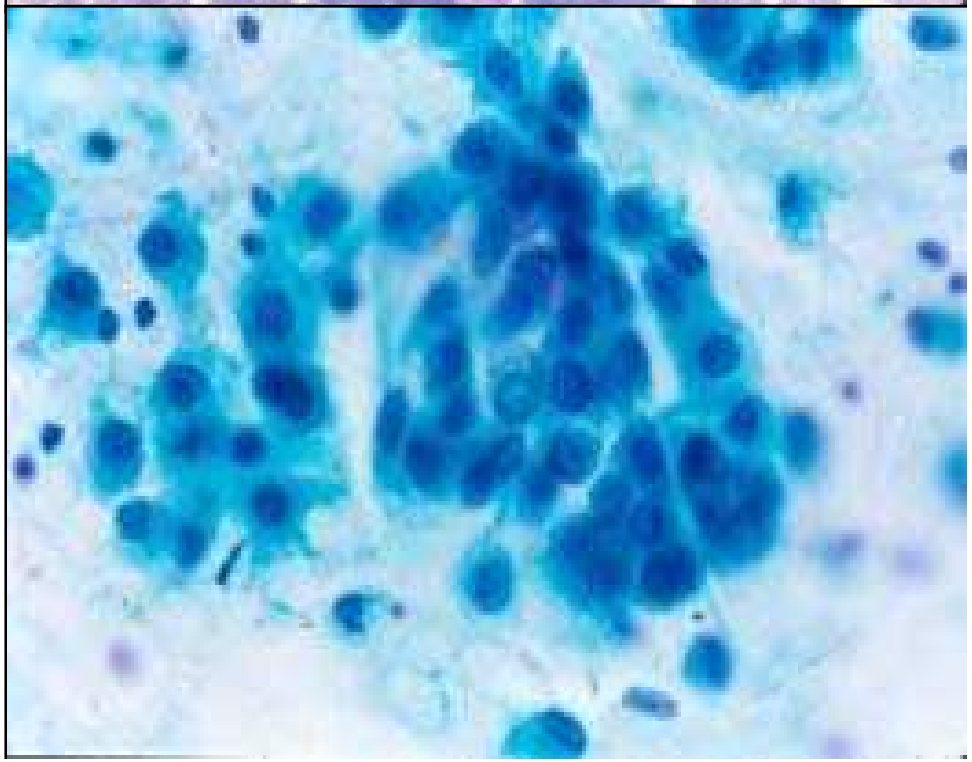
Collecting Duct Carcinoma (Bellini Tumor)

- Rare 1%
- 1981 WHO distinct variant of RCC
- Arises in renal medulla (unlike RCC arises from proximal tubule CD Ca arises from collecting duct epithelium)
- Cytology: Arranged in papillary/ tubular structures
- DDX: Papillary RCC, TCC, metastasis
- Some have trisomy 7, 17 like papillary RCC, others have trisomies of 1, 6, 14,22
- Immunostains: K903 (+) 50%, LMWCK(+), EMA(+), *Ulex* (+), LeuM1 and vimentin (+/-)

Collecting Duct Carcinoma (Bellini Tumor)

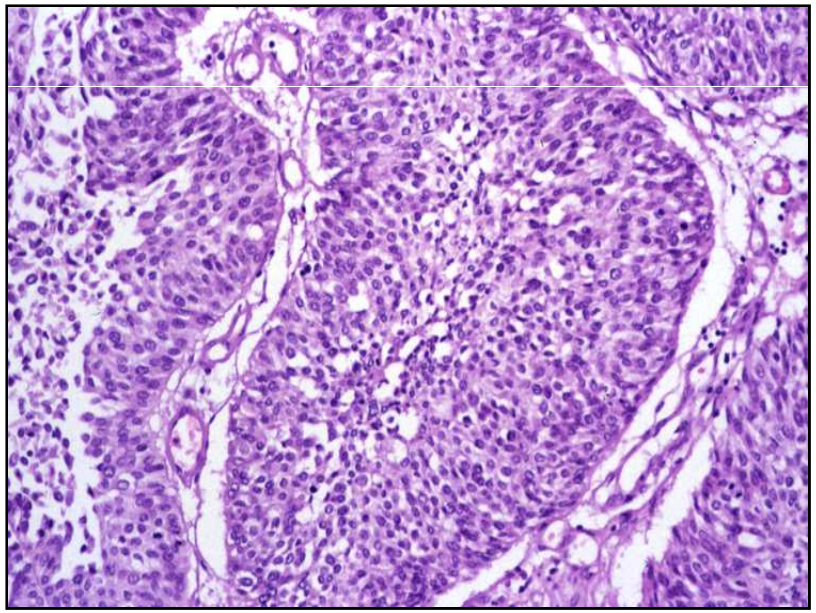


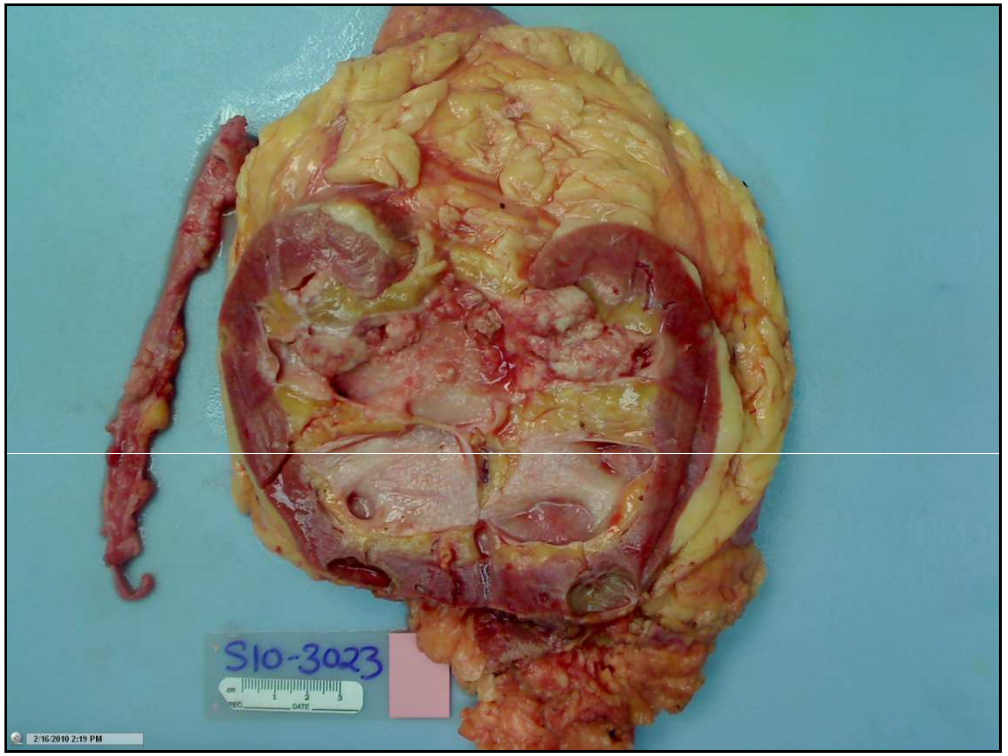


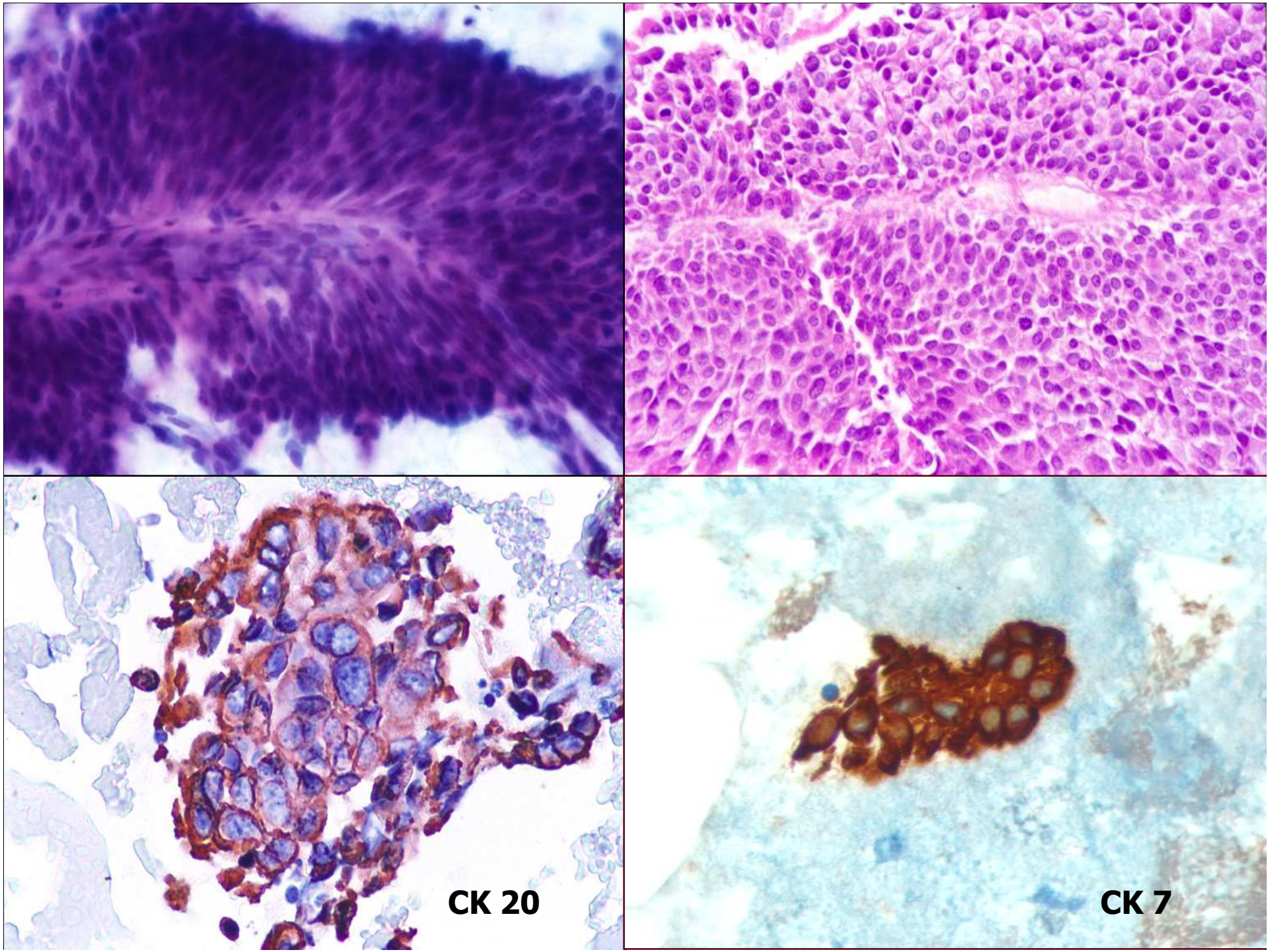


Urothelial Carcinoma

Only 5-10% of
all renal masses






CK 20
CK 7

Metastatic tumors:

Tumors Metastatic to the Kidney: A Clinicopathological Study of 29 Cases. Barkan and Zhou et al.

Loyola University Medical Center, IL and

Cleveland Clinic, OH

- 5611 (nephrectomy +FNA) - 30 cases met neoplasm to kidney
- Tumors metastatic to the kidney are rare, accounting for 0.5% of all the renal tumors. The most common primary tumors are **lung squamous cell carcinoma and adenocarcinoma, and melanoma**, although other primary tumors are also observed.

Based on evolving therapeutic concepts in RCC what is the role for the cytopathology?

- Be able to classify renal masses as benign vs. malignant
- Be familiar and be able to use immunohistochemistry, cytogenetics and FISH applications in order to subtype the renal neoplasms
- Know the limitations of cytology in diagnosing renal neoplasms
- As targeted neoadjuvant therapy is gaining more popularity cytology is becoming one of the surveillance methods

Clinical Trials on Targeted Therapy

- **SURGICAL MORBIDITY ASSOCIATED WITH ADMINISTRATION OF TARGETED MOLECULAR THERAPIES PRIOR TO CYTOREDUCTIVE NEPHRECTOMY FOR METASTATIC RENAL CELL CARCINOMA**
  Margulis V et al. MDACC,Houston TX . 2008

- **SAFETY AND EFFICACY OF SUNITINIB IN METASTATIC RENAL CELL CARCINOMA (mRCC): PRELIMINARY ASSESSMENT OF AN ITALIAN EXPANDED−ACCESS PROGRAM (EAP) WITH SUBPOPULATION ANALYSIS**
  Sternberg C. et al Italy, 2008

- **NEOADJUVANT TARGETED THERAPY AND ADVANCED KIDNEY CANCER: OBSERVATIONS AND IMPLICATIONS FOR A NEW TREATMENT PARADIGM.**
  Shuch B et al BJU Int. 2008

- **TEMSIROLIMUS IN THE TREATMENT OF RENAL CELL CARCINOMA ASSOCIATED WITH XP11.2 TRANSLOCATION/TFE GENE FUSION PROTEINS: A CASE REPORT AND REVIEW OF LITERATURE.**
  Parikh et al. Rare Tumors 2009; volume 1:e53

SUMMARY

- Solid renal tumors can be accurately diagnosed with FNA
- Core biopsy and FNA are equivalent in diagnosing solid renal tumors
- The number of renal FNAs are on the rise, combined with the trend of molecular profiling of the tumors it is useful to be familiar with the ‘molecular tricks’ and especially if in doubt ask for cytogenetics as well as CB during the FNA
- Beware of pitfalls:
  - Papillary tumors (Papillary RCC, Papillary TCC, Collecting Duct Ca)
  - Oncocytoma vs. RCC
  - Keep rare entities in mind lymphoma, metastasis
  - If material insufficient diagnosis = nondiagnostic