

30th Annual Park City
Anatomic Pathology Update

The Lodges at Deer Valley
Park City, UT

February 6–10, 2017

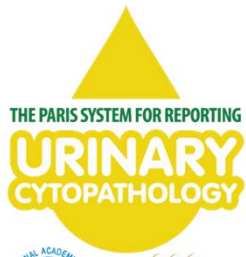


The Paris system for Reporting Urinary Cytology: The quest to develop a standardized terminology

Eva M. Wojcik, MD

Chair and Professor of Pathology and Urology

Loyola University, Chicago, IL



Outlines

- What is the goal of urine cytology?
- Why to standardize, why Paris?
- What is the guiding principle?
- What are diagnostic categories?
- What are the criteria?
- What adjuvant studies?
- What are future clinical and research needs?

The main purpose of urine cytology

**To detect bladder
cancer**



Bladder cancer - current status

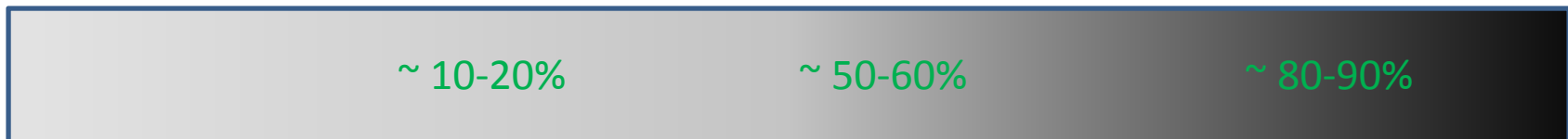
- ~ 76,900 new cases in 2016 in the USA
 - ~ 16,390 deaths due to bladder cancer
 - 4th most common ca in men and 9th in women (1 in 44 people)
 - 9th most common cause of cancer death (F>M)
 - ~ 75% non-muscle invasive bladder cancers (superficial bladder cancers), Ta, Tis, T1
 - ~ 30% - 70% - recurrence
 - ~ 5% - 15% - progression (<1% LG Ta)
 - > 535,000 people in the US are survivors of this cancer
 - Highest per patient cost from dx to death of all cancers
 - \$4.1 billion/year spent to tx bladder cancer
- ACS
- Urine Cytology

Classifications

WHO 1973

Papilloma	Grade I	Grade II	Grade III
Papilloma	PUNLMP	Low Grade	High Grade

WHO/ISUP 2004



URINE CYTOLOGY SENSITIVITY



Very high probability that we are going to be wrong

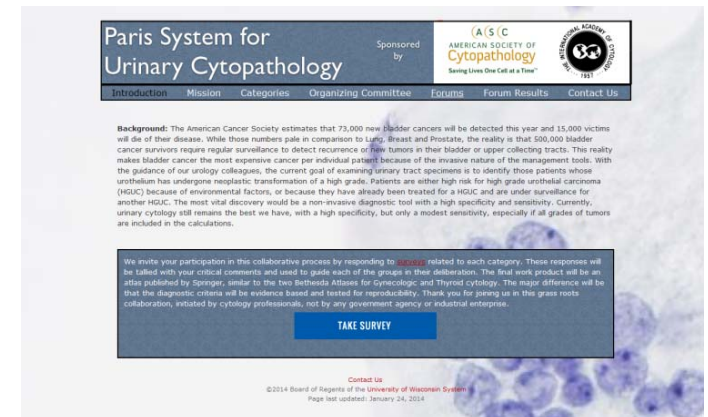
Why to standardize reporting of urinary cytology?

- Reproducibility
- Improvement of communication
- Atypical cells
 - Wide intraobserver variability
- Nationally rates of atypical vary among institutions
 - Range from 2% to 30% (51% atypical + suspicious)



Where did we start?

- 18th International Congress of Cytology, Paris, May, 2013
 - “Paris Group” – all participants of two Urine Cytology Symposia
 - Outline of the Paris System for Reporting Urinary Cytopathology
 - **Ultimate goal – detection of HGUC**
- Sponsorship by the ASC and IAC
- Contract with Springer
- Numerous face-to-face meetings



2. The goal of urine cytology is to detect clinically significant high grade lesions (HGUC).

#	Answer	Bar	Response	%
1	I agree with this statement	<div></div>	127	85%
2	I disagree with this statement	<div></div>	22	15%
3	Comments/Suggestions:	<div></div>	18	12%

The Paris Working Group consisted of 49 members, 28 from 12 US states, and 21 from 9 countries including Canada, France, Italy, Japan, Korea, Luxembourg, Slovenia, Switzerland, and the United Kingdom.



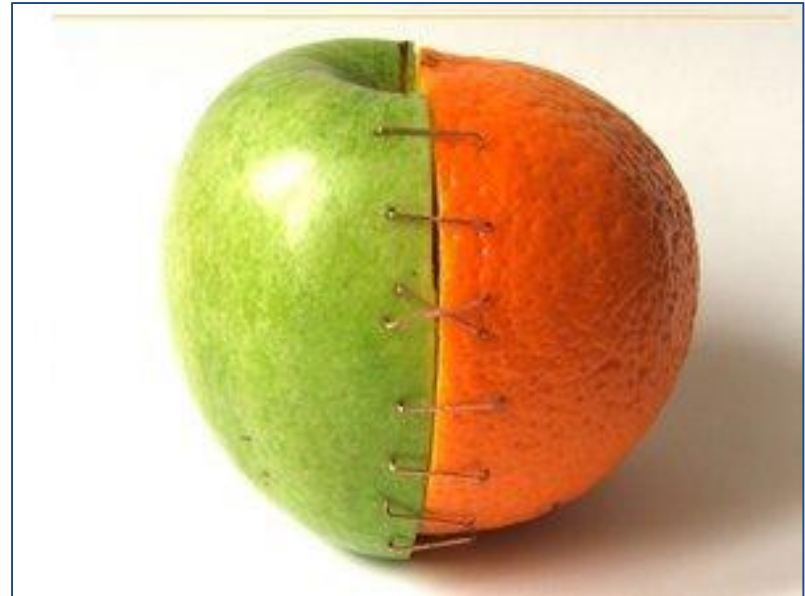
The Paris System for Reporting Urinary Cytology

Dorothy L. Rosenthal
Eva M. Wojcik
Daniel F.I. Kurtycz
Editors

- I. Pathogenesis of Urothelial Carcinoma
- II. Adequacy
- III. Negative **for High Grade Urothelial Carcinoma**
- IV. Atypical Urothelial Cells
- V. Suspicious **for High Grade Urothelial Carcinoma**
- VI. High Grade Urothelial Carcinoma
- VII. Low Grade Urothelial **Neoplasm**
- VIII. Other malignancies, both primary and secondary
- IX. Ancillary Studies
- X. Clinical management
- XI. Preparatory techniques relative to Urinary Tract samples

System has to be build based on:

- Consensus
- Evidence
- Inclusion
- Acceptance
- Understanding



Urothelial Carcinoma

Pathogenesis of Urothelial Carcinoma

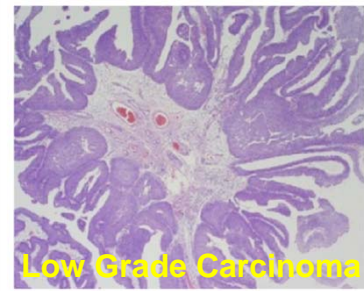
Eva M. Wojcik and Stefan E. Pambuccian

Papillary Pathway

80%



Genetically Stable
FGFR3 (~85%)

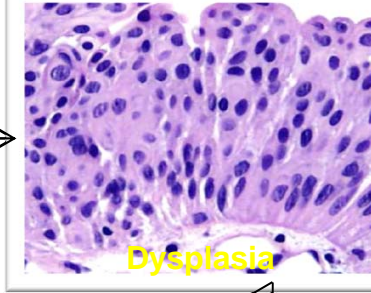


Recurrence

9p-, 9q-
p16

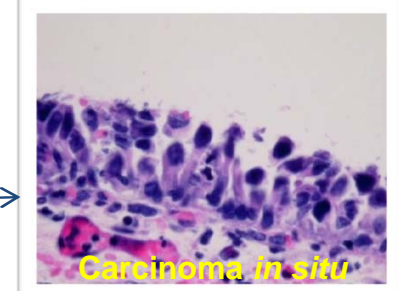
Non-Papillary Pathway

20%



Genetically Unstable
p53 (~60%)

<10%

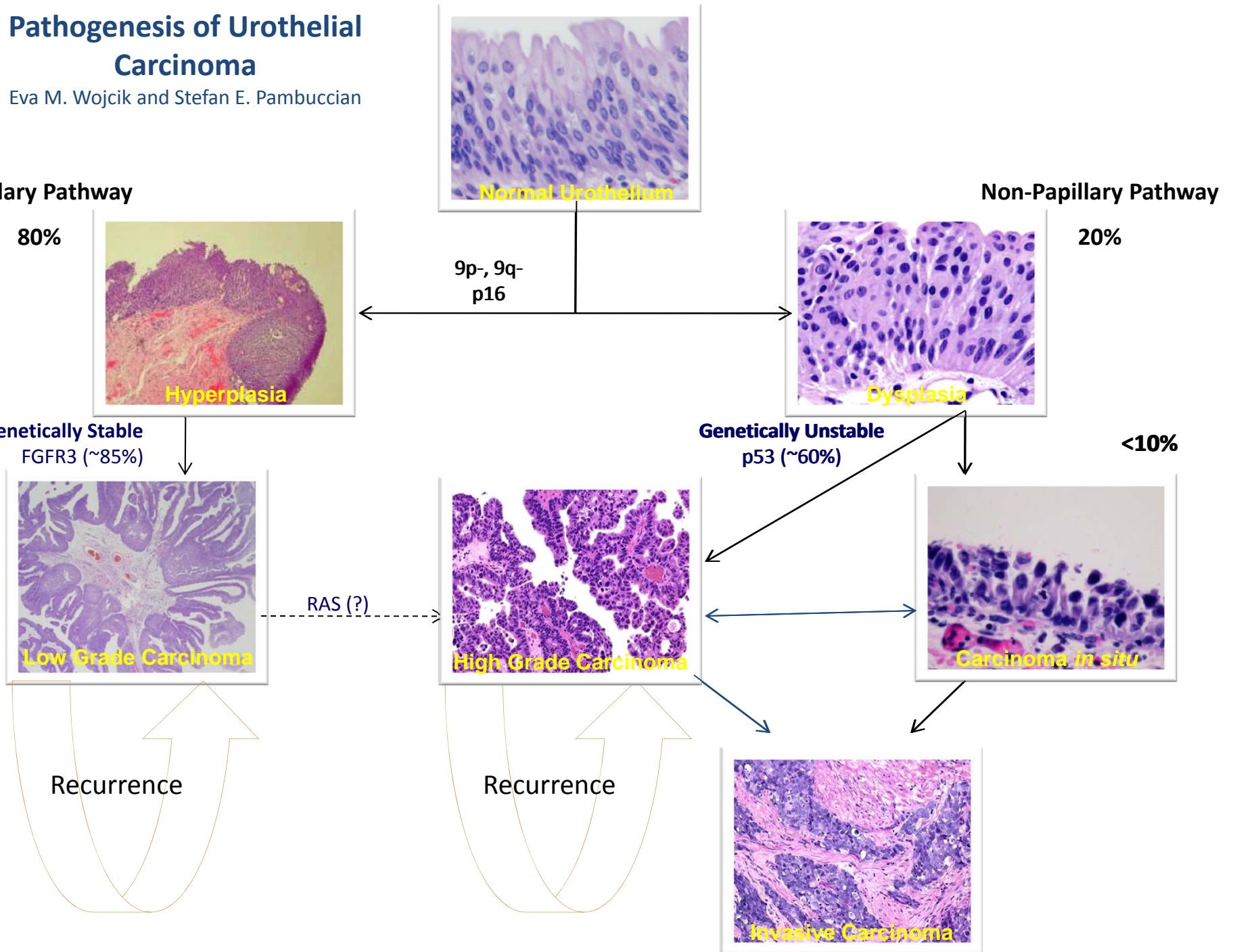


Invasive Carcinoma

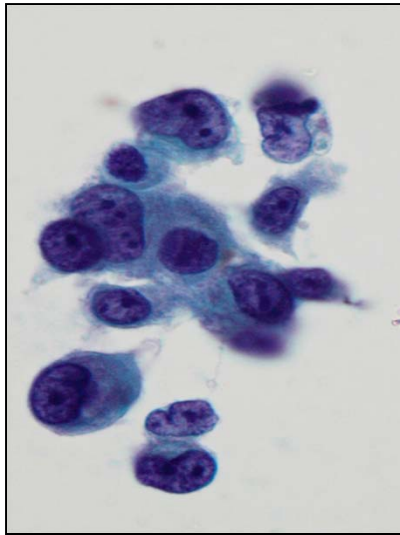
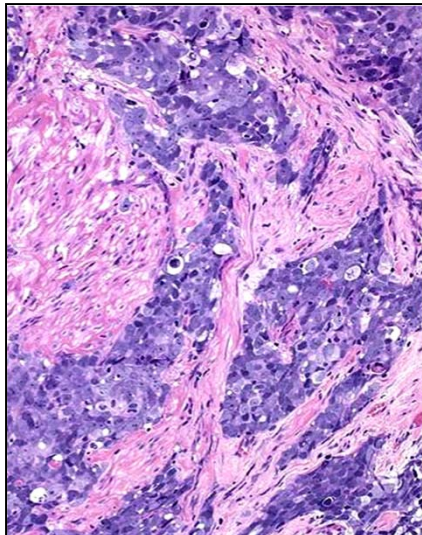
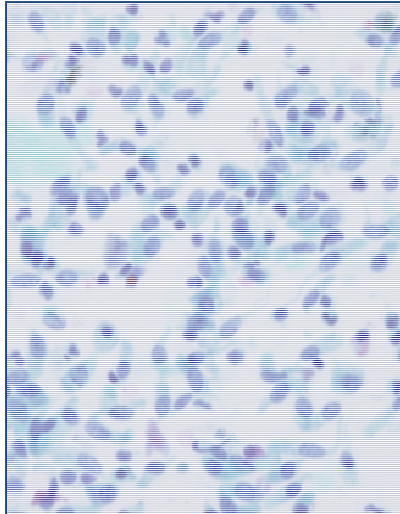
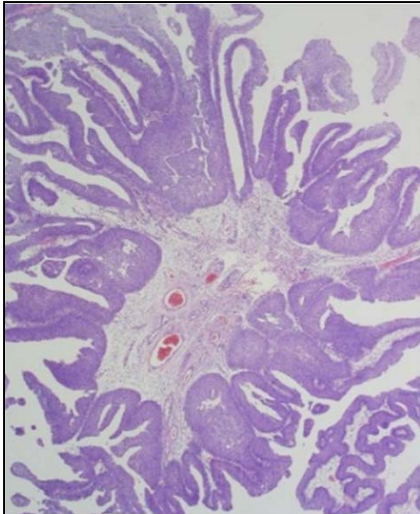
High Grade Carcinoma

Recurrence

RAS (?)



Bladder cancer – more than one disease?



- ~ 75 % Non-Muscle-Invasive (Ta/T1)
 - Good prognosis
 - Recurrence
 - 10%-15% progression (LG Ta - <1%)*
- ~ 25 % Muscle-Invasive (\geq T2)
 - >60% overall survival

*Nielsen ME et al. Trends in Stage-Specific Incidence Rates for Urothelial Carcinoma of the Bladder In the United States: 1998-2006. Cancer 2014;120:86

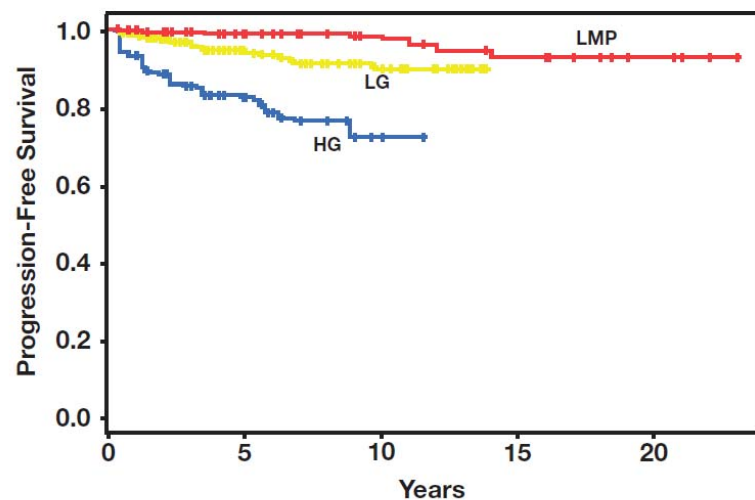
A Review of Outcomes for Stage Ta Bladder Tumors

Robin T. Vollmer, MD

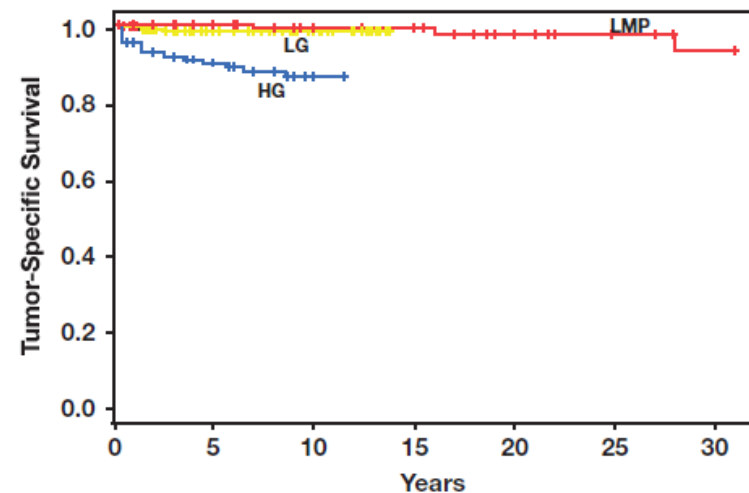
From the VA and Duke University Medical Centers, Durham, NC.

Key Words: Urothelial tumors; Tumor grade; Outcomes; Evidence based; Survival times

Am J Clin Pathol August 2016;146:215-220



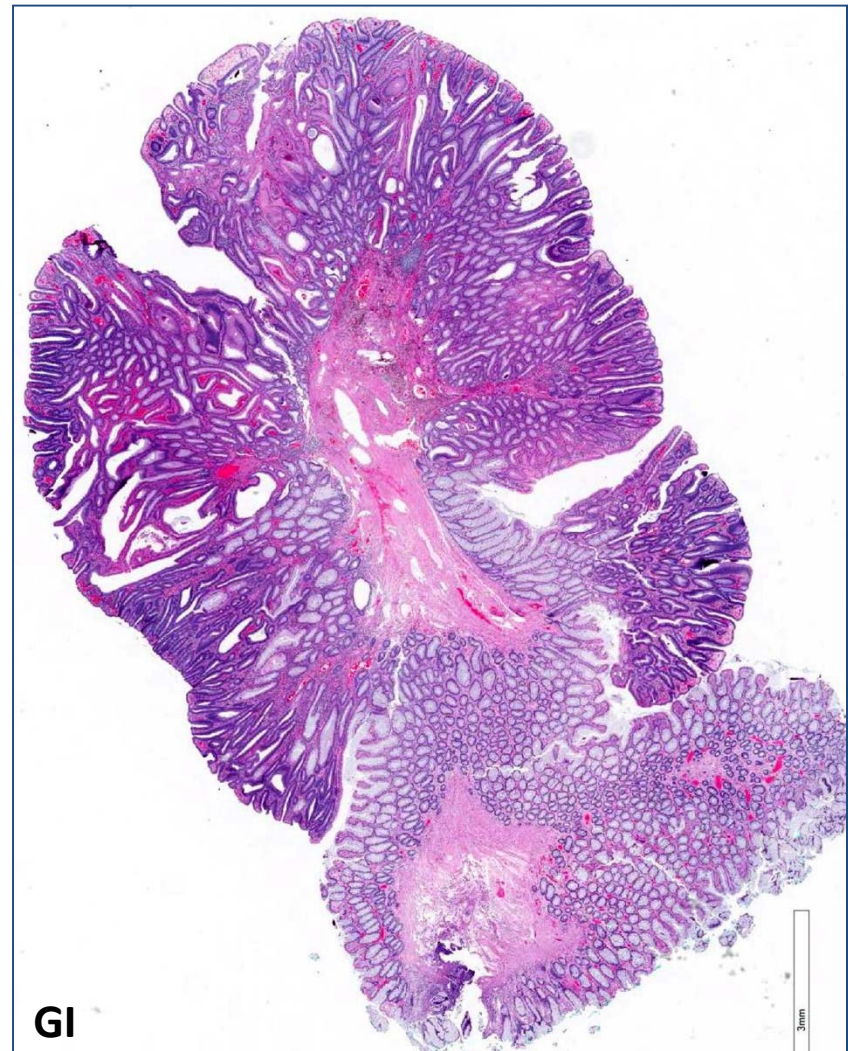
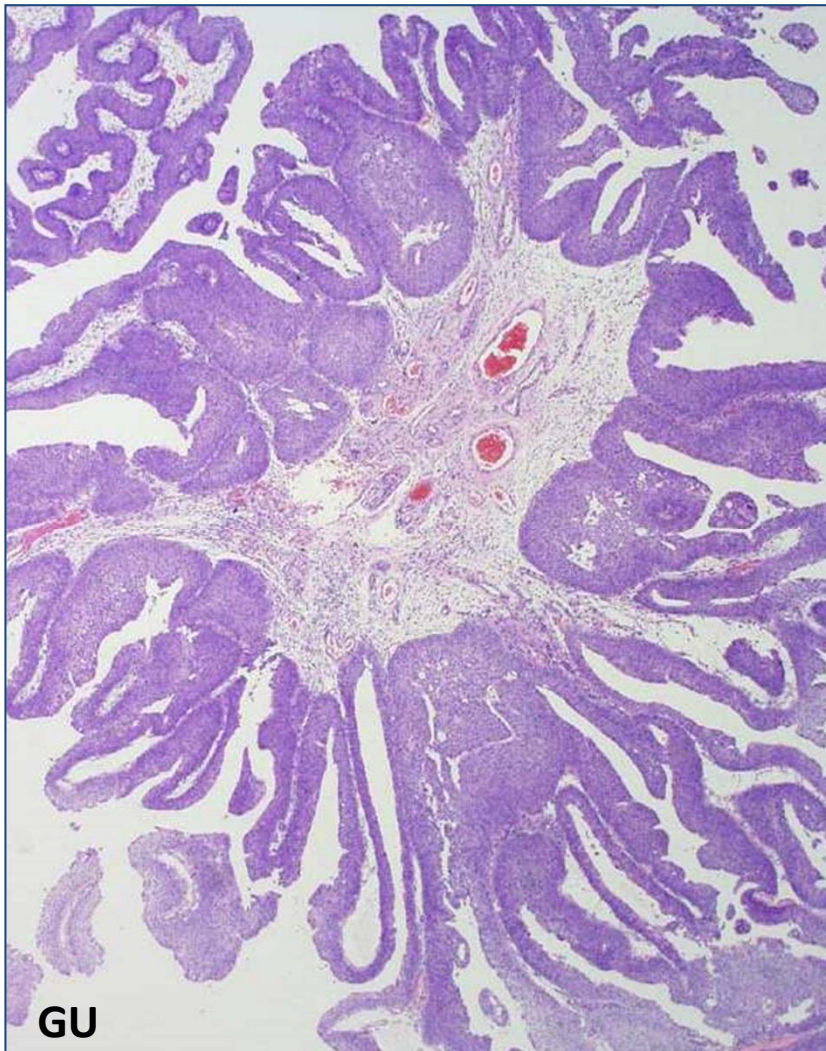
■ **Figure 5** ■ Kaplan-Meier plots of the probability of being free of invasive tumor vs years of follow-up stratified according to the 2004 World Health Organization grades. HG, high grade; LG, low grade; LMP, papillary tumors of low malignant potential.



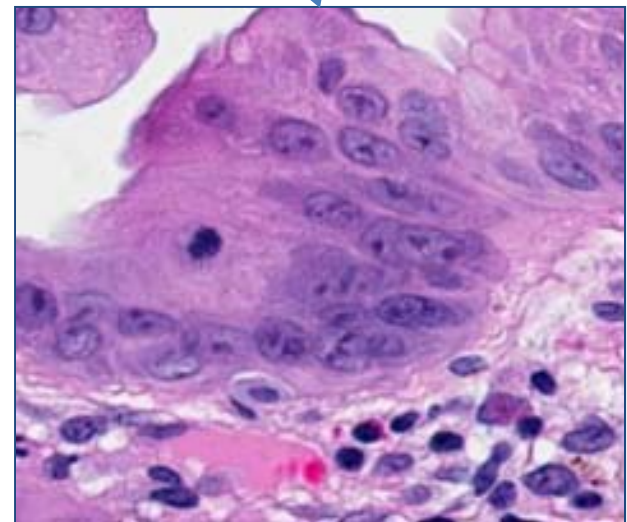
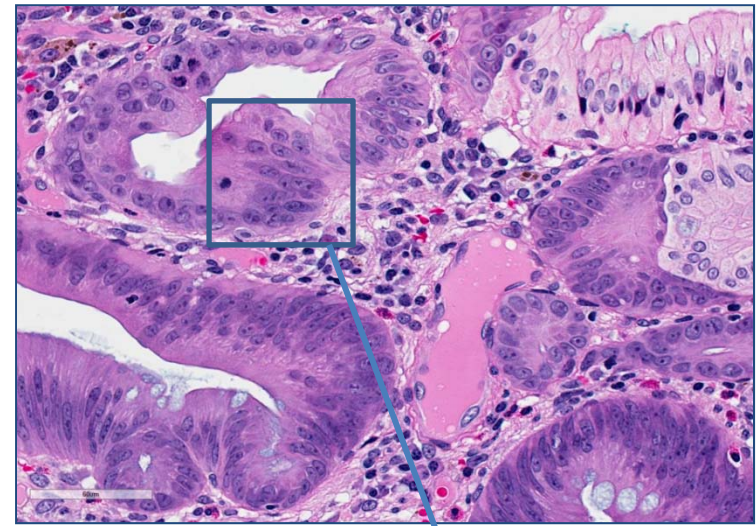
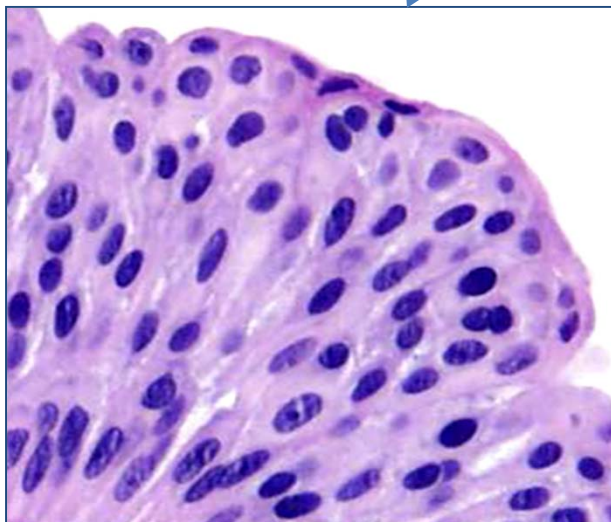
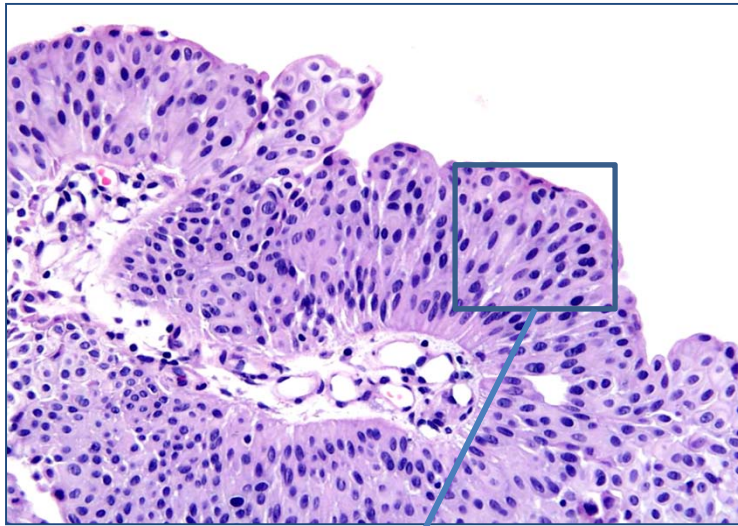
■ **Figure 7** ■ Kaplan-Meier plots of the probability of tumor-specific survival vs years of follow-up stratified according to the 2004 World Health Organization grades. HG, high grade; LG, low grade; LMP, papillary tumors of low malignant potential.

“Approximately 80% (of Ta bladder tumors) appear to follow a benign course without developing invasive tumors or dying of bladder cancer”

Question.... “Carcinoma”?



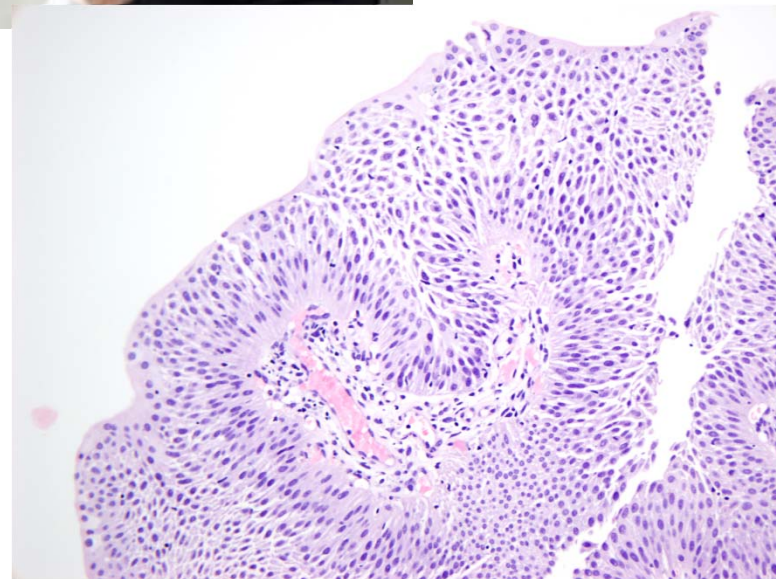
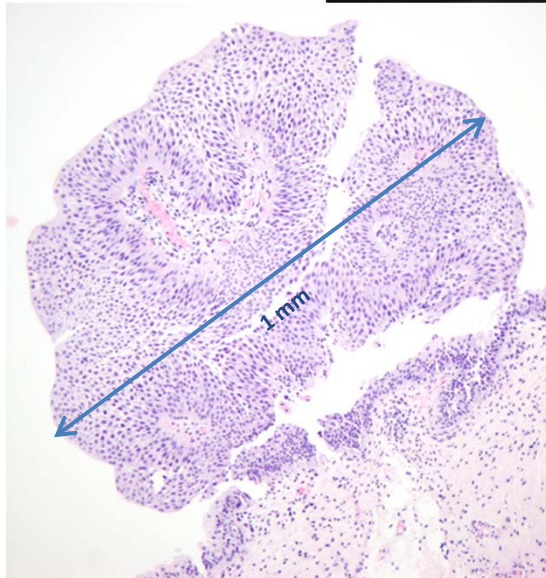
Question.... “Carcinoma”?



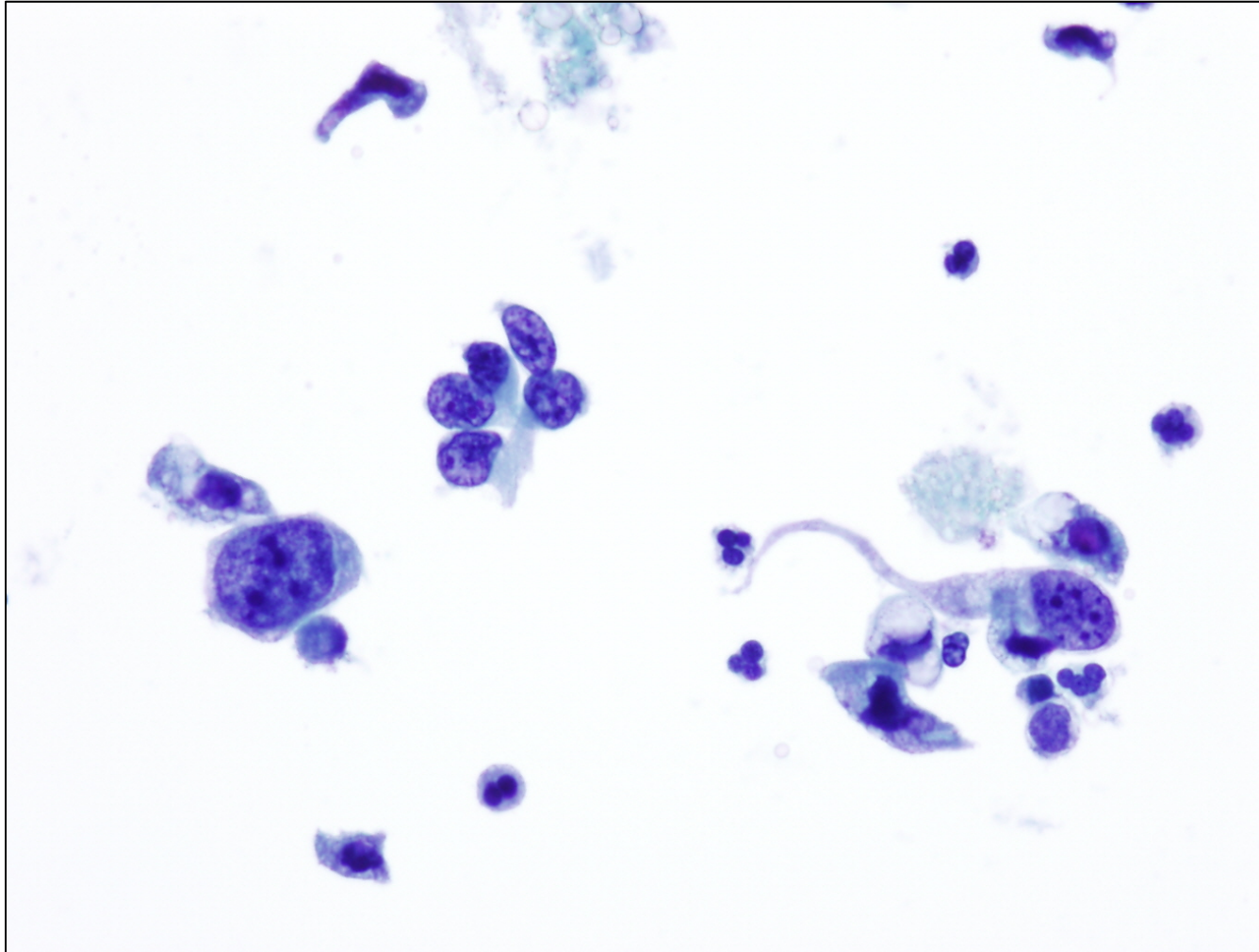
←
CARCINOMA

ADENOMA
→

Mr. Smith - You have a bladder cancer



What really matters?



High Grade Urothelial Carcinoma

Diagnostic Categories

Hope

HGUC

Everything else

Reality

Positive

Atypical/Suspicious

Negative

Evolution of the Classification

Cytologic Classification						Histologic Classification	
Papanicolaou 1947 ⁵ (Papanicolaou Classification System)	Koss 1985 ¹⁰	Murphy 1984 ¹¹	Ooms & Veldhuizen 1993 ¹²	Layfield et al 2004 ¹³ (Papanicolaou Society of Cytopathology)	Hopkins Template ^a	Mostofi & Torloni 1973 ⁹ (WHO ^a)	Epstein 1998 ¹⁴ (WHO/ISUP)
I	Benign cells, ATY 1 cells, few clusters	Negative	Negative	Negative	NUAM	Papilloma TCC, grade 1	Papilloma
II							PUNLMP
III	Clusters, nuclear elongation, few ATY 2 cells	Dysplastic cells	Atypical, significance uncertain	Atypical urothelial cells	AUC-US	TCC, grade 2	LGUC
IV		Suspicious	Suspicious		AUC-H		
V	Malignant tumor cells, many ATY 2 cells	Malignant cells	Neoplastic cells present	Urothelial carcinoma	Urothelial carcinoma		HGUC
						TCC, grade 3	

?LG
?HG

Abbreviations: ATY 1, atypical cells with hyperchromasia and predominantly round or oval contours; ATY 2, cells with hyperchromasia and nuclear membrane abnormalities; AUC-H, atypical urothelial cells cannot exclude high-grade urothelial carcinoma; AUC-US, atypical urothelial cells of uncertain significance; HGUC; high-grade papillary urothelial carcinoma; ISUP, International Society of Urological Pathology; LGUC, low-grade papillary urothelial carcinoma; NUAM, no urothelial atypia or dysplasia identified; PUNLMP, papillary urothelial malignancy of uncertain malignant potential; TCC, transitional cell carcinoma; WHO, World Health Organization. See Table 7.

Owens et al. Cancer Cytopathology 2013

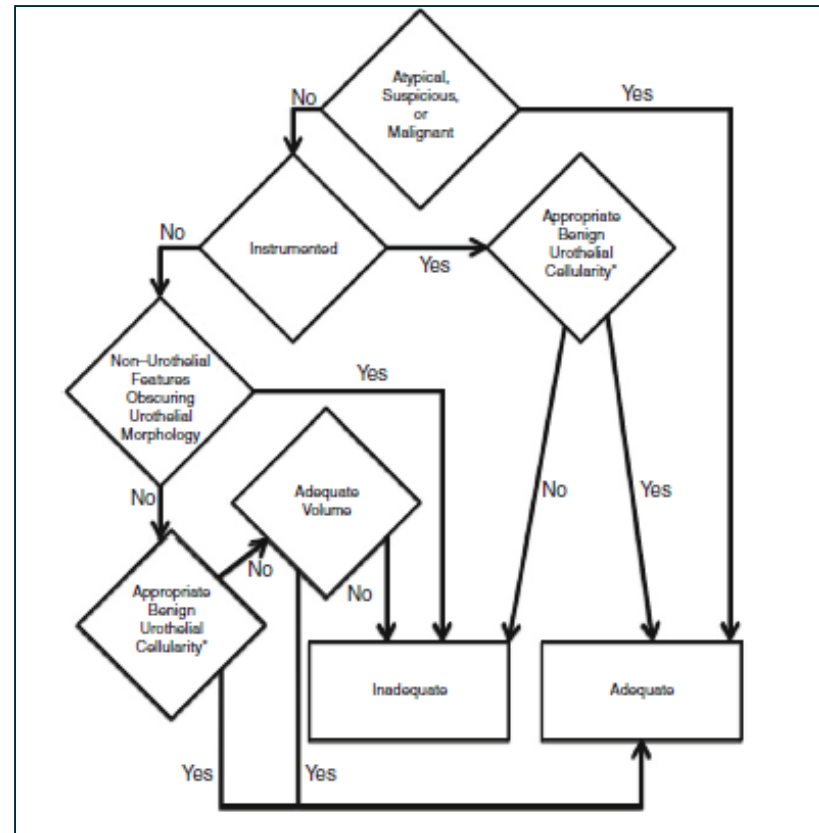
NEW paradigm

- It is all about High Grade Urothelial Carcinoma
↓
- Negative for High Grade Urothelial Carcinoma
- AUC $\xrightarrow{\text{Quality and Quantity}}$ SHGUC $\xrightarrow{\text{Quantity}}$ HGUC
- LGUN – Low Grade Urothelial Neoplasm

Adequacy of Urine Specimens (Adequacy)

Matthew T. Olson , Güliz A. Barkan , Monique Courtade-Saïdi , Z. Laura Tabatabai , Yuji Tokuda , Toyonori Tsuzuki , and Christopher J. VandenBussche

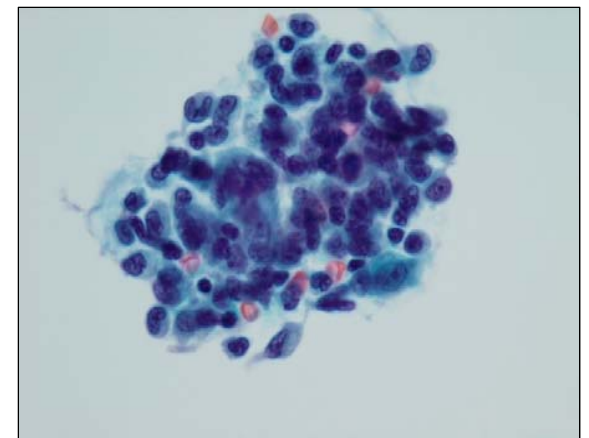
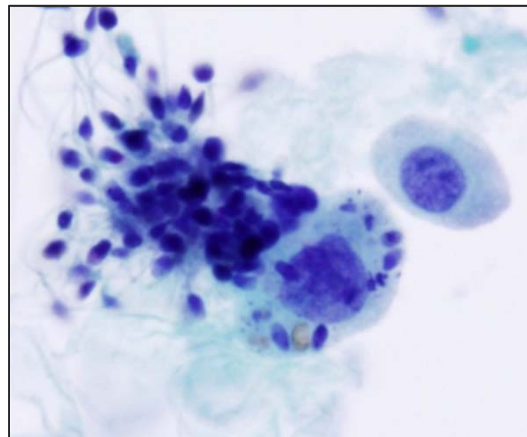
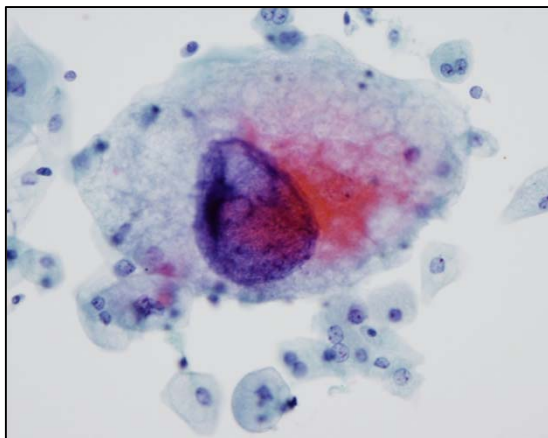
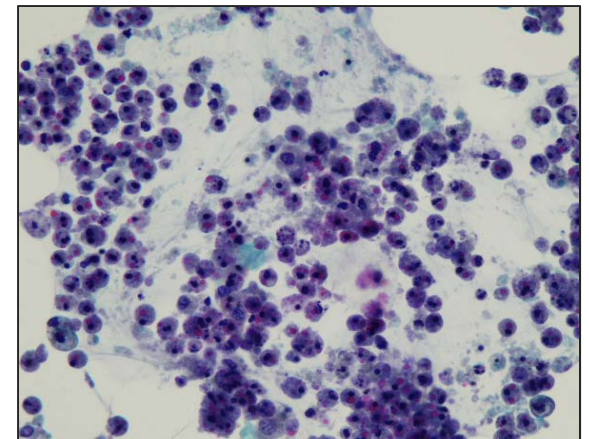
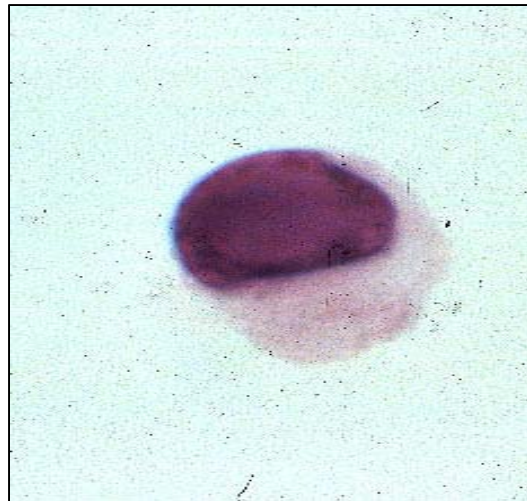
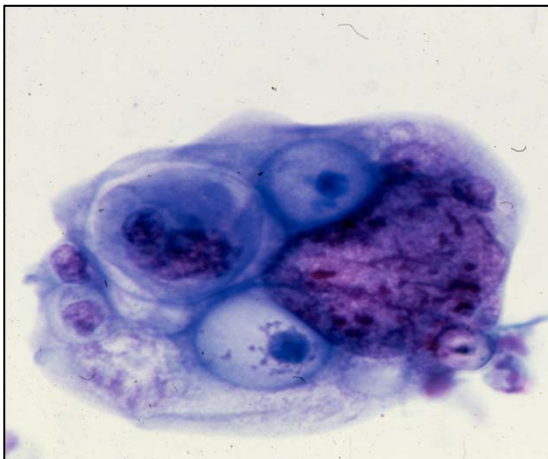
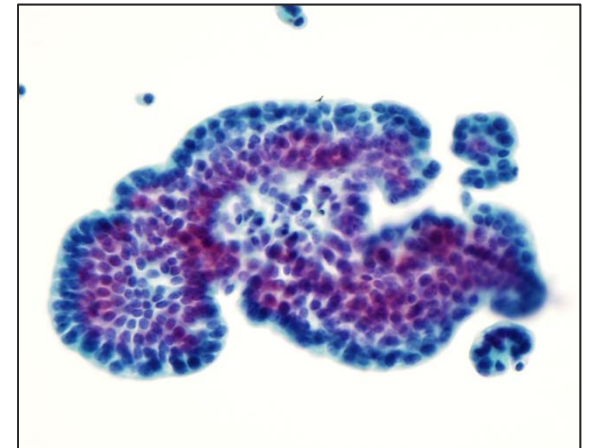
- Presence of atypical or malignant cells
- Specimen type
 - **Instrumented** (Cellularity, 2600 cells, 2 urothelial cells/10HPF) (*)
 - **Voided** (>30mL more likely “adequate”) (**)
- Obscuring elements (blood, lubricant, etc.)



(*) Prather J, Arville B, Chatt G, et al. Evidence-based adequacy criteria for urinary bladder barbotage cytology. Journal of the American Society of Cytopathology.4: 57-62.

(**) VandenBussche CJ, Rosenthal DL, Olson MT. Adequacy in voided urine cytology specimens: The role of volume and a repeat void upon predictive values for high-grade urothelial carcinoma. Cancer Cytopathol. 2015.

“Negative, NOT atypia”



Wojcik EM: What should not be reported as atypia
in urine cytology: JASC 2015;4;3;30-36

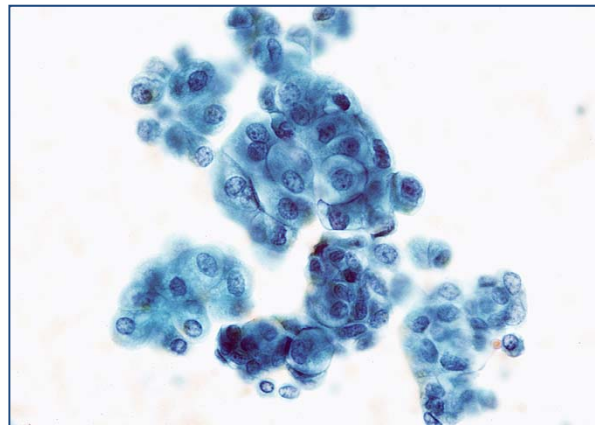
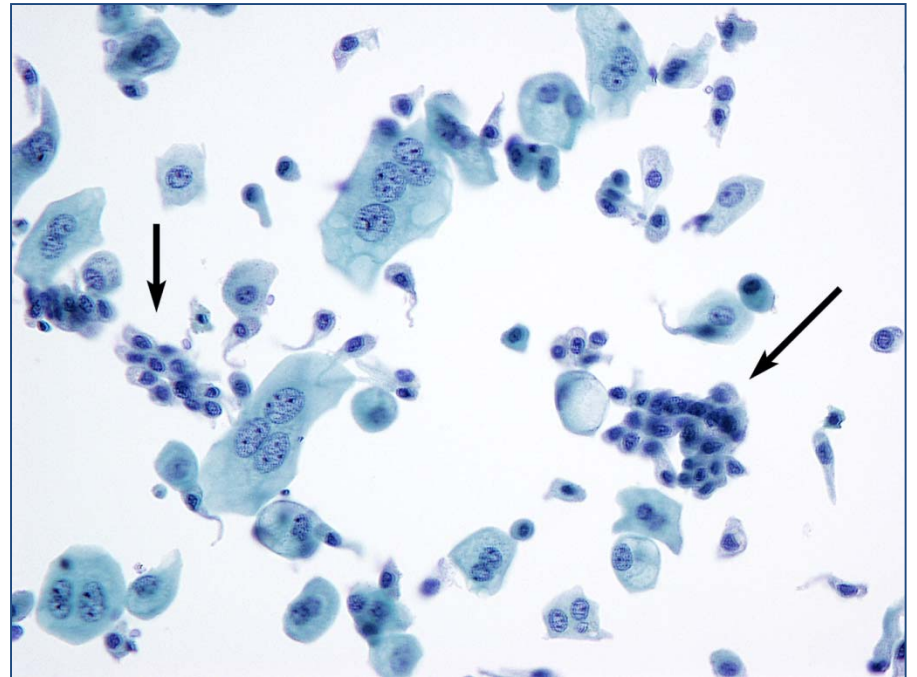
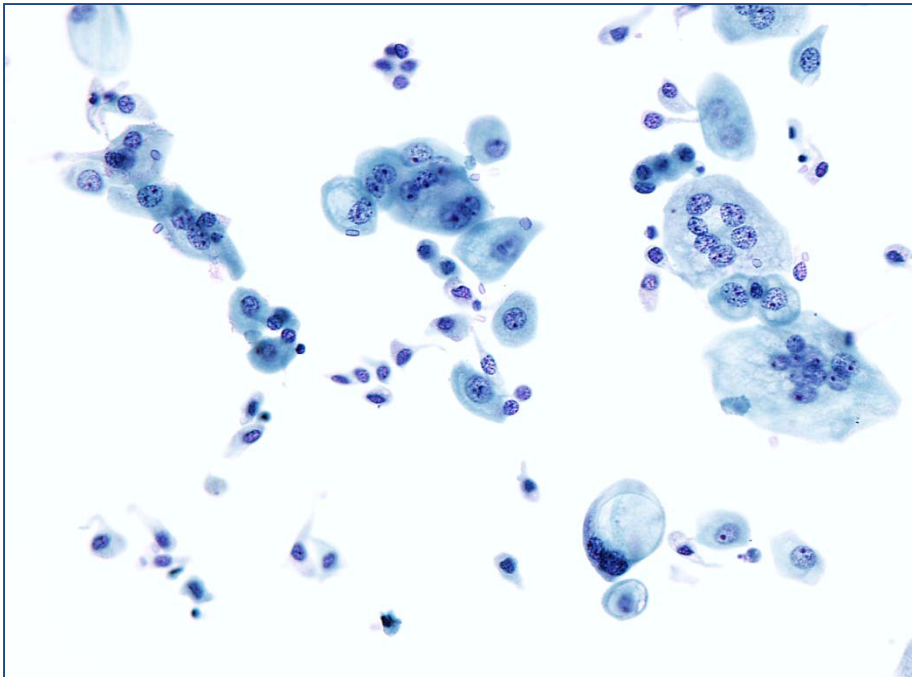
Negative for High-Grade Urothelial Carcinoma (Negative)

Dorothy L. Rosenthal, Michael B. Cohen, Hui Guan, Christopher L. Owens, Yuji Tokuda, and Eva M. Wojcik

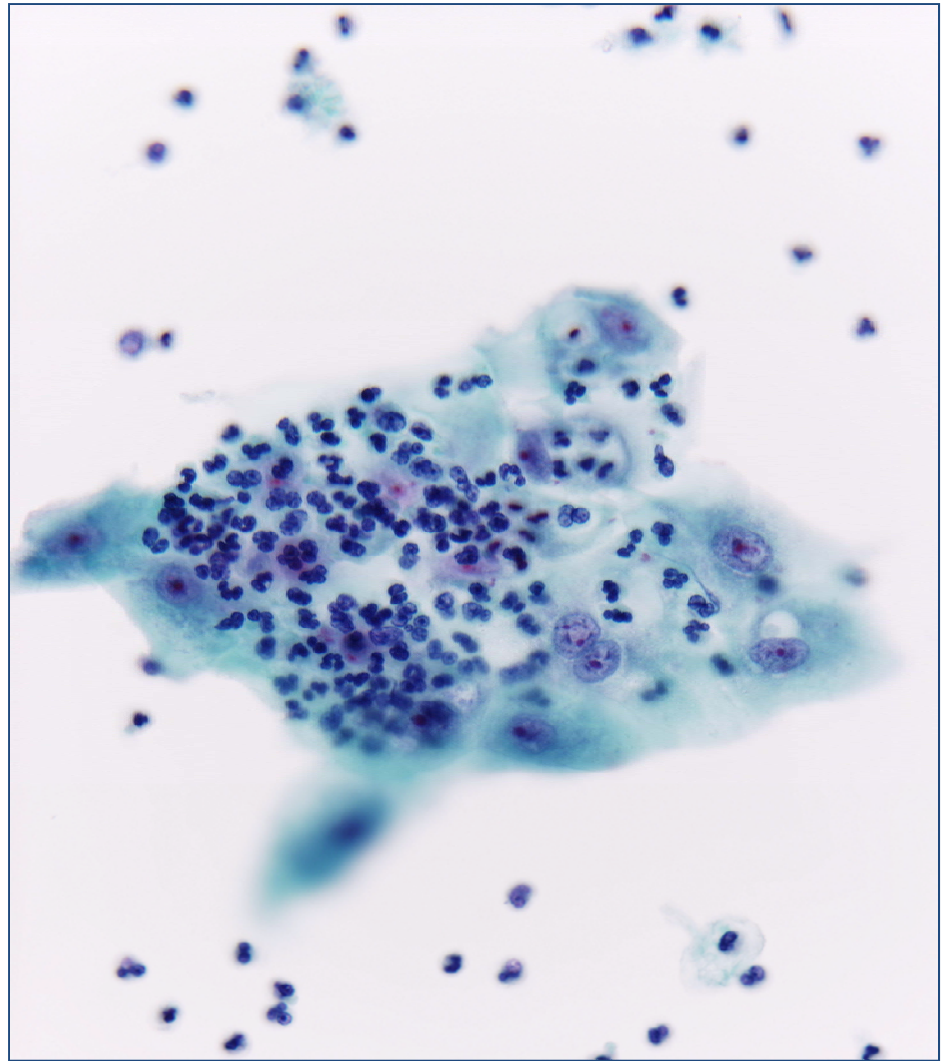
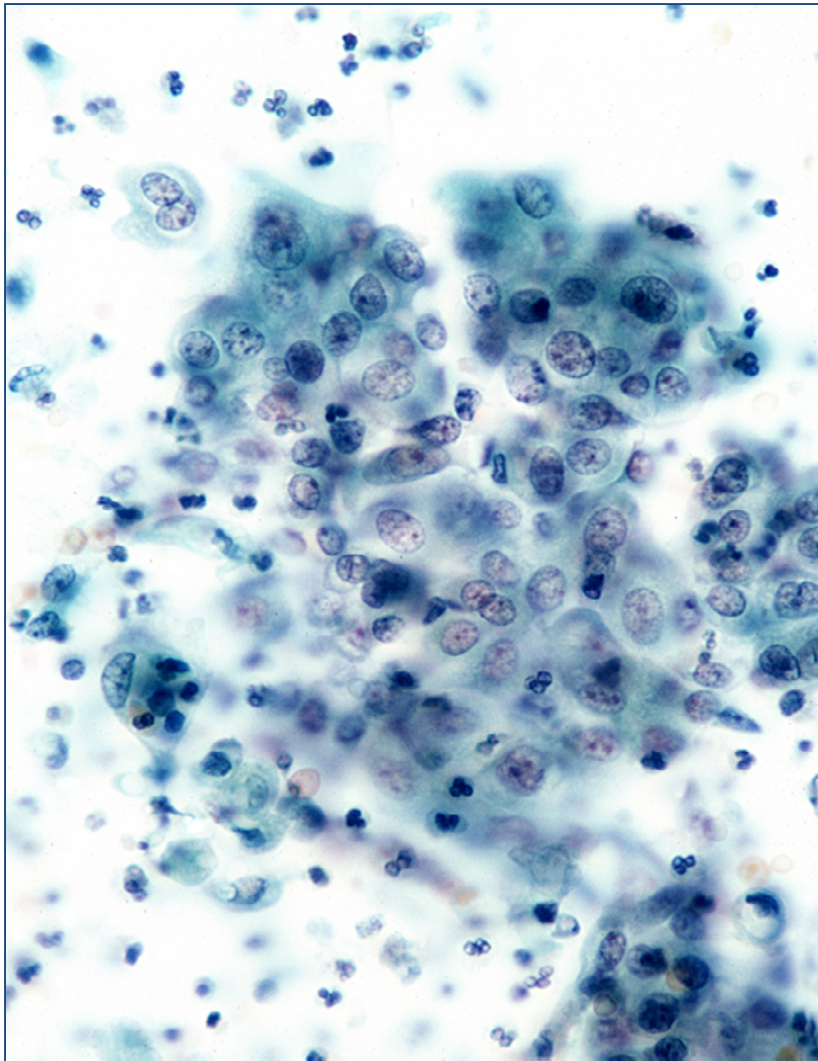
Definition of Negative for High-Grade Urothelial Carcinoma

- A sample of urine, either voided or instrumented, may be considered benign, i.e., NHGUC, if any of the following components are present in the specimen:
 - Benign urothelial, glandular, and squamous cells
 - Benign urothelial tissue fragments (BUTF) and urothelial sheets or clusters
 - Changes associated with lithiasis
 - Viral cytopathic effect; polyoma virus (BK virus—decoy cells)
 - Post-therapy effect, including epithelial cells from urinary diversions

Benign Superficial (Umbrella) Urothelial Cells

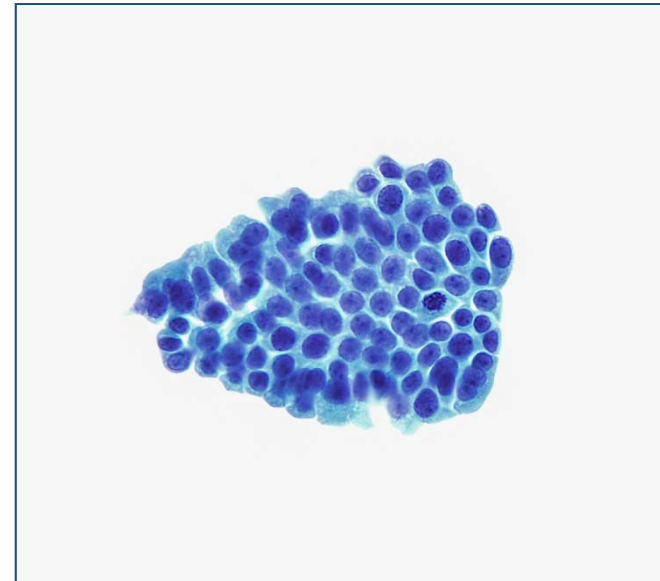
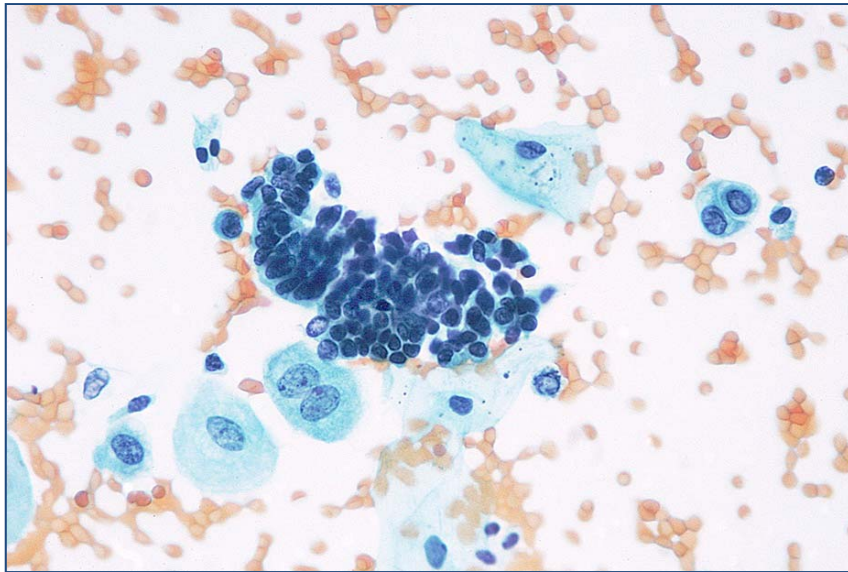


“Atypical” Umbrella Cells

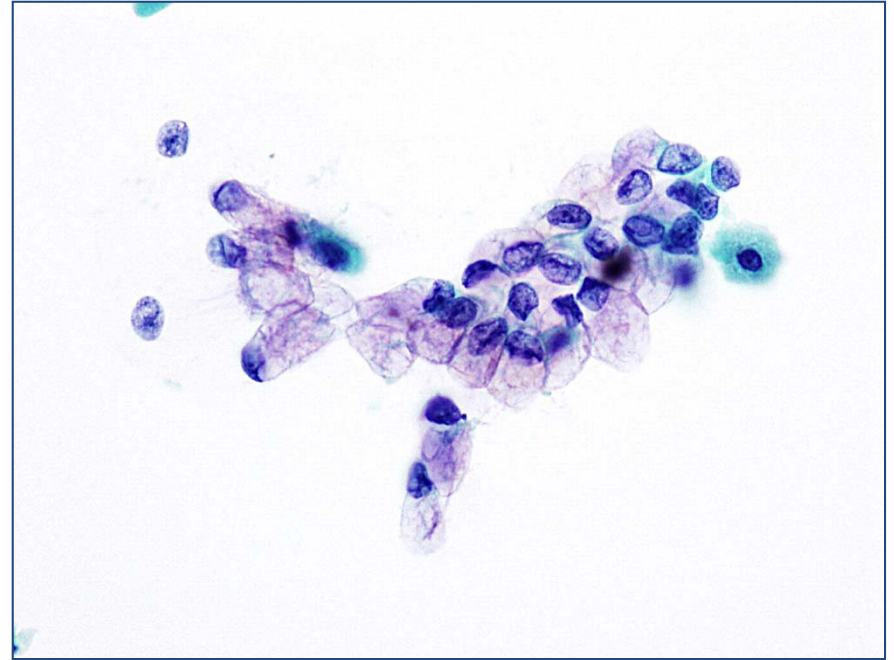
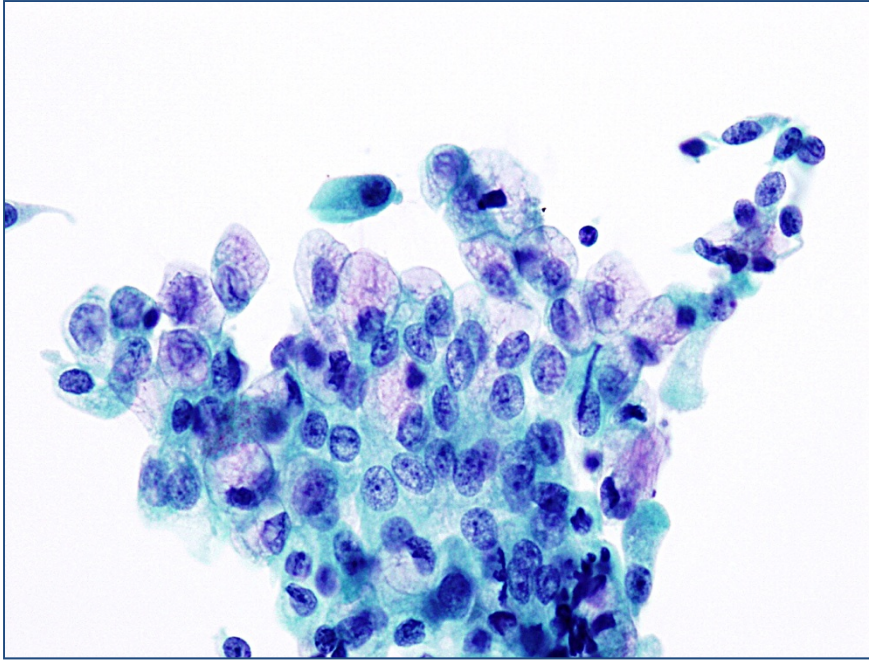


Glandular Cells

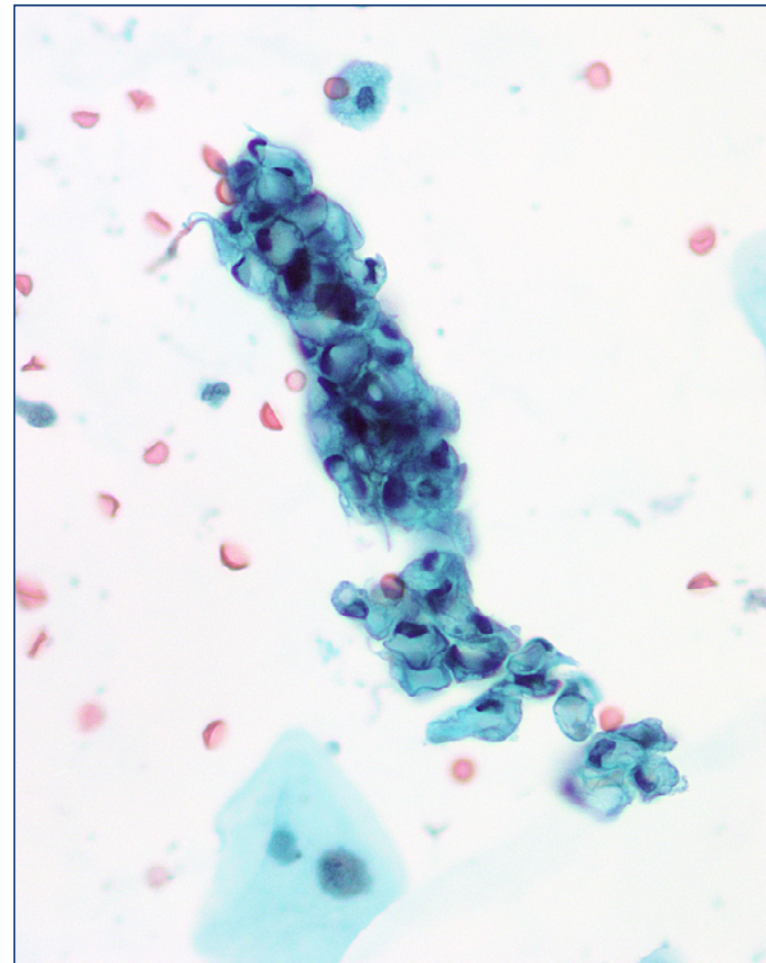
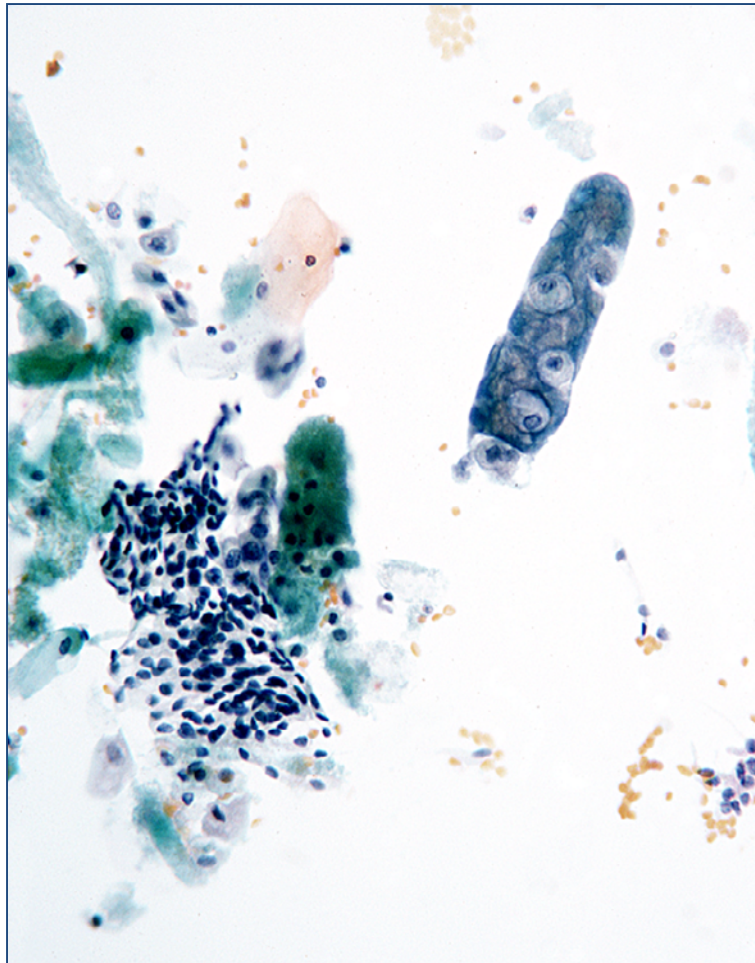
- Sources: endometrium, prostate, kidneys, urachal remnants, metaplasia



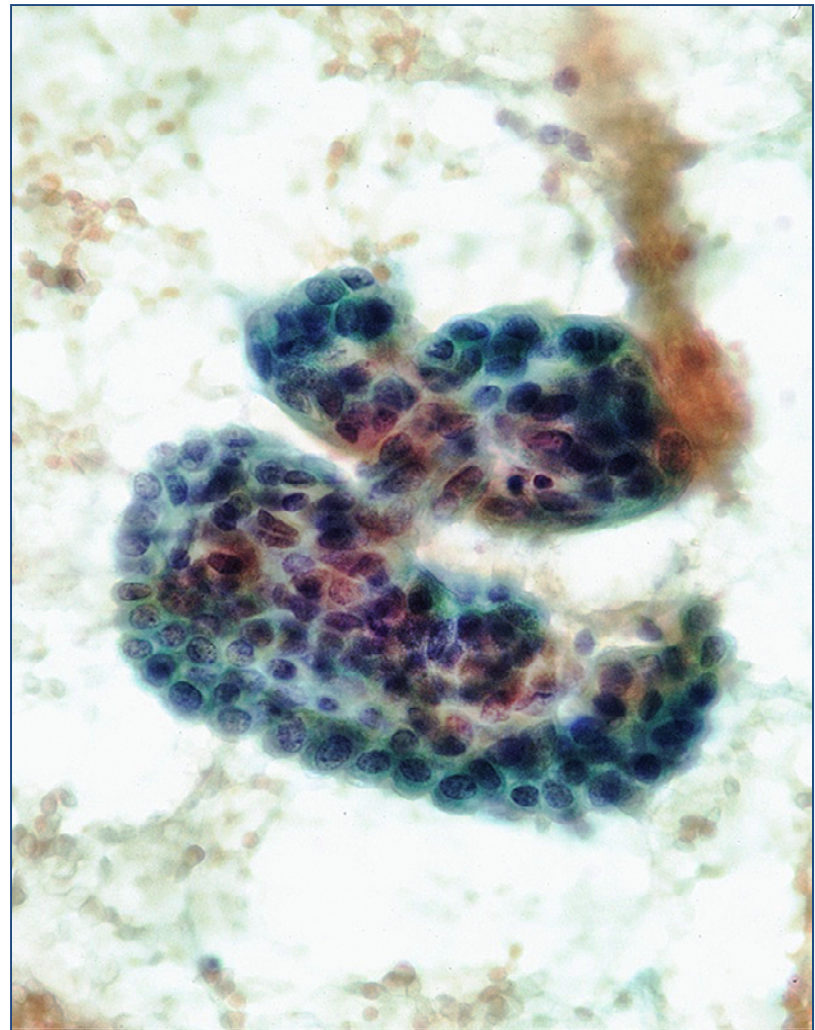
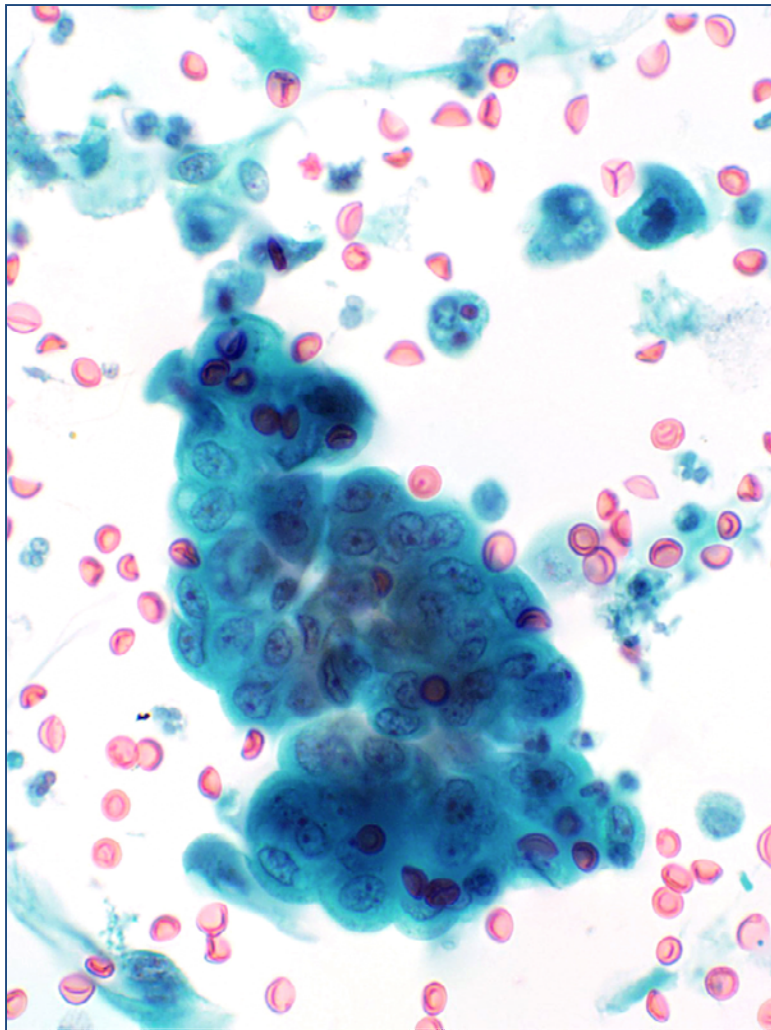
Cystitis cystica/glandularis



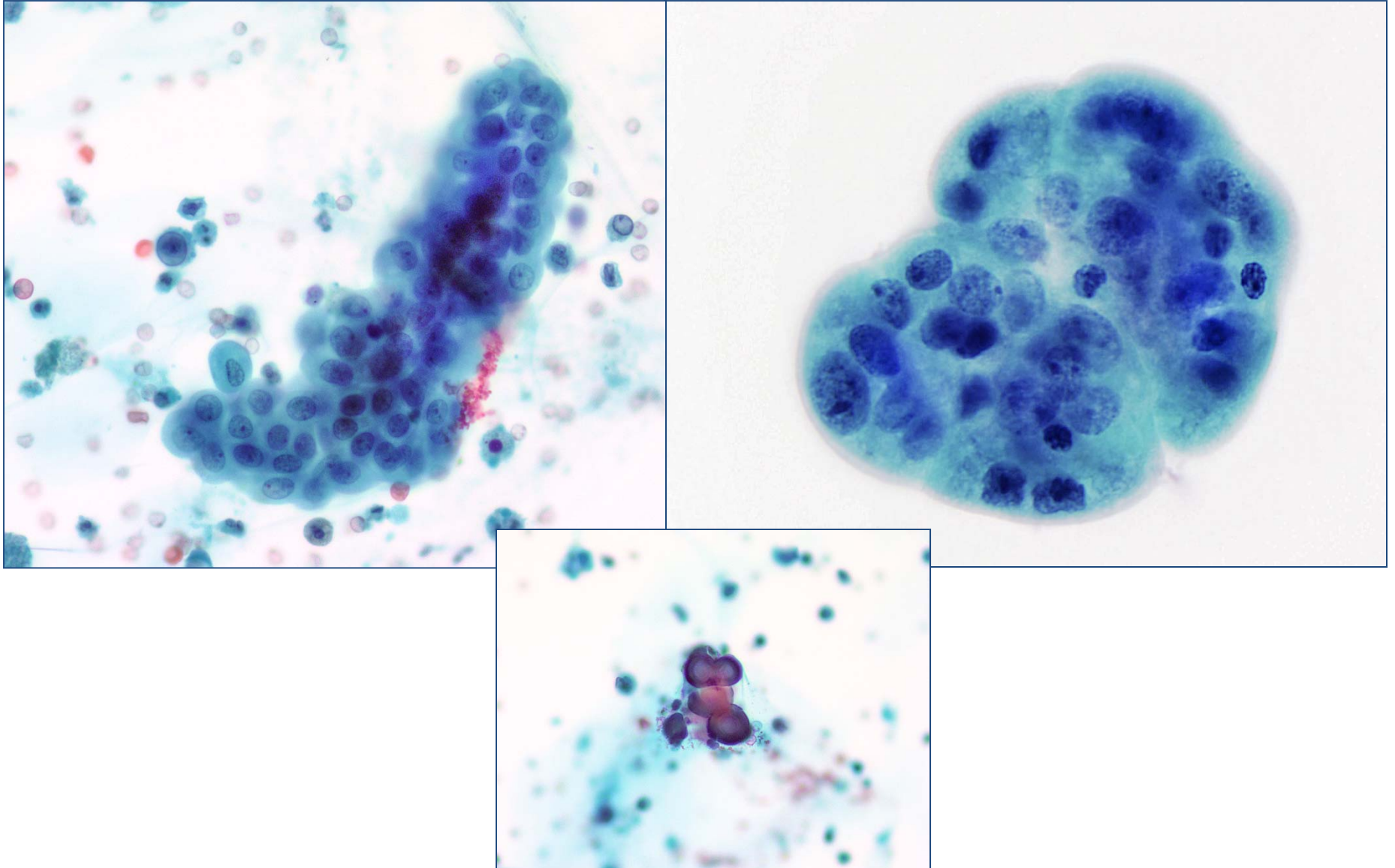
Renal Tubular Epithelial Cells



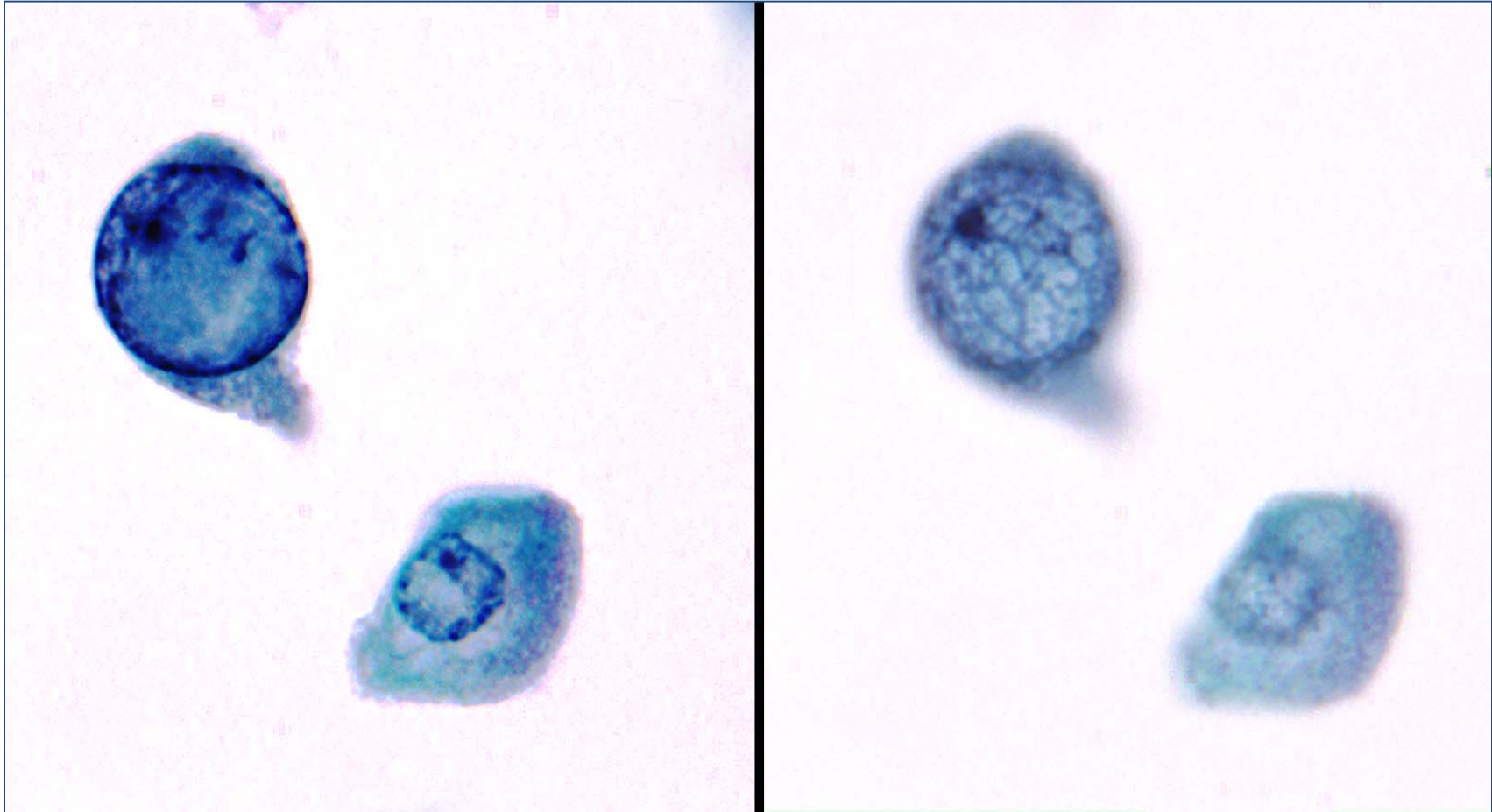
Benign Urothelial Tissue Fragments - BUTF



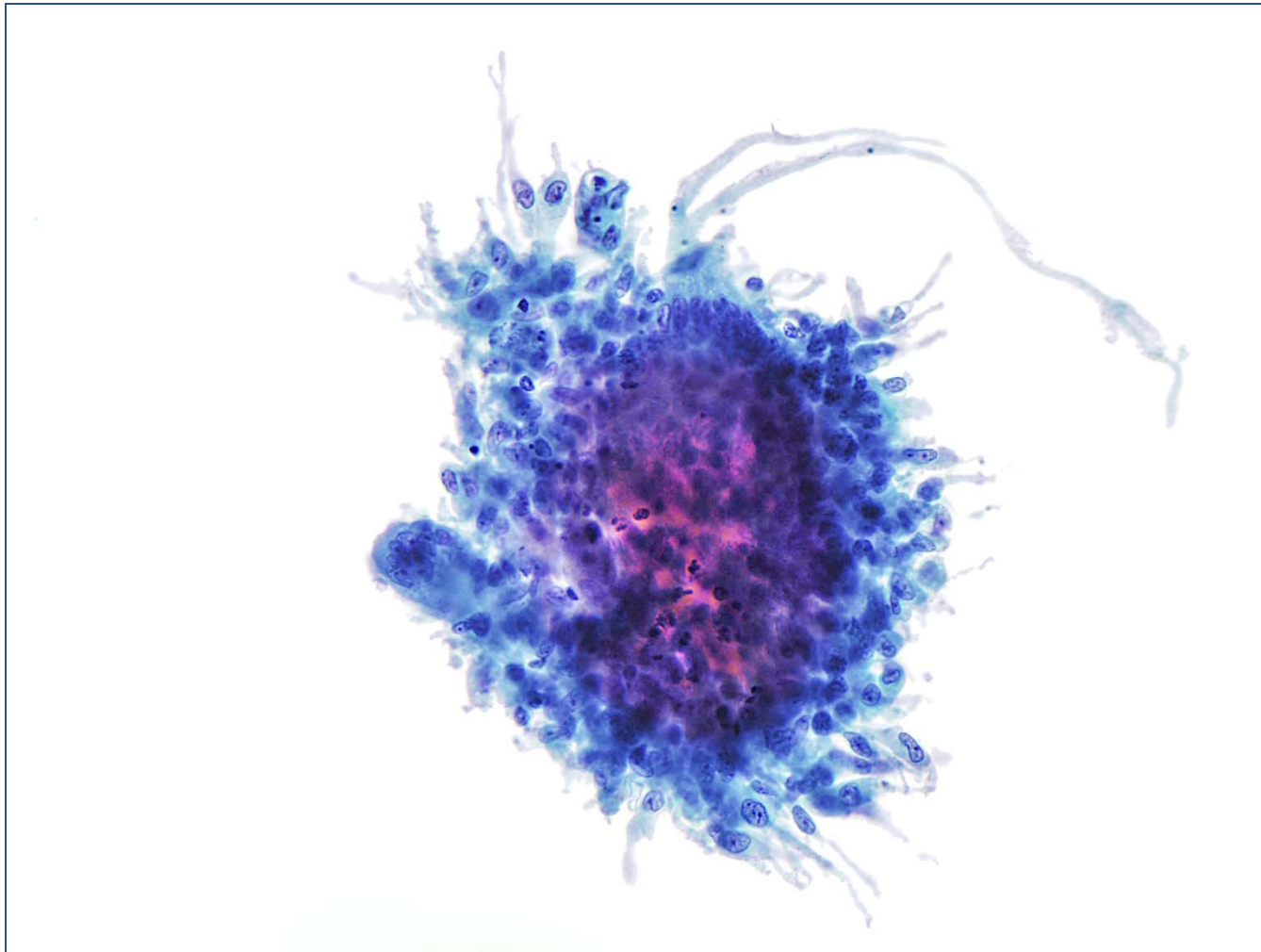
Nephrolithiasis – 3D fragments



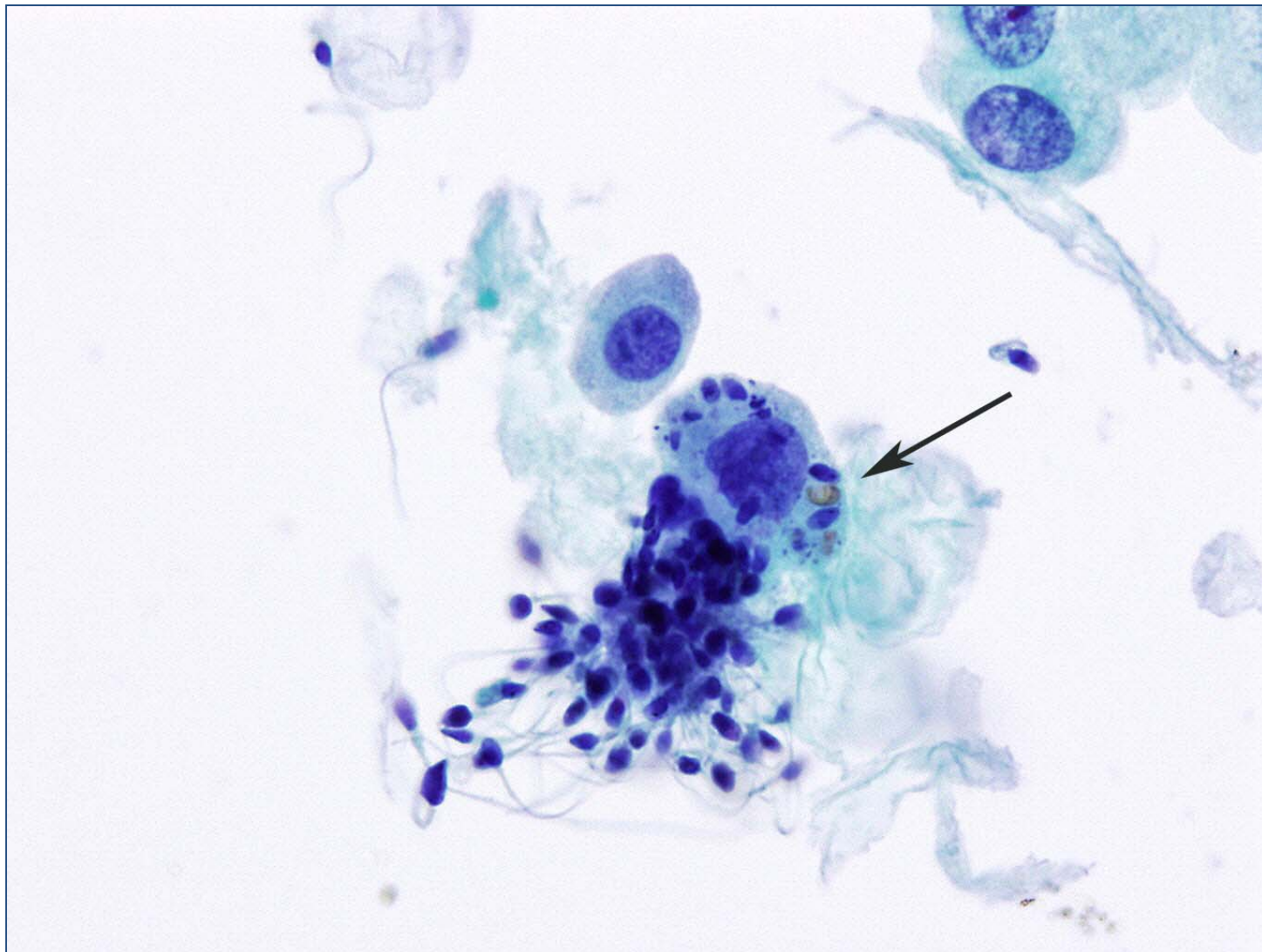
Viral Cytopathic Effects



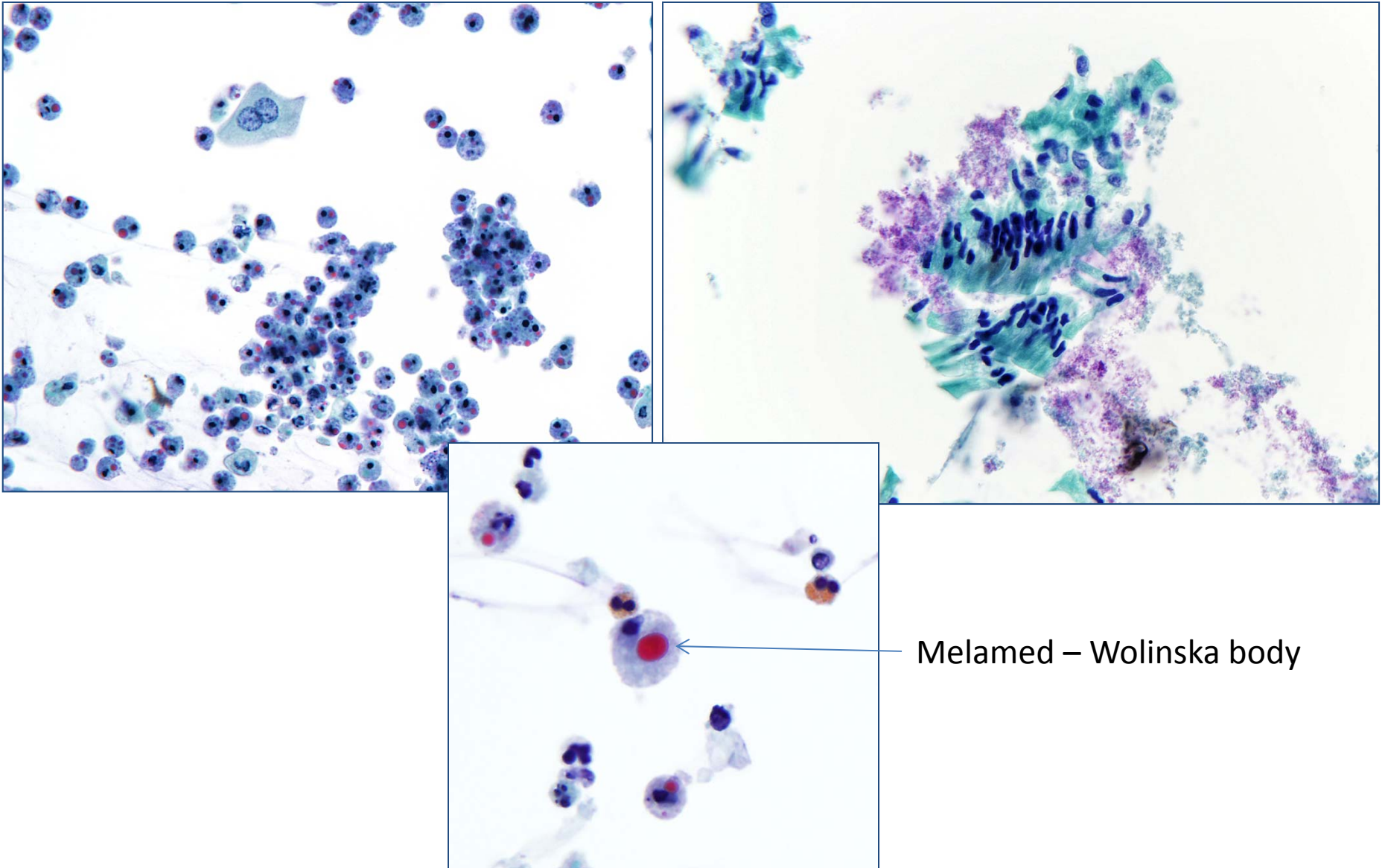
Immunotherapy



Seminal Vesicle Cells



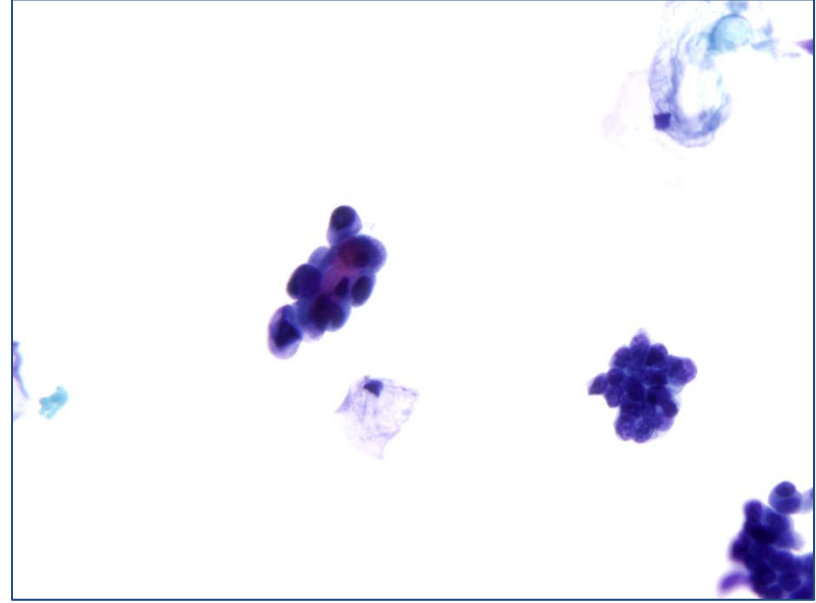
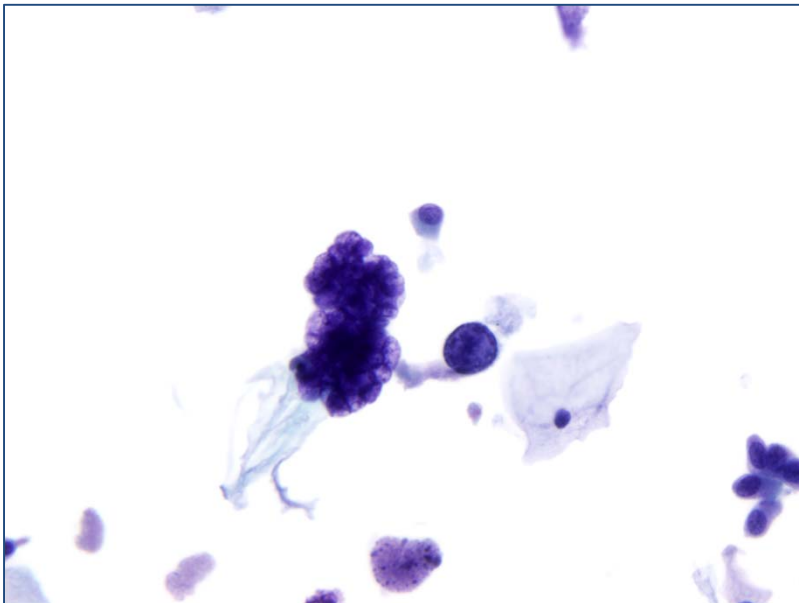
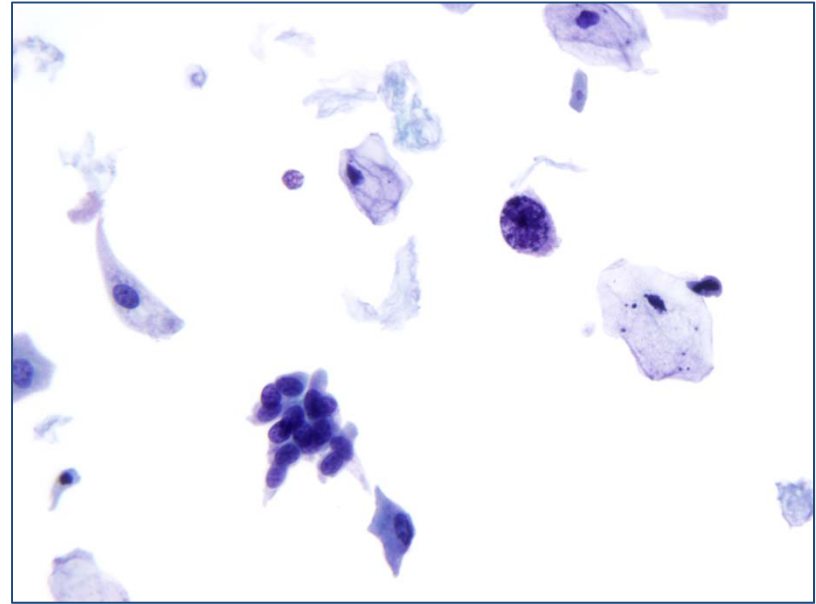
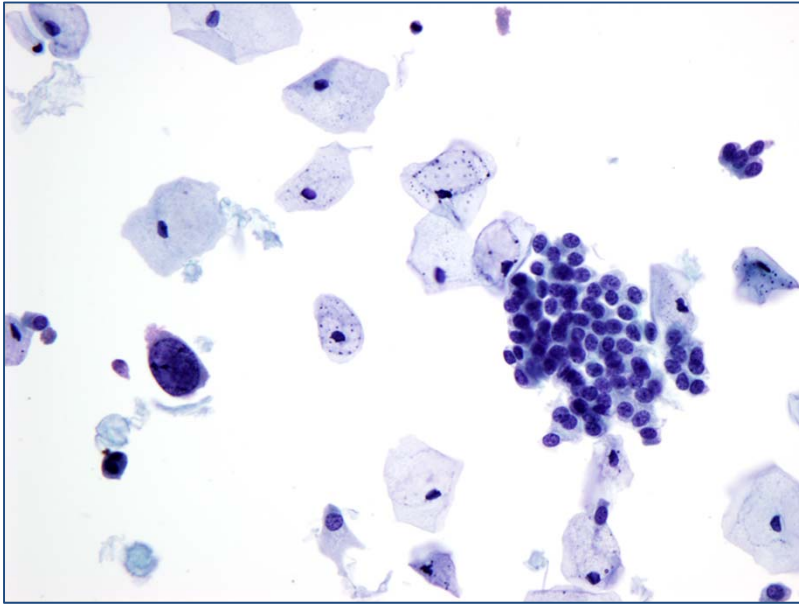
Bladder Diversion Urine

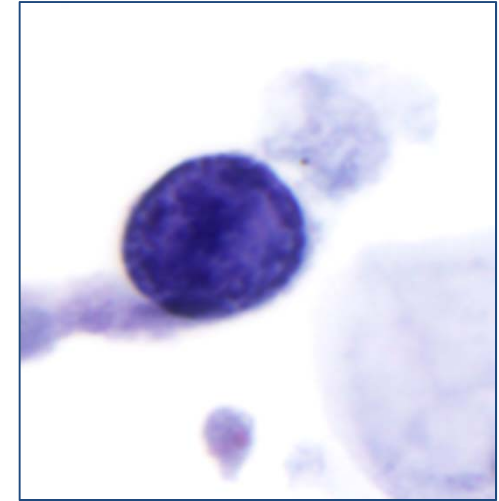
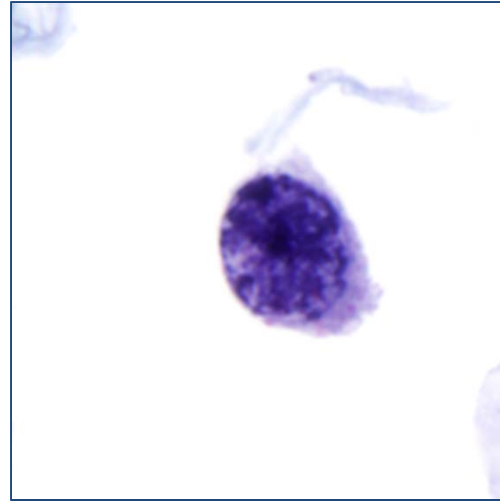
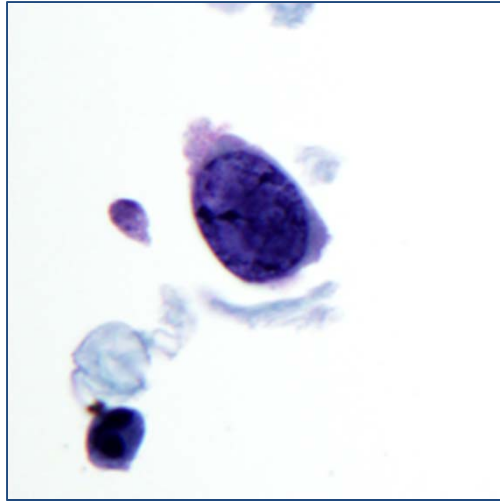


Negative - Summary

- **Negative for High Grade Urothelial Carcinoma**
 - This diagnostic category will include cases where “low grade urothelial carcinoma can not be excluded”
- If there is a cause for “atypia” i.e. urolithiasis, treatment related changes etc. – it is negative!

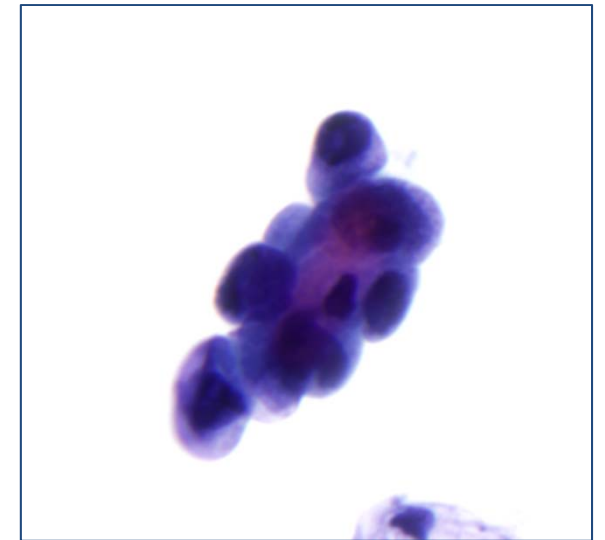
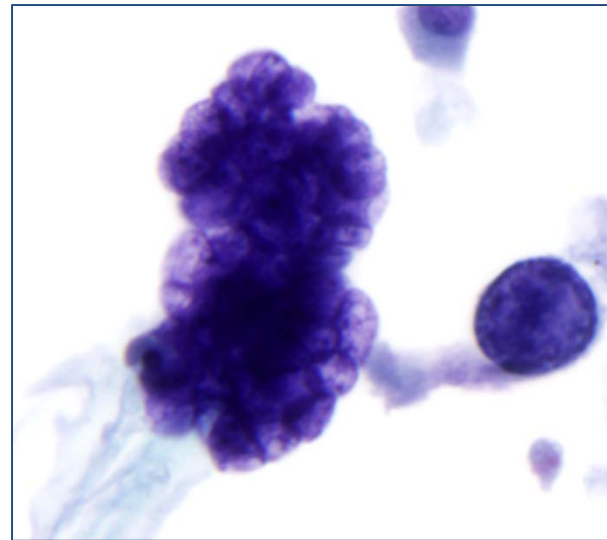
88-year-old man with a history of T1 HGUC previously treated by local excision. F/U bx negative. Cystoscopy – negative.





- Polyoma → Negative for High Grade Urothelial Carcinoma

How about these?



What is Atypia

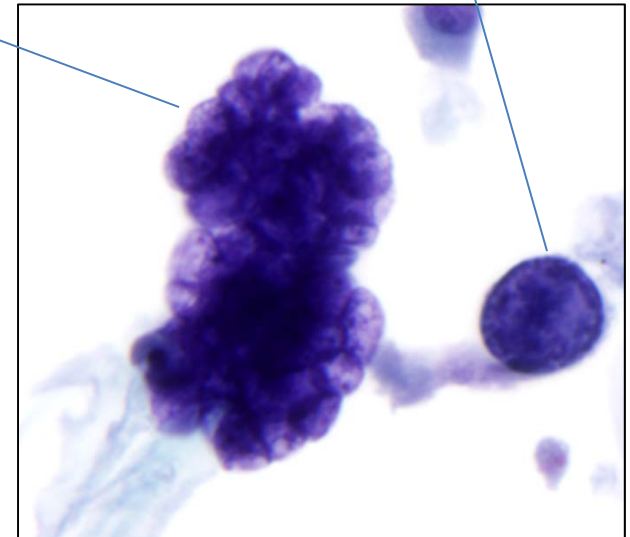
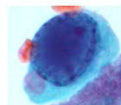
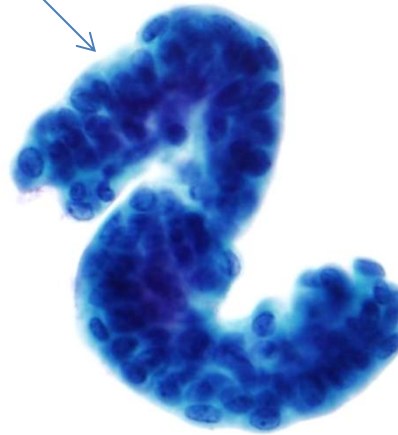
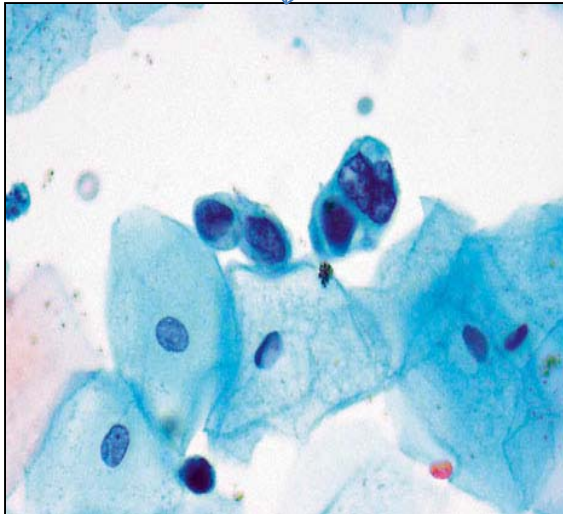


Positive

Suspicious

Atypical

Negative



Survey: What do YOU call atypia in urine specimens?

1. There are rare cells, reminiscent to that of high grade UC
2. Lots of clusters, worrisome for low grade UC
3. Other (degenerated cells, cells/groups that don't fit in either group above)



Negative for High Grade Urothelial Carcinoma

Findings in literature

1. High nuclear cytoplasmic ratio (>0.7)
2. Nuclear hyperchromasia
3. Coarse, clumped chromatin
4. Irregular nuclear membranes



Atypia



Suspicious



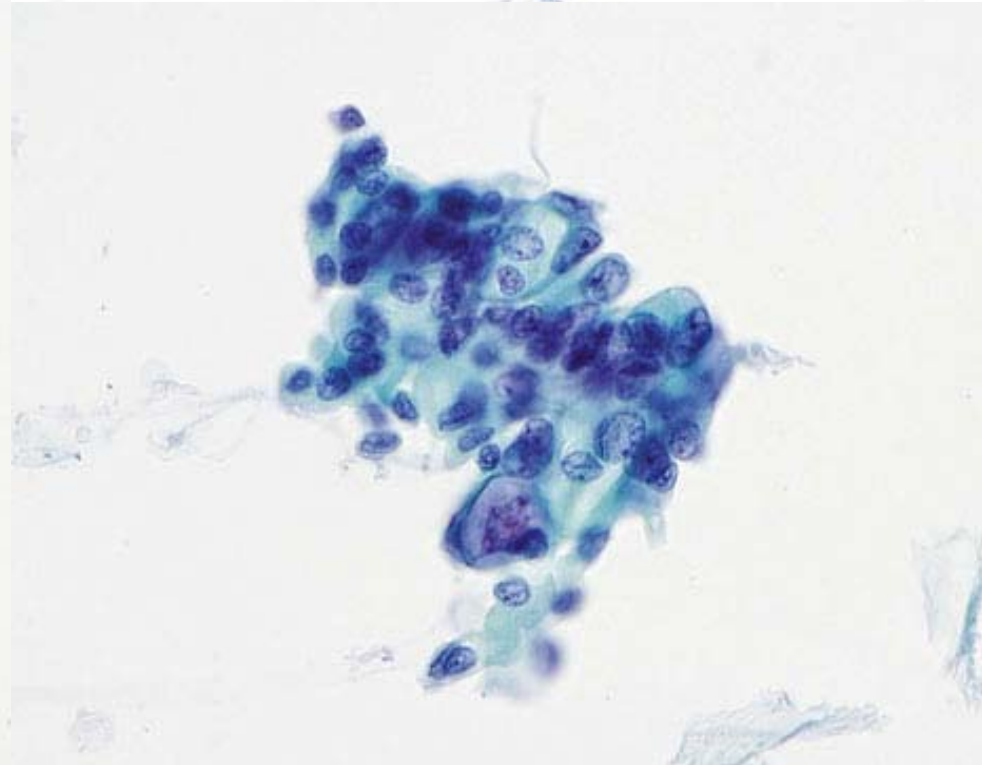
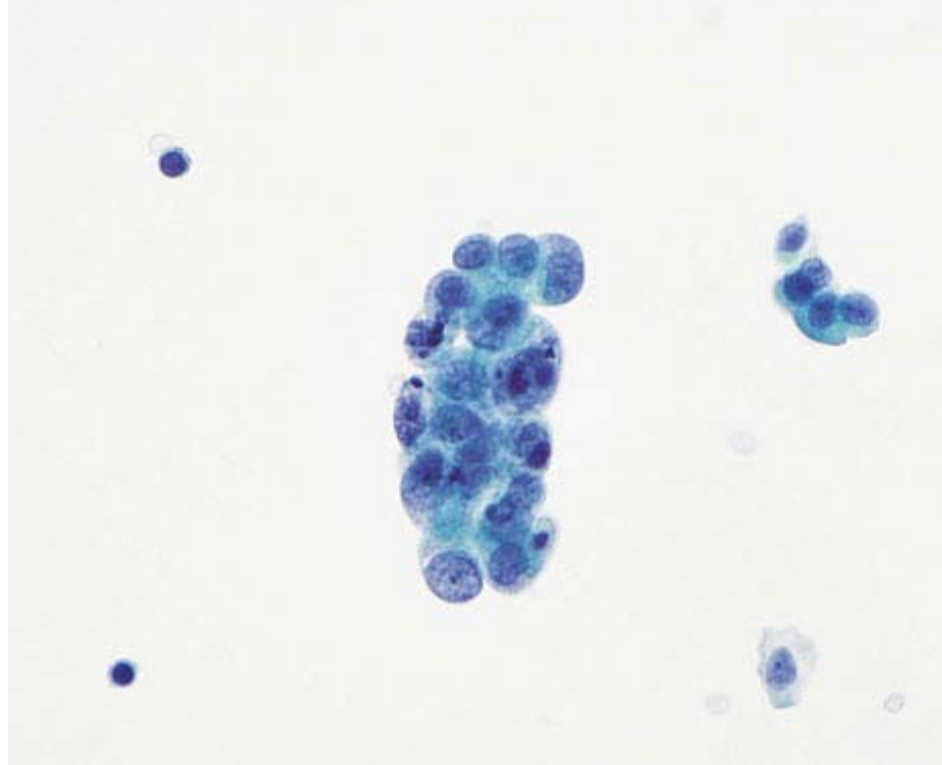
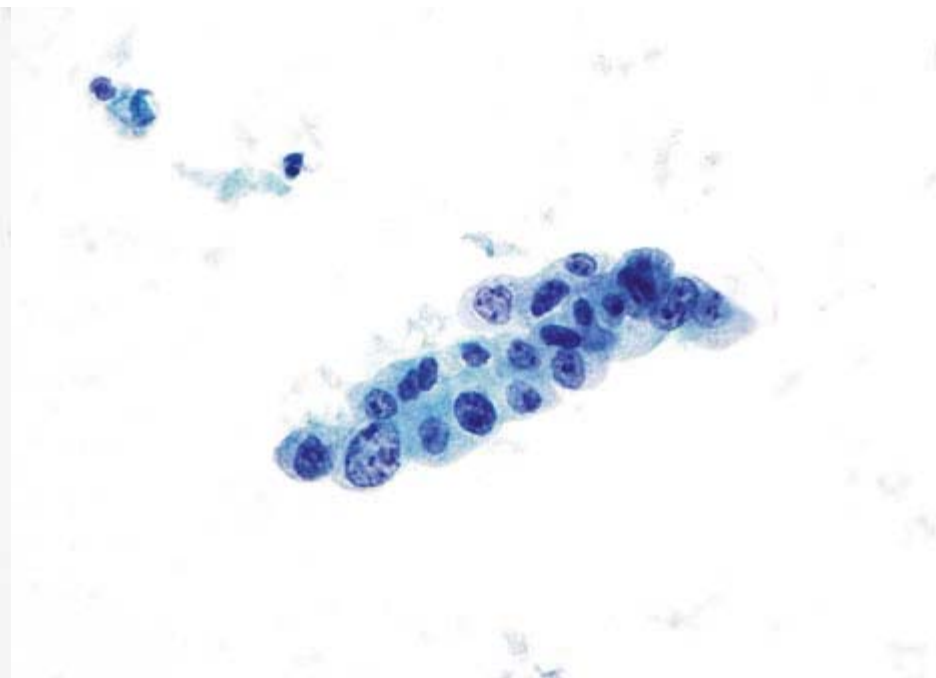
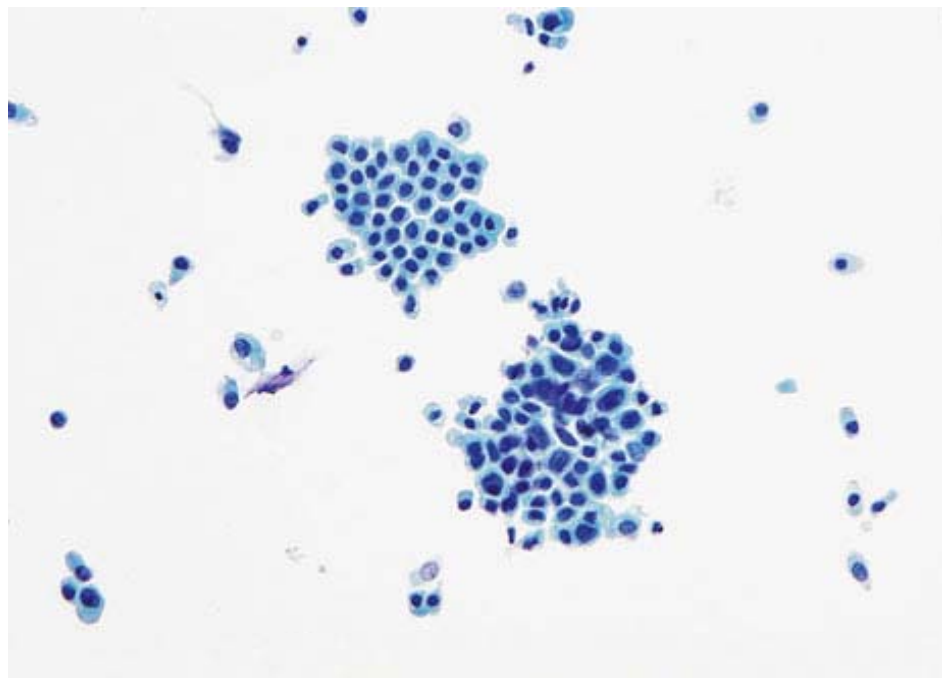
Positive

Atypical Urothelial Cells (AUC)

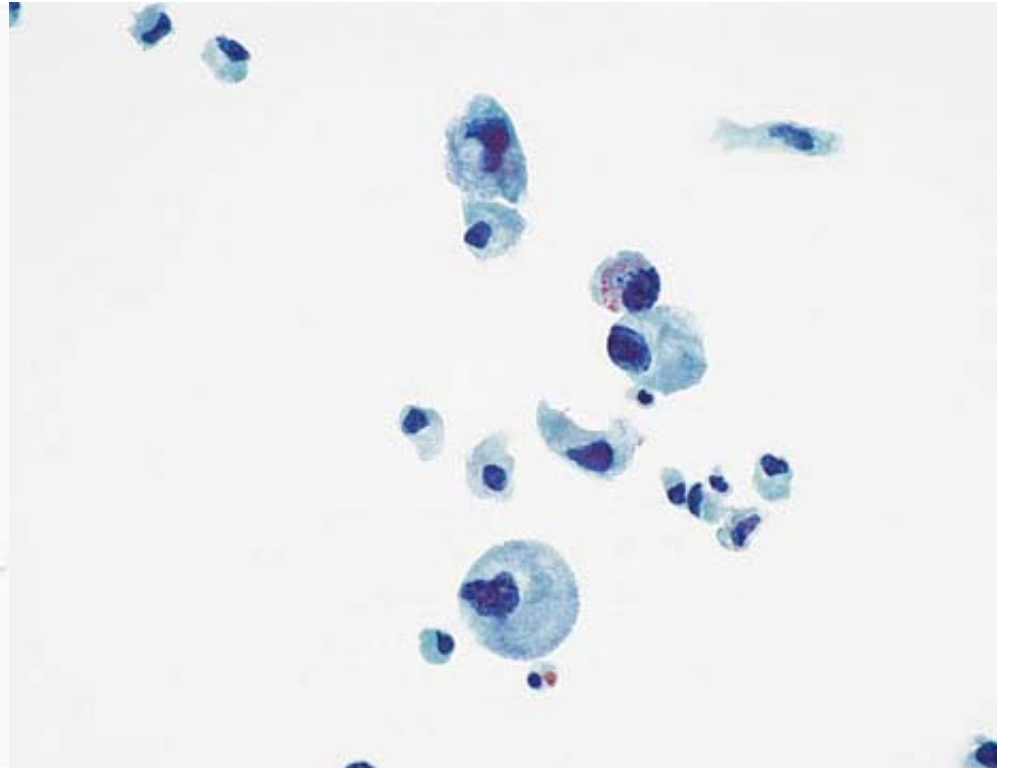
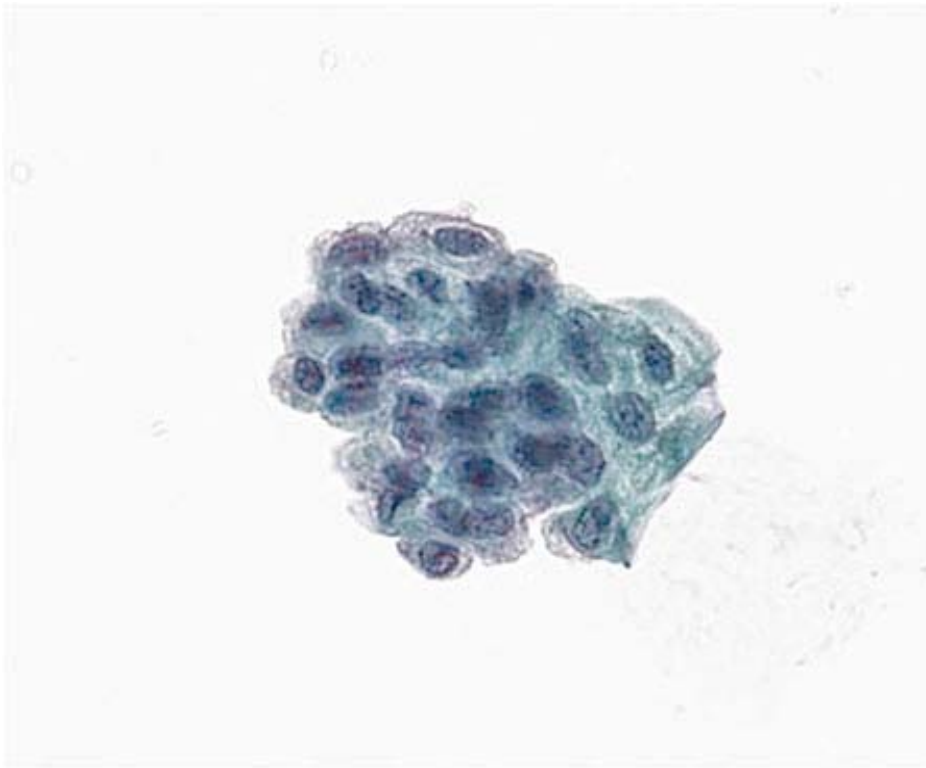
Güliz A. Barkan , Tarik M. Elsheikh , Daniel F. I. Kurtycz , Sachiko Minamiguchi , Hiroshi Ohtani , Eric Piaton , Spasenija Savic Prince , Z. Laura Tabatabai , and Christopher J. VandenBussche

Criteria for AUC

- Non-superficial and non-degenerated urothelial cells with an **high N/C ratio > 0.5 (required)**
and one of the following:
 - **Hyperchromasia** (compared to the umbrella cells or the intermediate squamous cell nucleus)
 - **Irregular clumpy chromatin**
 - **Irregular nuclear contours**



Degeneration



Suspicious for High-Grade Urothelial Carcinoma (Suspicious)

Fadi Brimo, Manon Auger, Tarik M. Elsheikh, Hui Guan, Mitsuru Kinjo, Eric Piaton, Dorothy L. Rosenthal, Tatsuro Shimokama, and Rosemary H. Tambouret

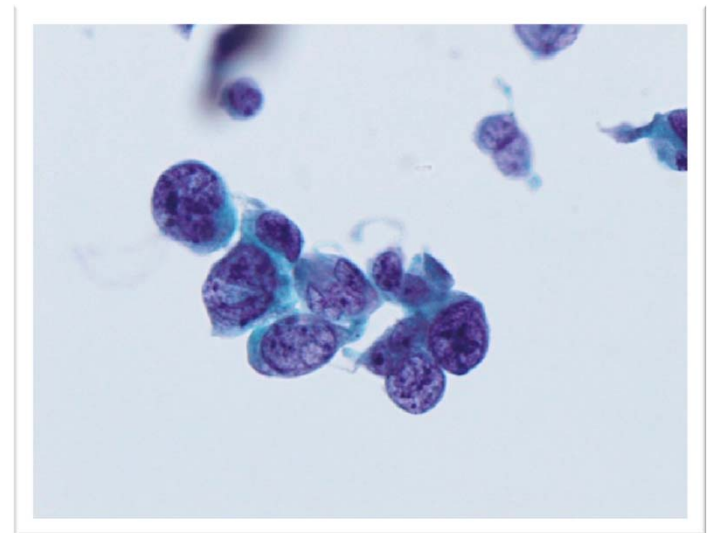
Criteria for SHGUC

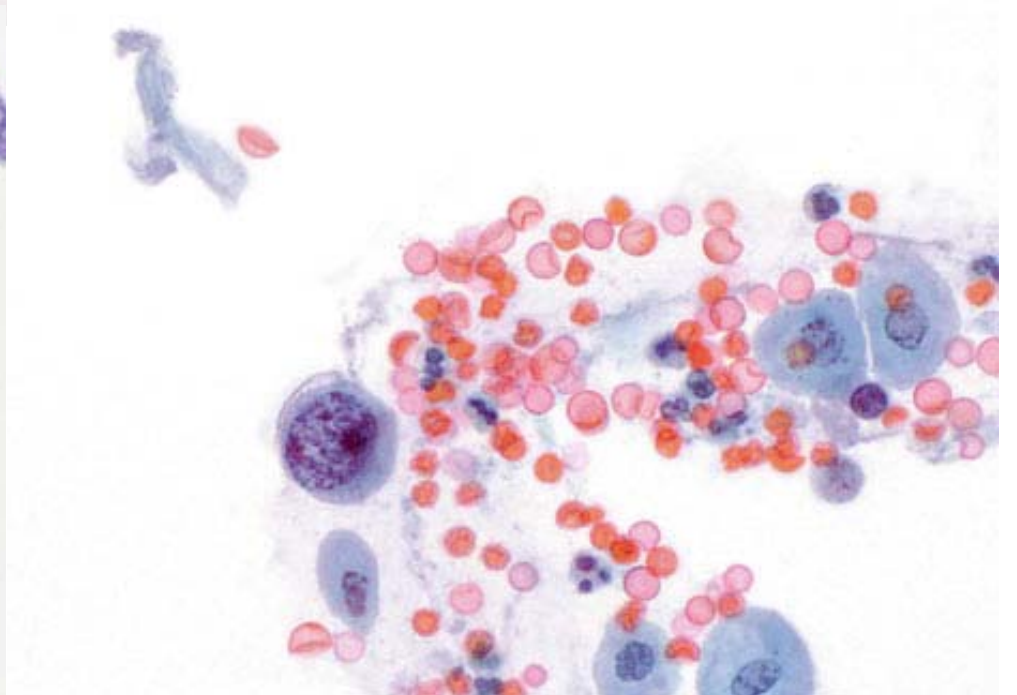
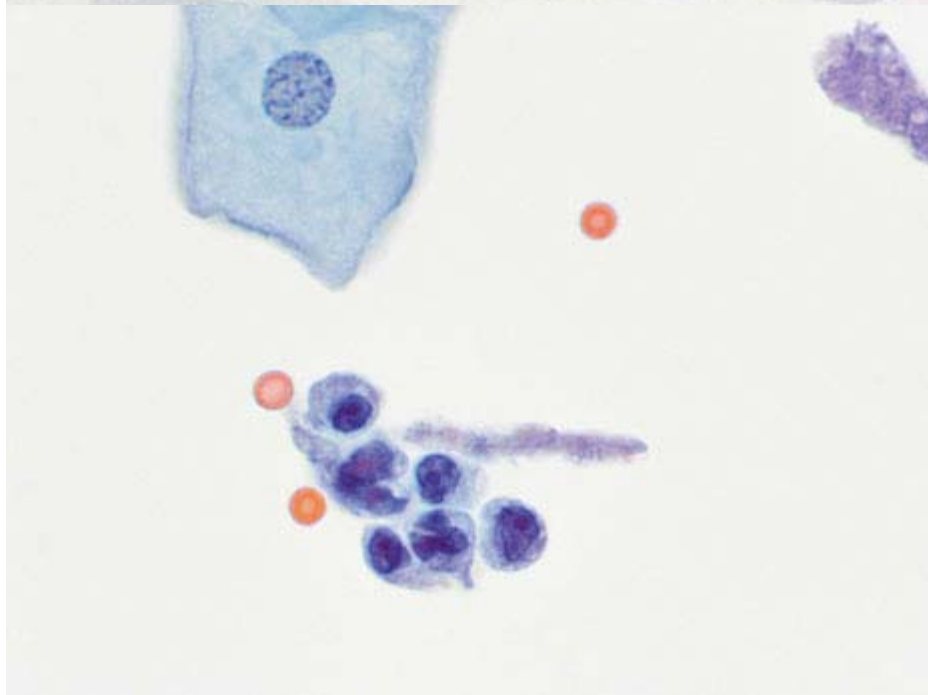
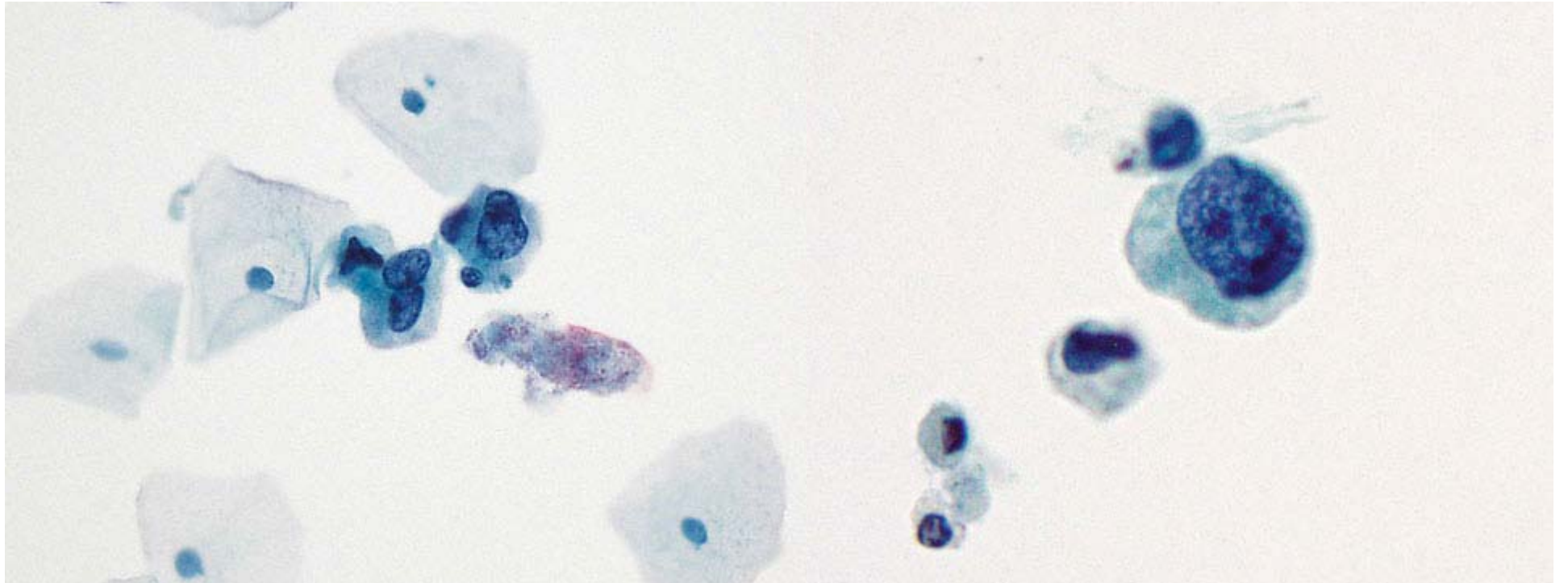
- Non-superficial and non-degenerated urothelial cells with an high **N/C ratio > 0.7** (required)
- **Hyperchromasia** (compared to the umbrella cells or the intermediate squamous cell nucleus) (required)

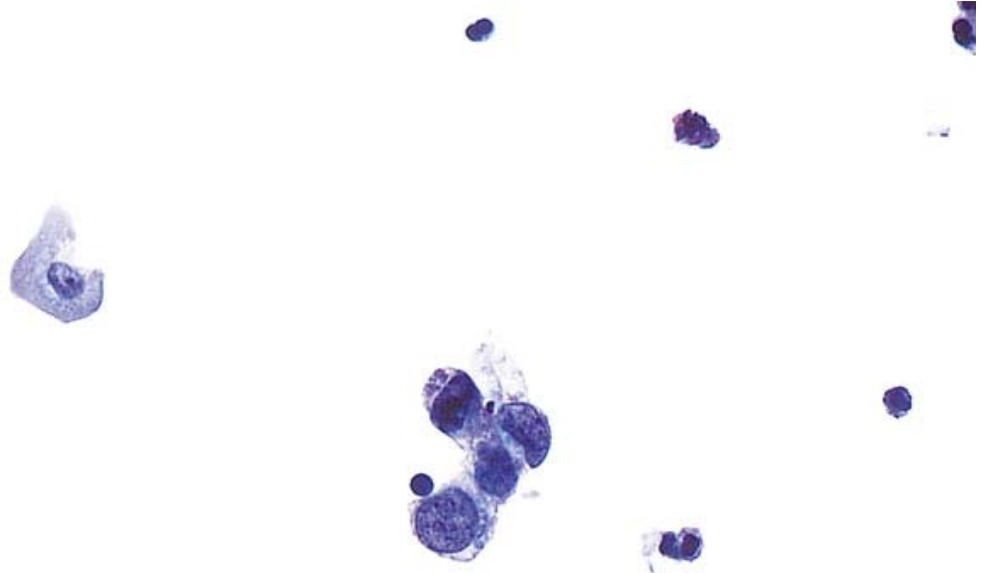
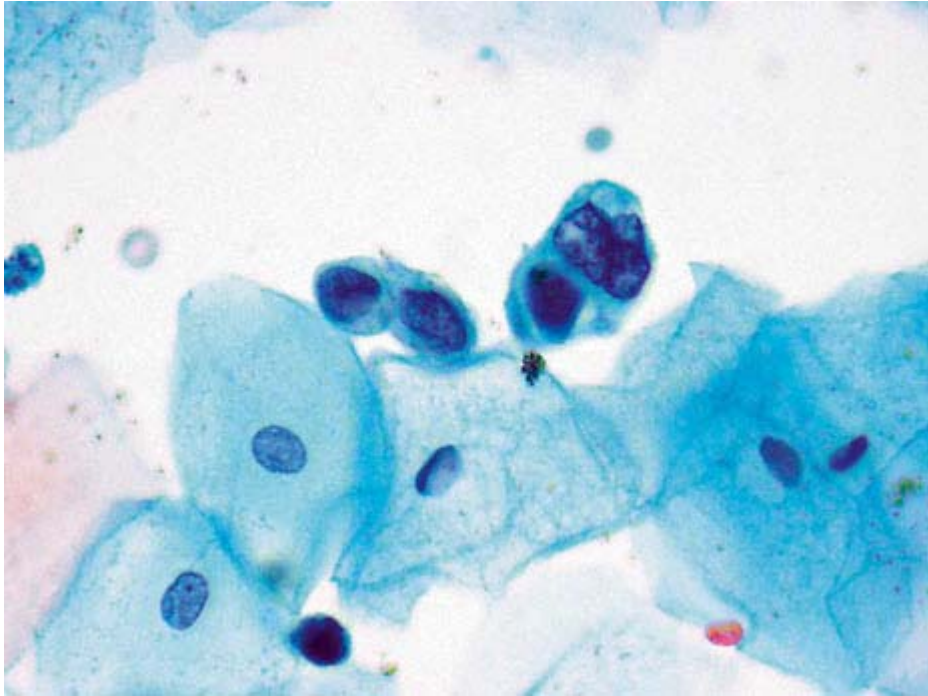
and one of the following:

- **Irregular clumpy chromatin**
- **Irregular nuclear membranes**

<10 cells







Suspicious for HGUC vs. Positive HGUC

Quantity matters..

“The number of atypical urothelial cells is an important criterion to classify urine cytology specimens into the ‘positive’ or the ‘suspicious’ categories. A cut-off number of **>10** cells to render a definitive diagnosis of HGUCA seems valid from the clinical standpoint .”

ORIGINAL ARTICLE

Urine cytology: does the number of atypical urothelial cells matter? A qualitative and quantitative study of 112 cases

Fadi Brimo, MD^{a,*}, Bin Xu, MD^a, Wassim Kassouf, MD^b,
Babak Ahmadi-Kaliji, MD^a, Michele Charbonneau, CT^a,
Ayoub Nahal, MD^a, Yonca Kanber, MD^a, Derin Caglar, MD^a,
Manon Auger, MD^a

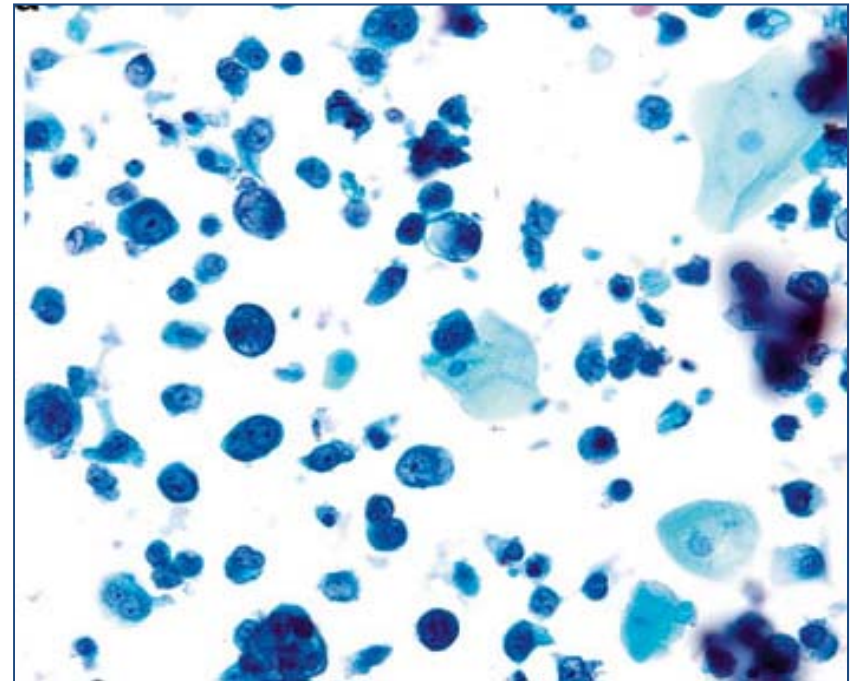
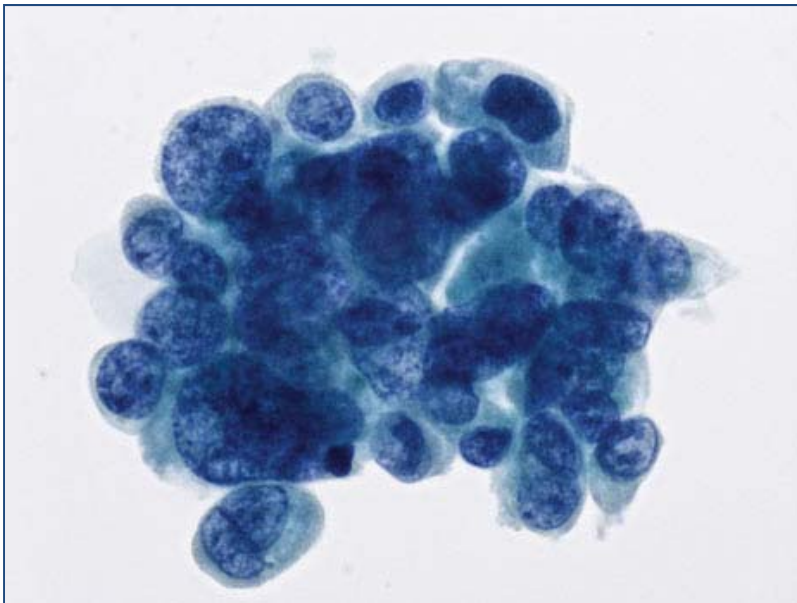
JASC 2015;4(4)232–238

5 – 10 cells – gray zone, based on experience, history, individual threshold, etc

High-Grade Urothelial Carcinoma (HGUC)

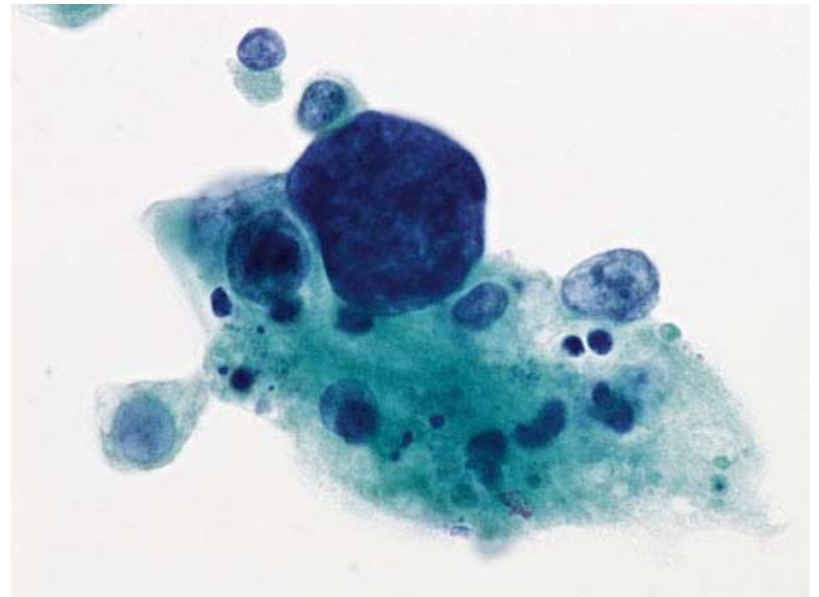
Momin T. Siddiqui, Guido Fadda, Jee-Young Han, Christopher L. Owens,
Z. Laura Tabatabai, and Toyonori Tsuzuki

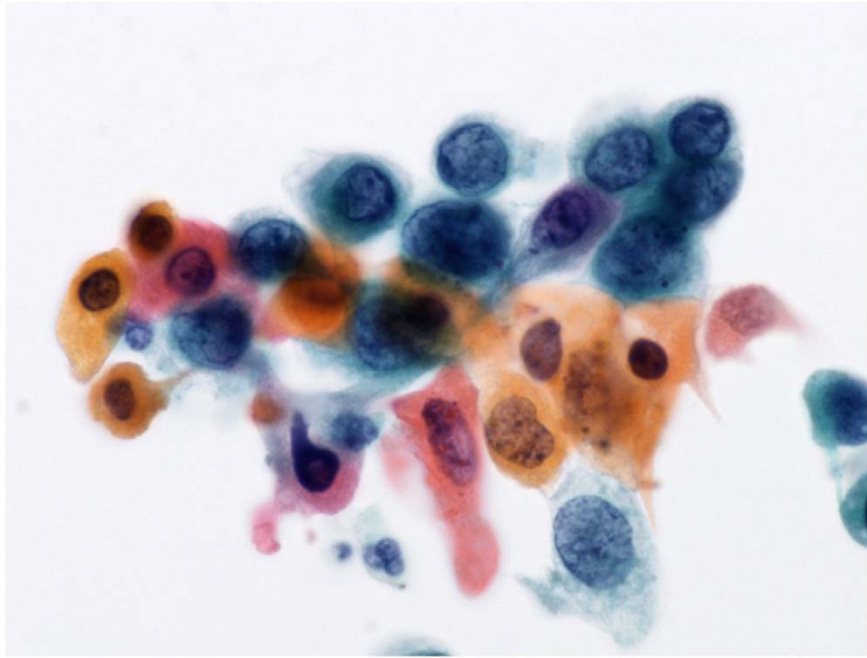
- Cellularity: At least 5–10 abnormal cells
- N/C ratio: 0.7 or greater
- Nucleus: Moderate to severe hyperchromasia
- Nuclear membrane: Markedly irregular
- Chromatin: Coarse/clumped



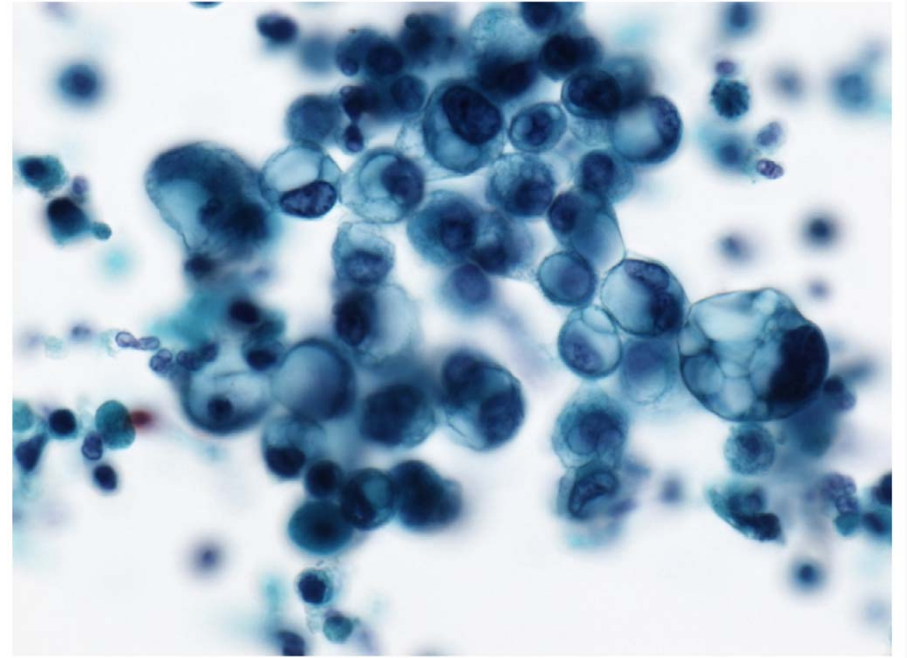
Other Notable Cytomorphologic Features

- Cellular pleomorphism
- Marked variation in cellular size and shapes, i.e., oval, rounded, elongated, or plasmacytoid (Comet cells)
- Scant, pale, or dense cytoplasm
- Prominent nucleoli
- Mitoses
- Necrotic debris
- Inflammation

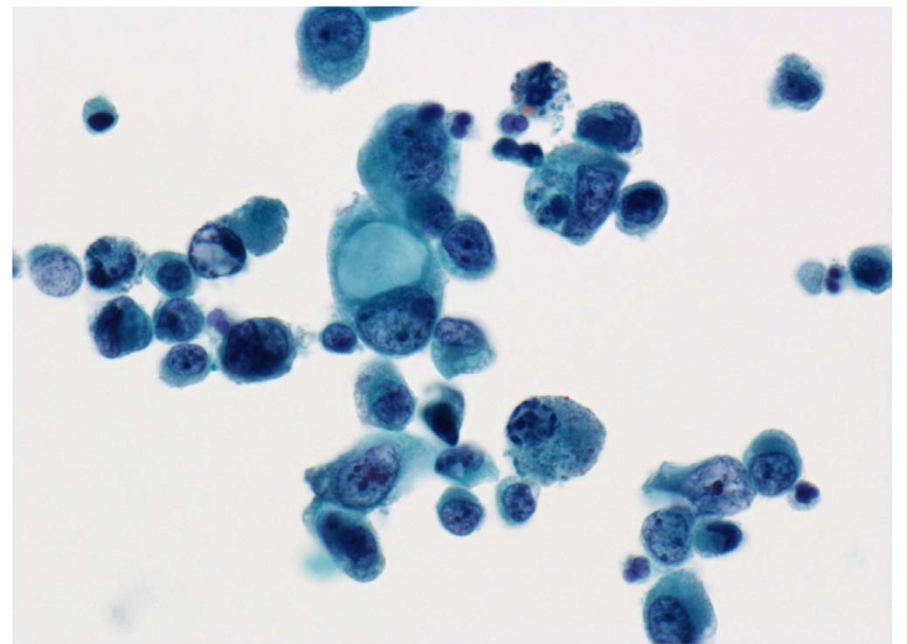
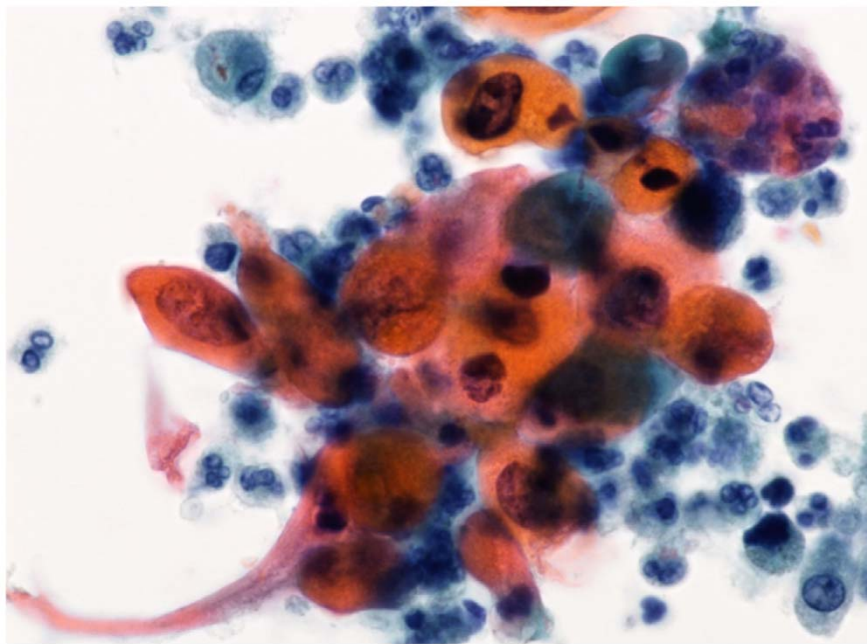




Squamous differentiation



Glandular differentiation



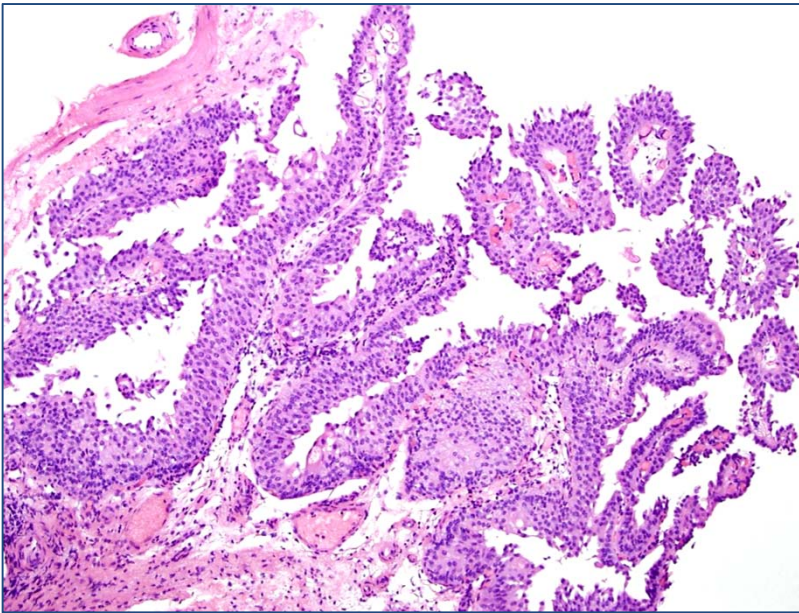
What happened to LGUC??

- Almost impossible to diagnose without a mini-biopsy with fibrovascular core
- Cytologically normal nuclei
- Is it truly a carcinoma?
- More common than HGUC
- BUT, not life threatening

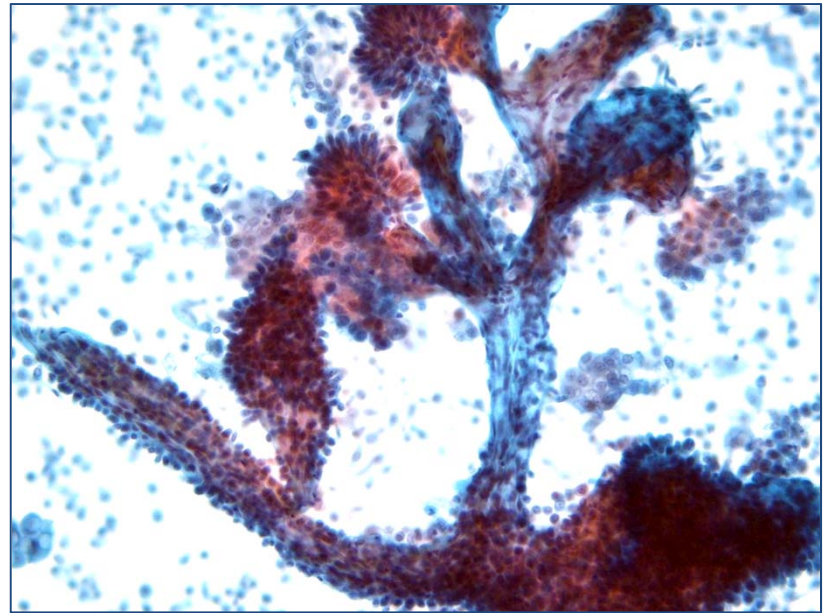
Low-Grade Urothelial Neoplasia (LGUN)

Eva M. Wojcik, Tatjana Antic, Ashish Chandra, Michael B. Cohen, Zulfia McCroskey, Jae Y. Ro, and Taizo Shiraish

- LGUN - combined cytologic term for low grade papillary urothelial neoplasms (LGPUN) (which include urothelial papilloma, PUNLMP and LGPUC) and flat, low grade intraurothelial neoplasia



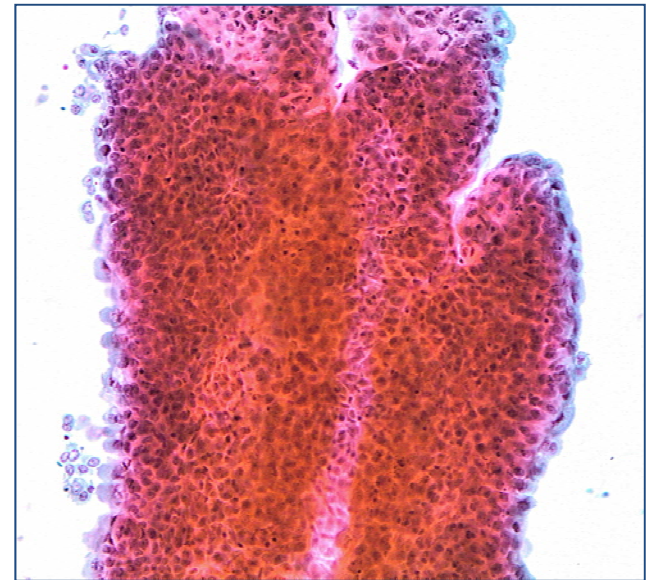
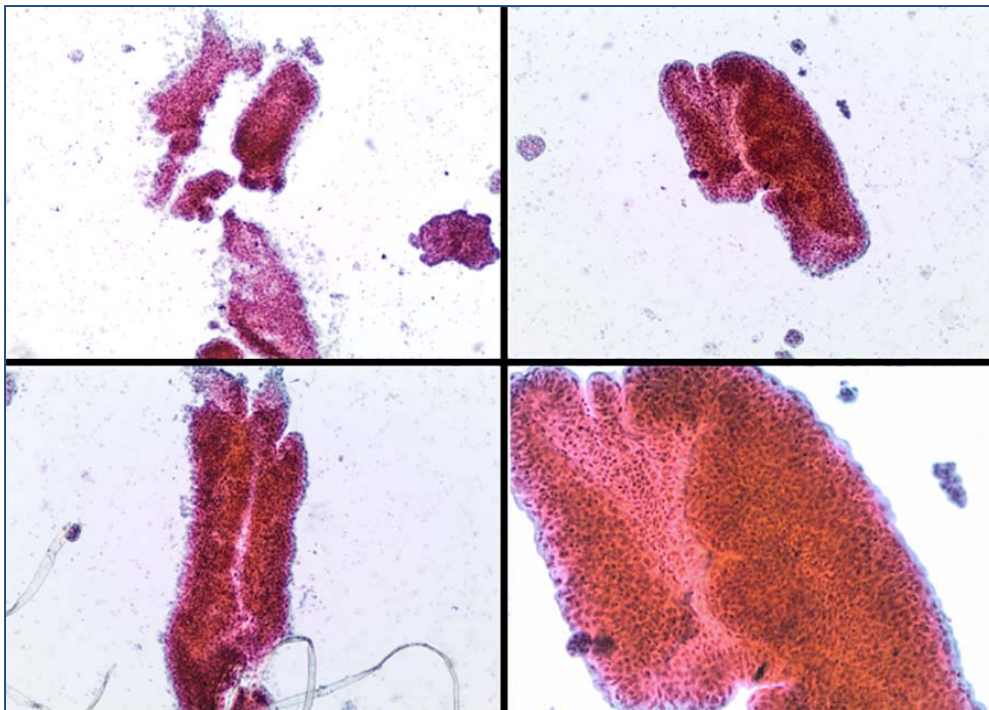
LGUC



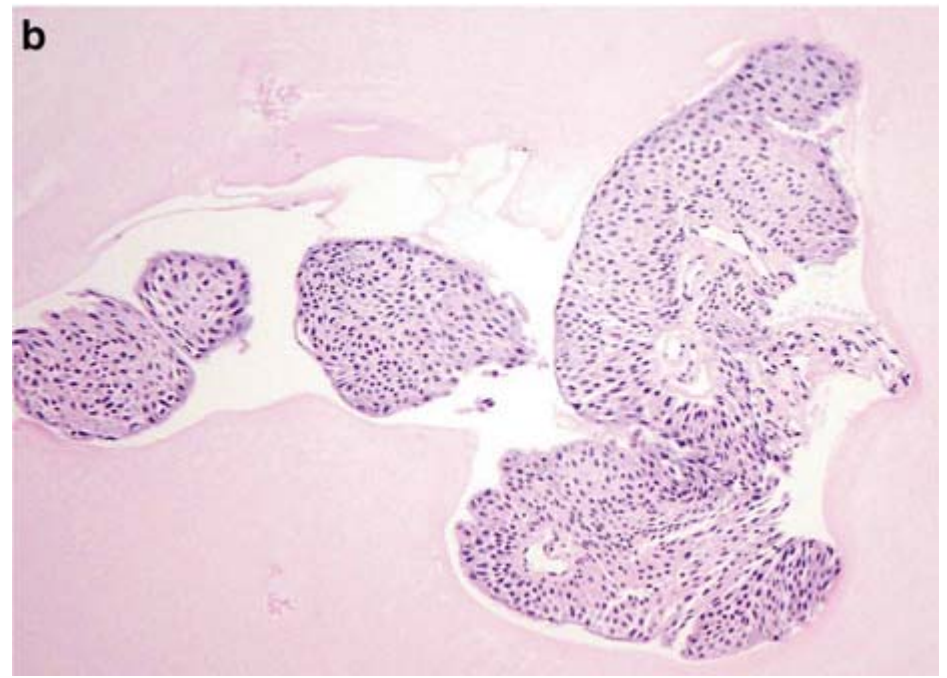
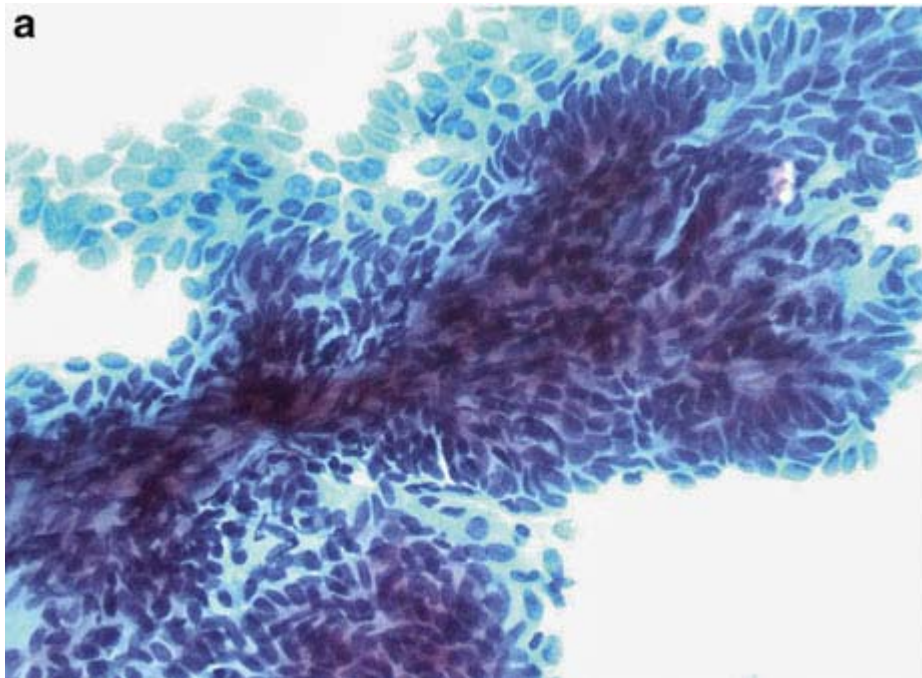
LGUN

Cytologic Criteria of Low Grade Urothelial Neoplasia (LGUN) (regardless of the specimen type: voided or instrumented):

- Three-dimensional cellular papillary clusters (defined as clusters of cells with nuclear overlapping, forming "papillae") with fibrovascular cores with capillaries



Cytologic Criteria of Low Grade Urothelial Neoplasia (LGUN) (regardless of the specimen type: voided or instrumented)

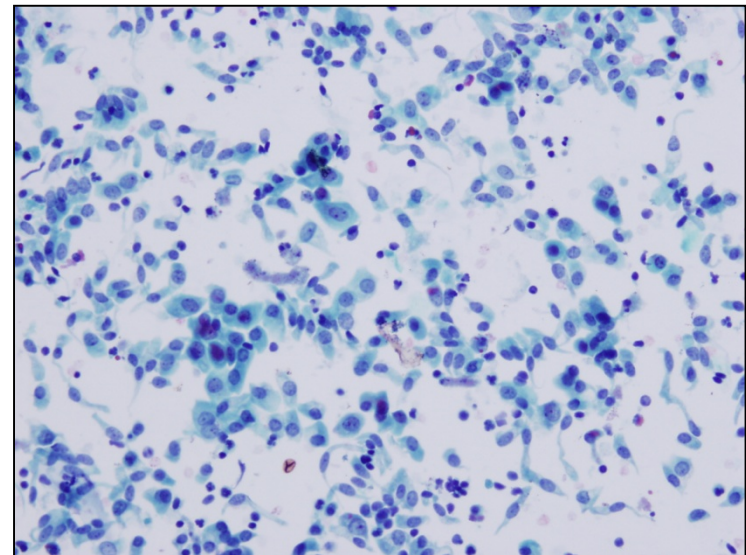
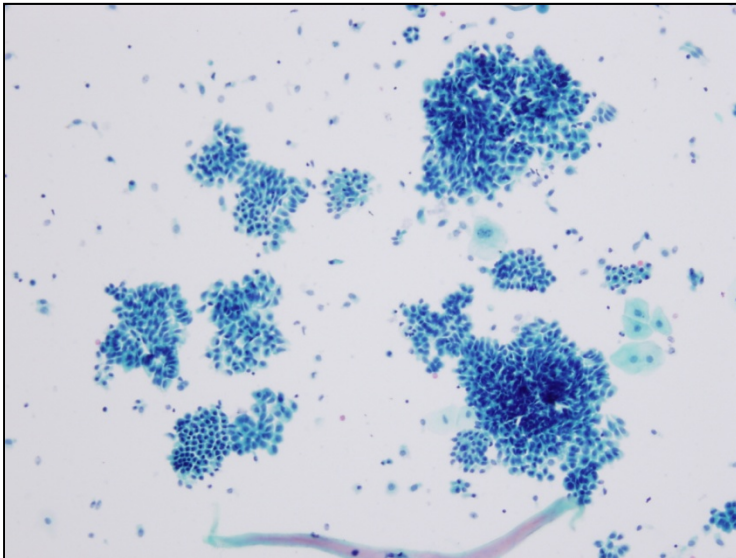


Cell Block

LGUN may be considered in correlation with cystoscopic or biopsy findings

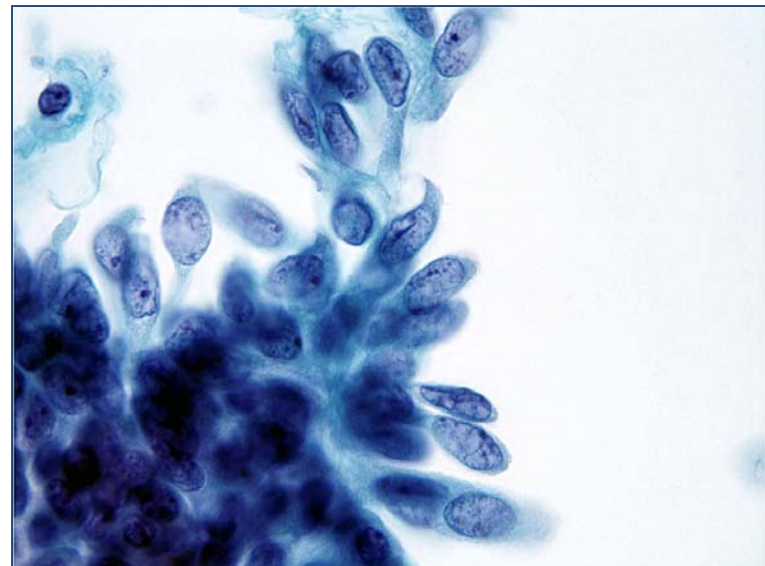
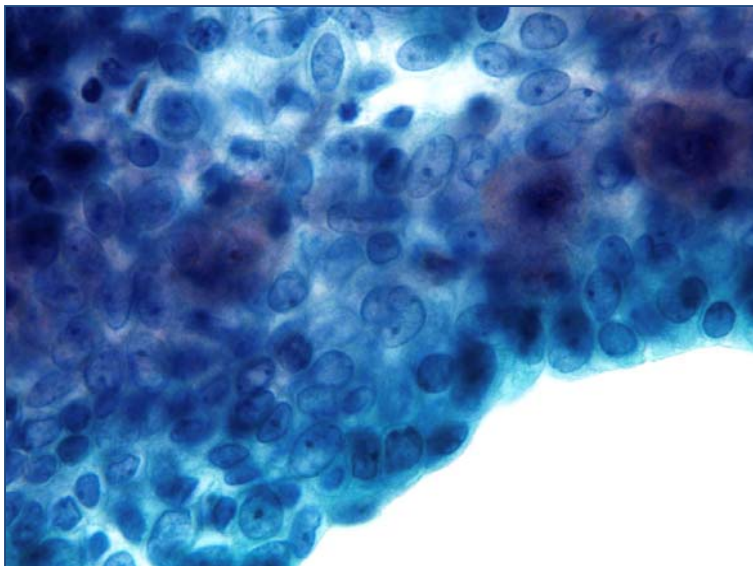
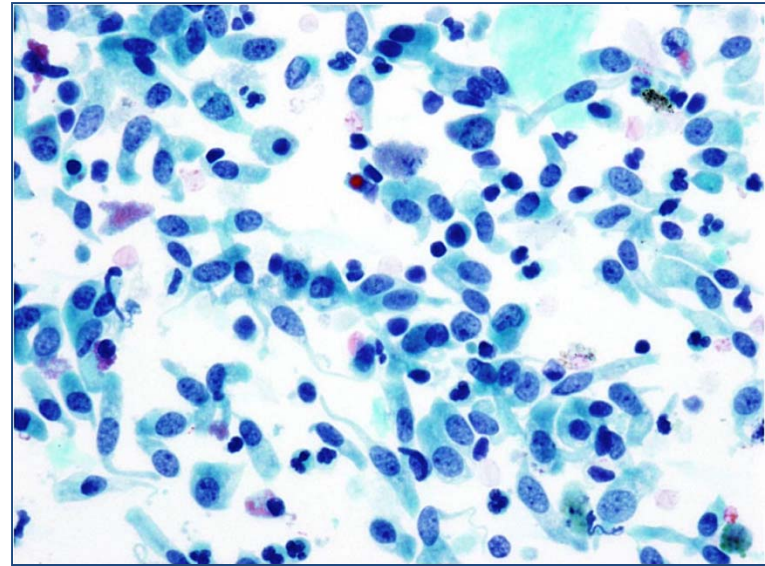
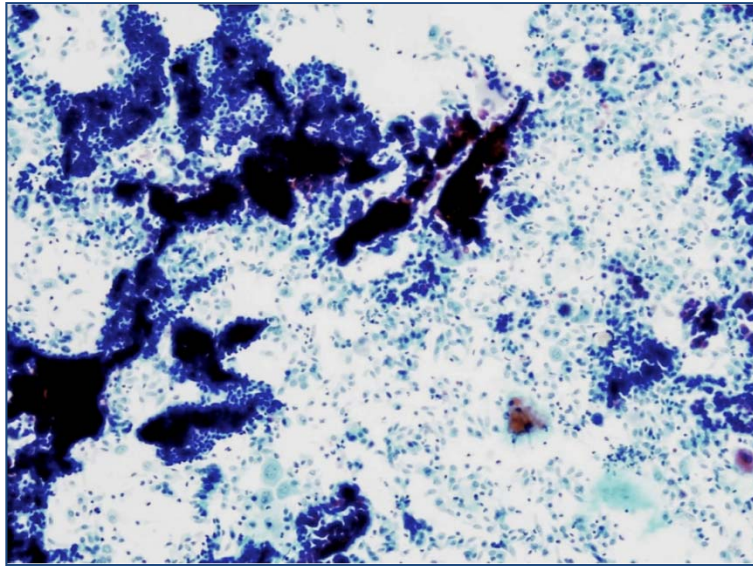
Diagnosis - NHGUC

- Three-dimensional cellular clusters without fibrovascular cores
- Increased numbers of monotonous single (non-umbrella) cells

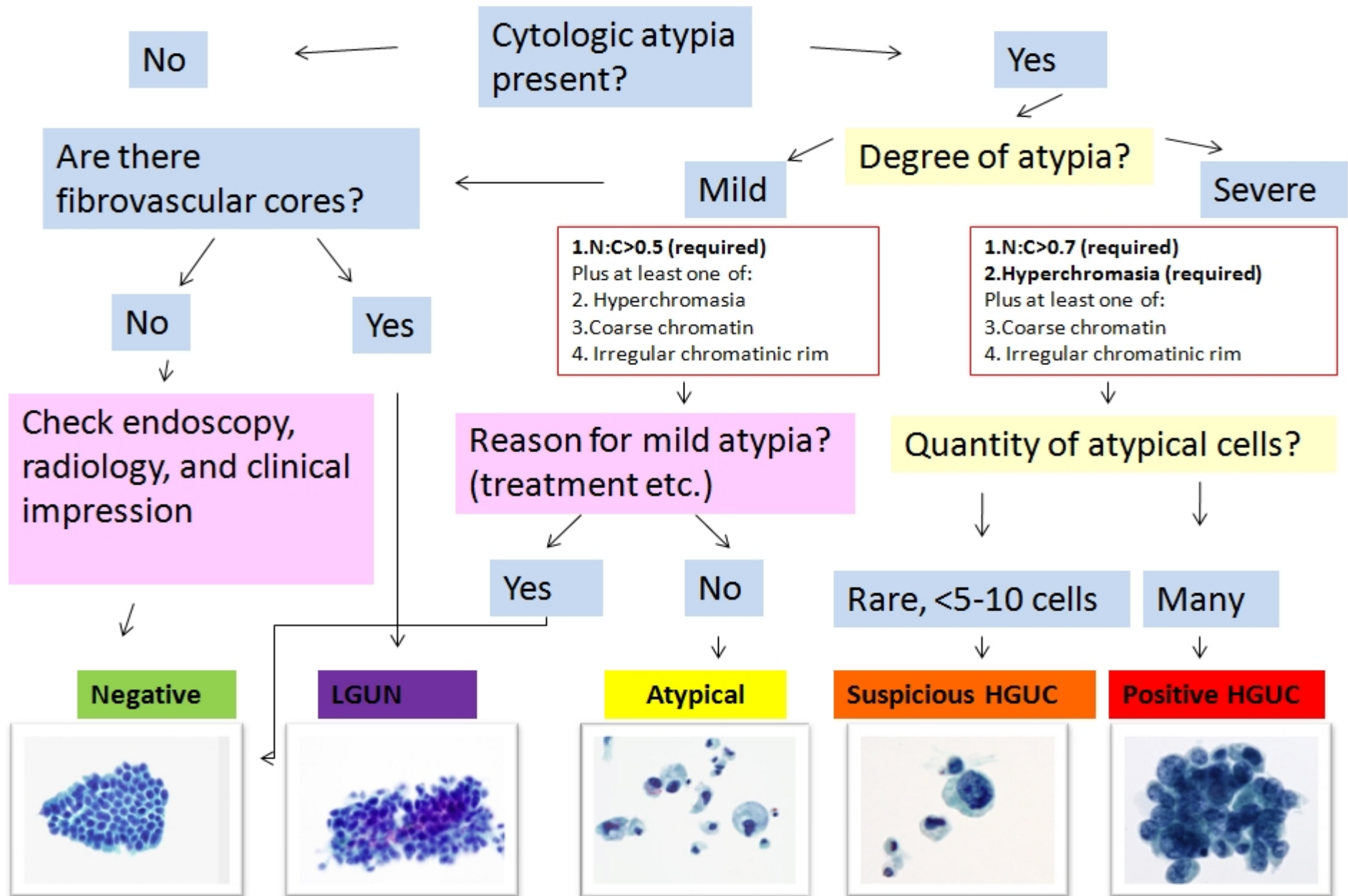


How about these – Negative for HGUC

Comment – Suggestive of LGUN

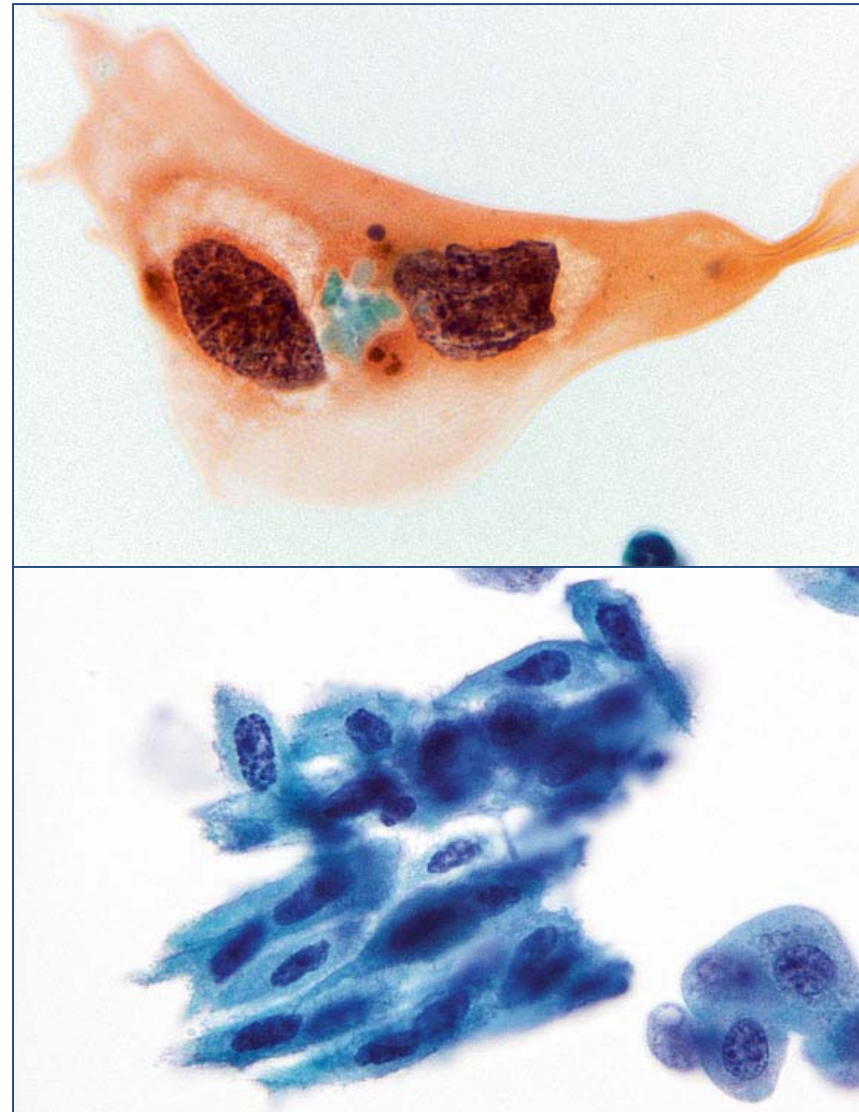
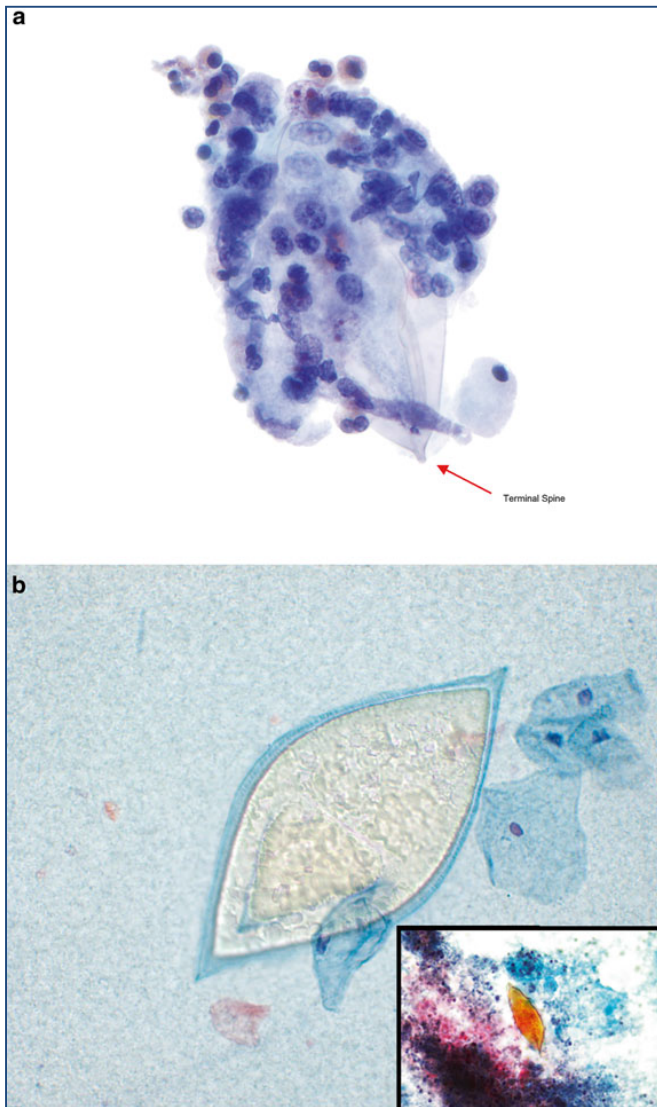


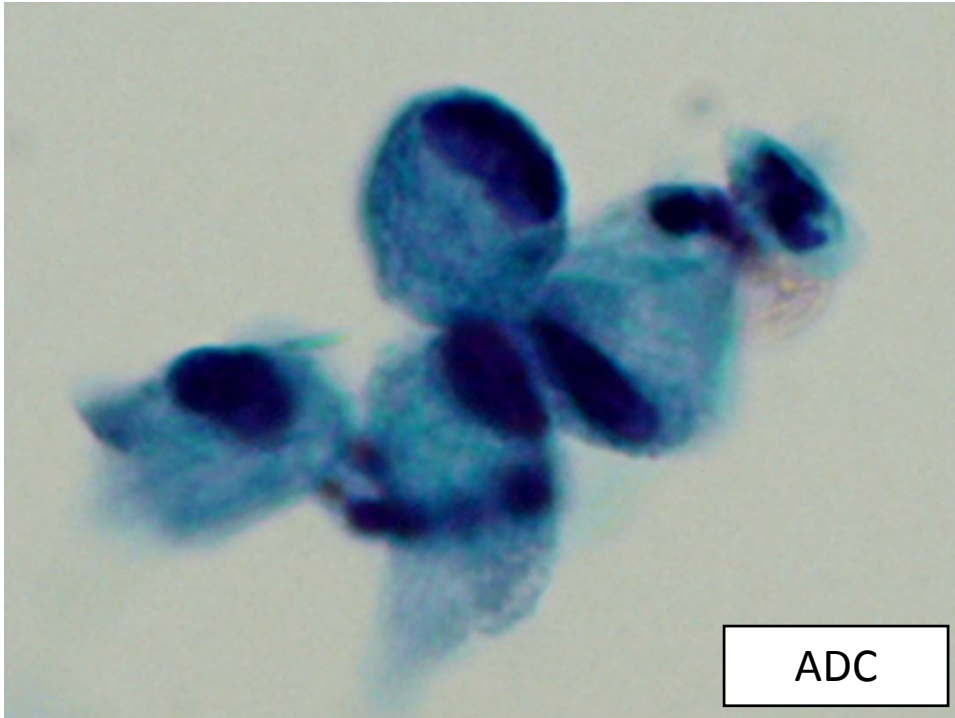
Approach to Diagnosis in Urinary Tract



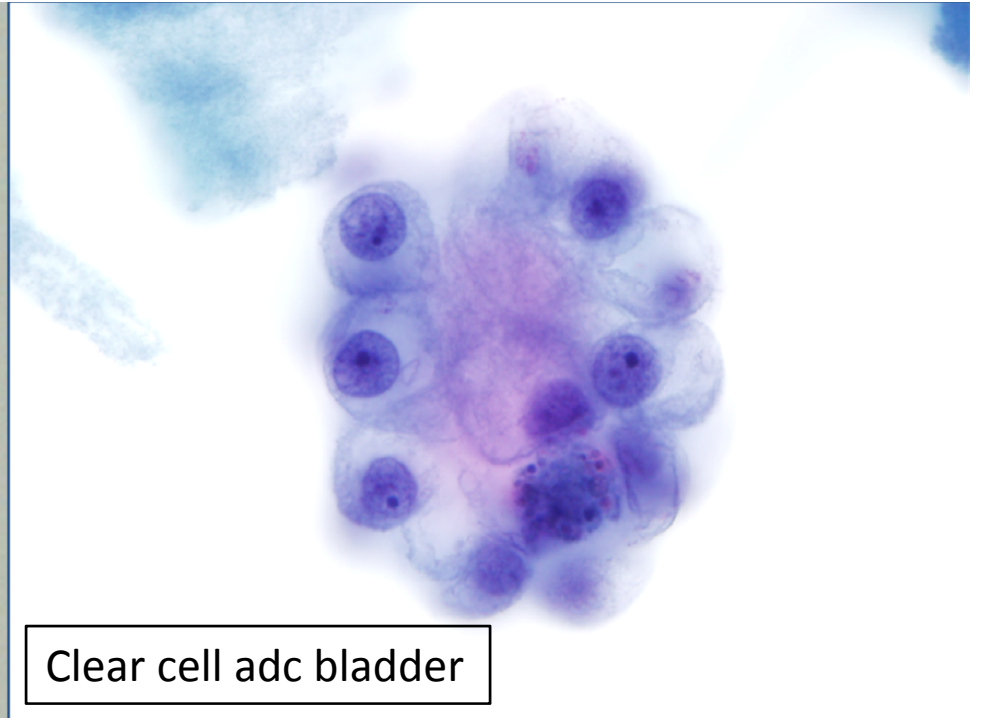
Other Malignancies Primary and Metastatic and Miscellaneous Lesions

Rana S. Hoda, Stefan E. Pambuccian, Jae Y. Ro, and Sun Hee Sung

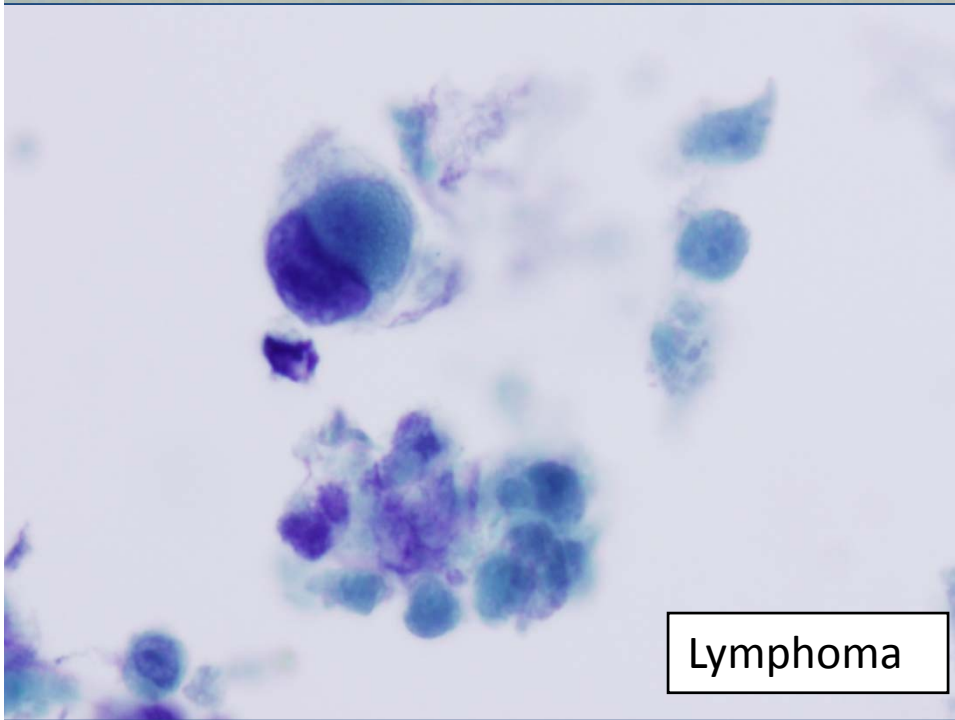




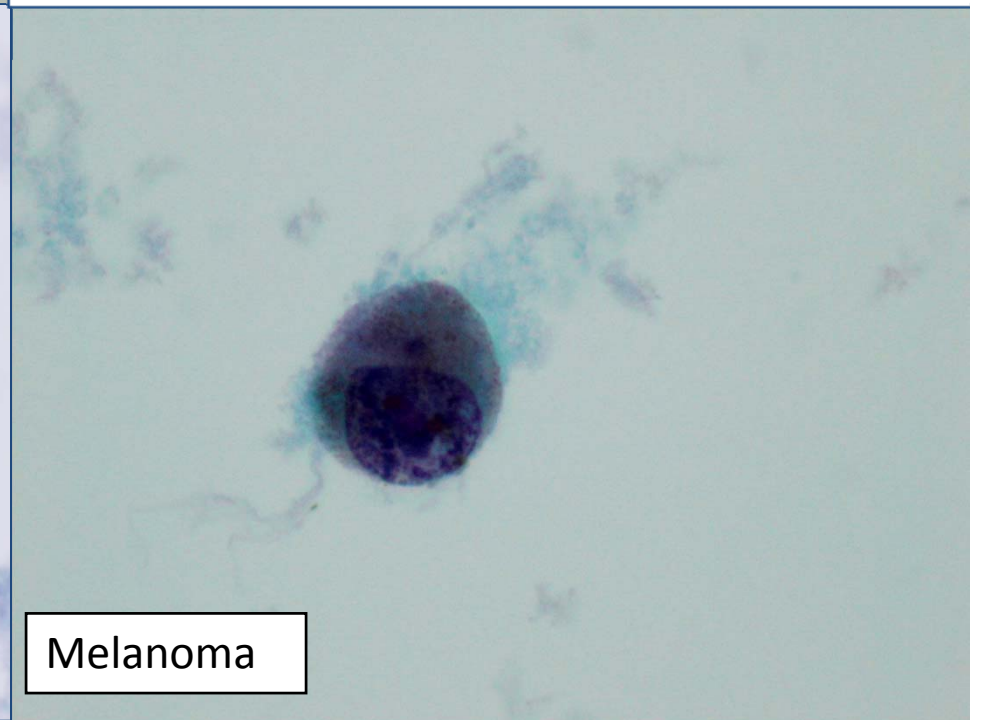
ADC



Clear cell adc bladder



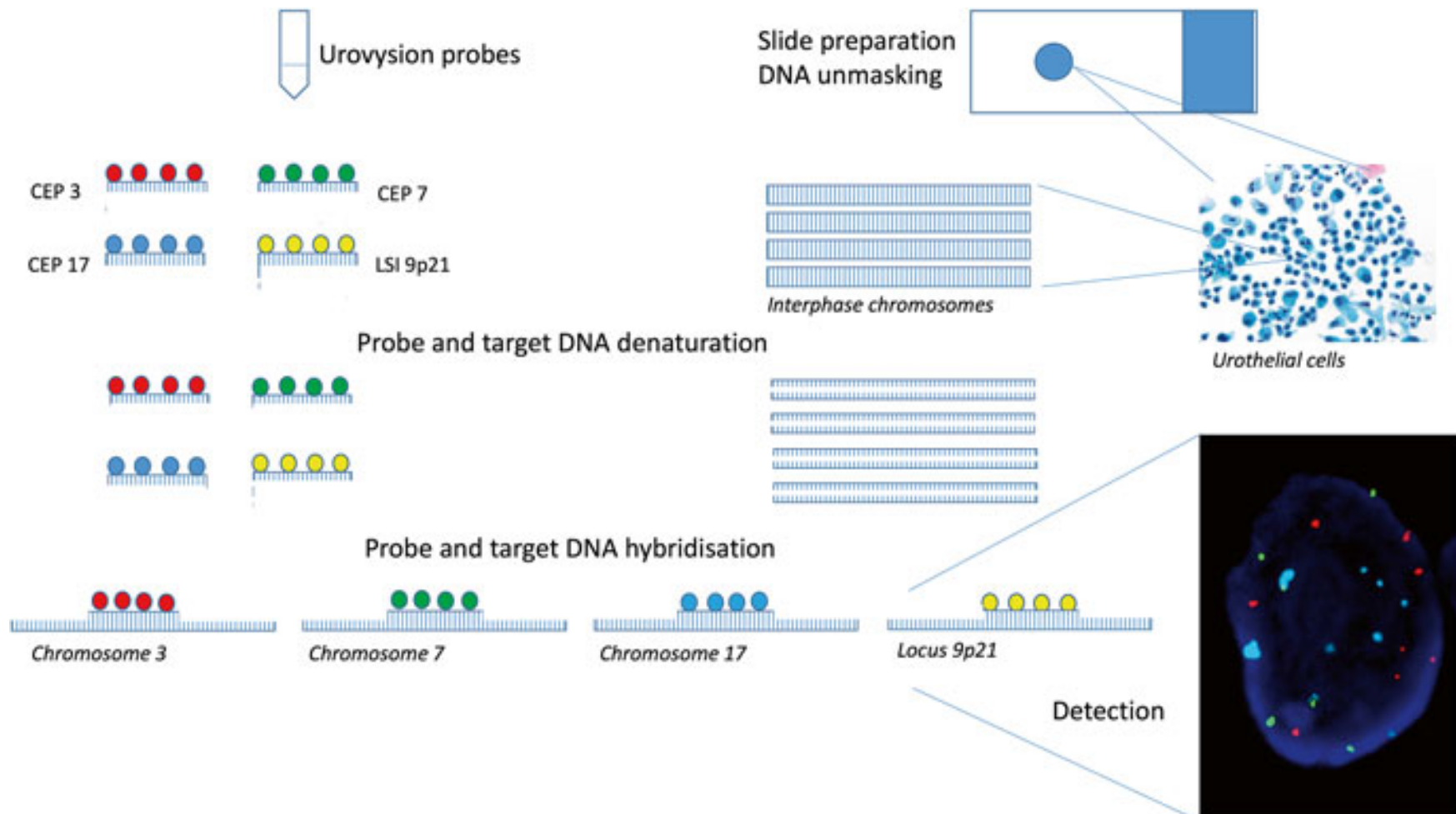
Lymphoma

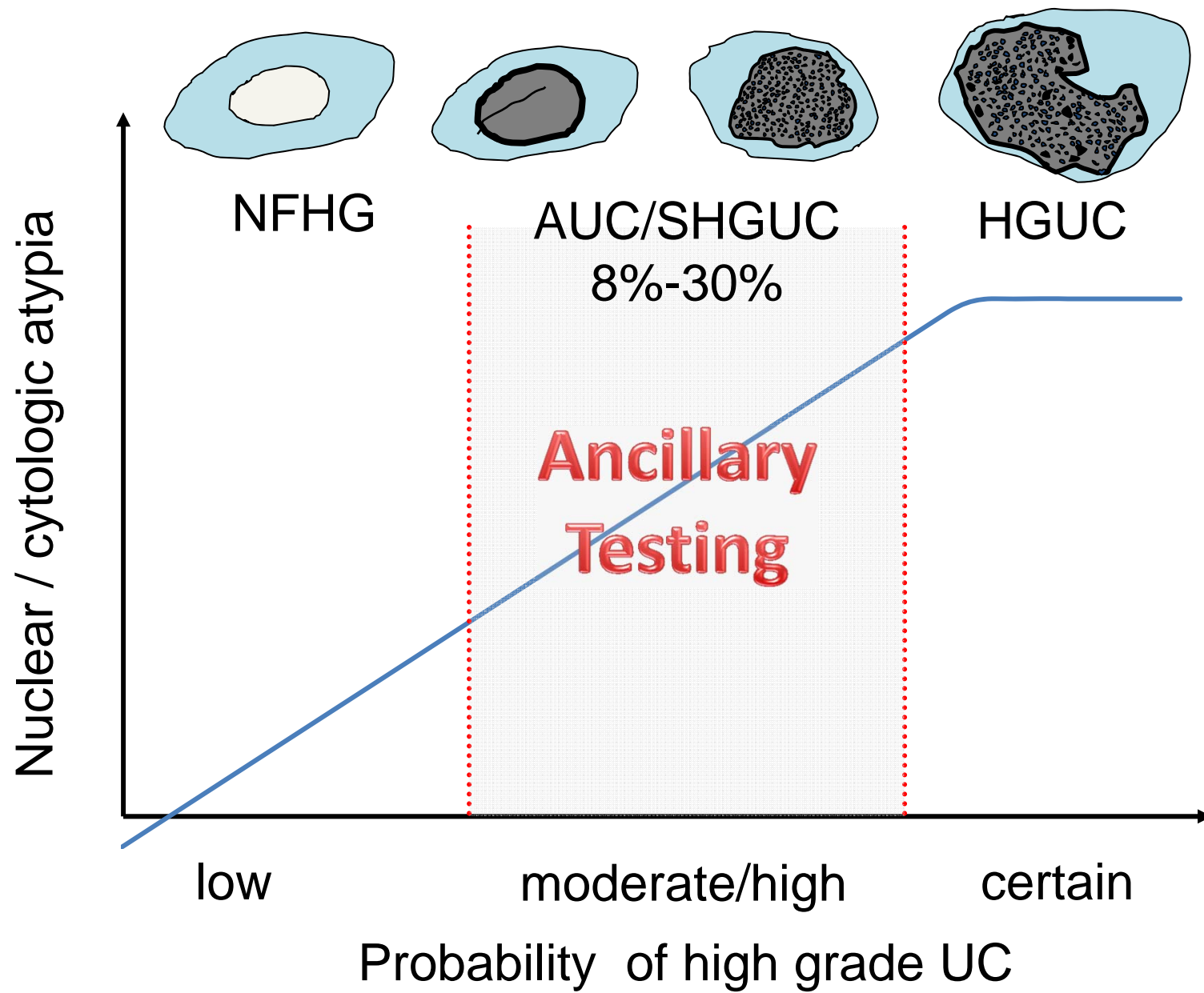


Melanoma

Ancillary Studies in Urinary Cytology

Lukas Bubendorf, Nancy P. Caraway, Andrew H. Fischer, Ruth L. Katz, Matthew T. Olson, Fernando Schmitt, Margareta Strojan Fležar, Theodorus H. Van Der Kwast, Philippe Vielh





Cytopreparatory Techniques

Gary W. Gill, William N. Crabtree, and Deidra P. Kelly

- No generally accepted best materials and methods of collecting and processing urine to detect urothelial malignancies

How are UT specimens processed in your laboratory? n = 739 (Multiple responses allowed)	No.	%
ThinPrep	424	57.4
Cytospin	336	45.5
Cell block	202	27.3
Conventional smear	69	9.3
SurePath	49	6.6
Filter preparation	16	2.2
Other	11	1.5

Clinical Management

Marcus L. Quek, Trinity J. Bivalacqua, Ashish M. Kamat, and Mark P. Schoenberg

- From the standpoint of the urologist, the workup for AUC should be individualized based on the risk assessment of the patient
- From a practical standpoint, the clinical management of “suspicious for HGUC” is similar to a “positive for HGUC” diagnosis
- Transurethral resection establishes the histologic diagnosis and is therapeutic for most solitary low grade tumors

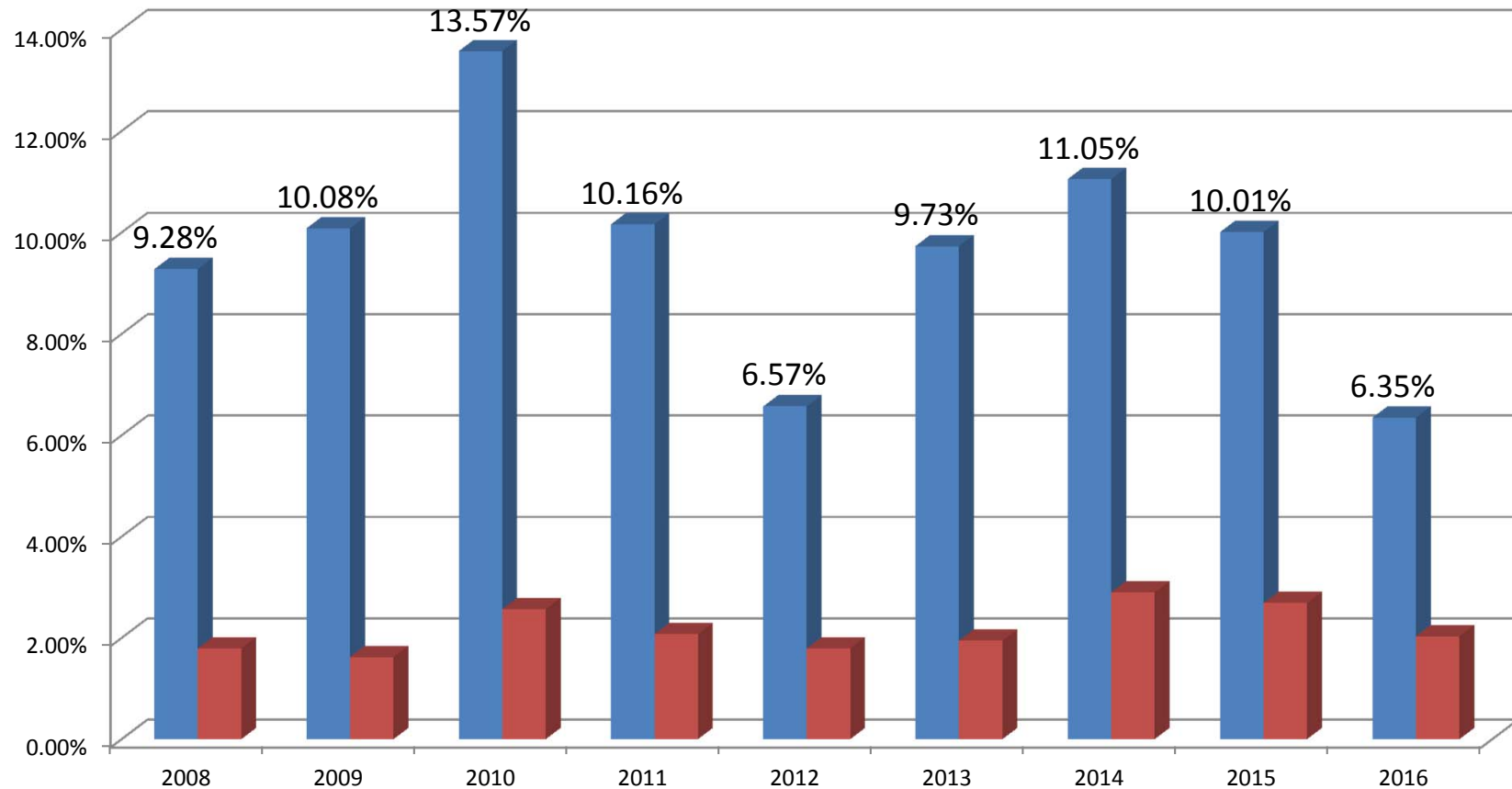
Clinical Management

Marcus L. Quek, Trinity J. Bivalacqua, Ashish M. Kamat, and Mark P. Schoenberg

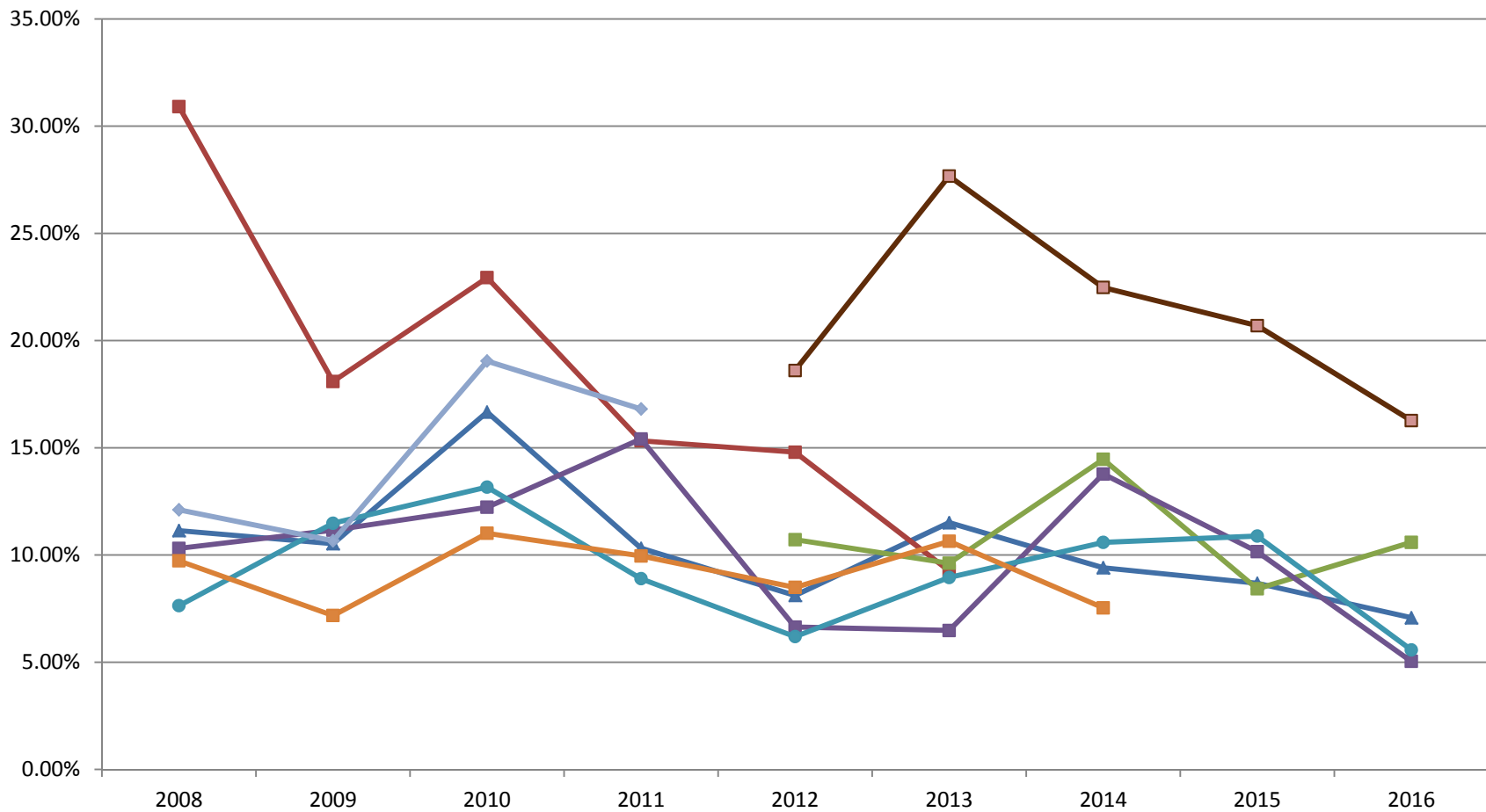
Risk of malignancy – ongoing studies

Category	Risk of Malignancy	Management
Unsatisfactory/Nondiagnostic	? (<5%)	Repeat cytology, cystoscopy in 3 months if increased clinical suspicion
Negative for HGUC	0-2%	Clinical follow up as needed
Atypical Urothelial Cells (AUC)	8-35%	Clinical follow up as needed. Use of ancillary testing.
Suspicious for HGUC	50-90%	More aggressive follow up, cystoscopy, biopsy
LGUN	~10%	Need biopsy to further evaluate grade and stage
High Grade UC	>90%	More aggressive follow up, cystoscopy, biopsy, staging
Other malignancy	>90%	More aggressive follow up, cystoscopy, biopsy, staging

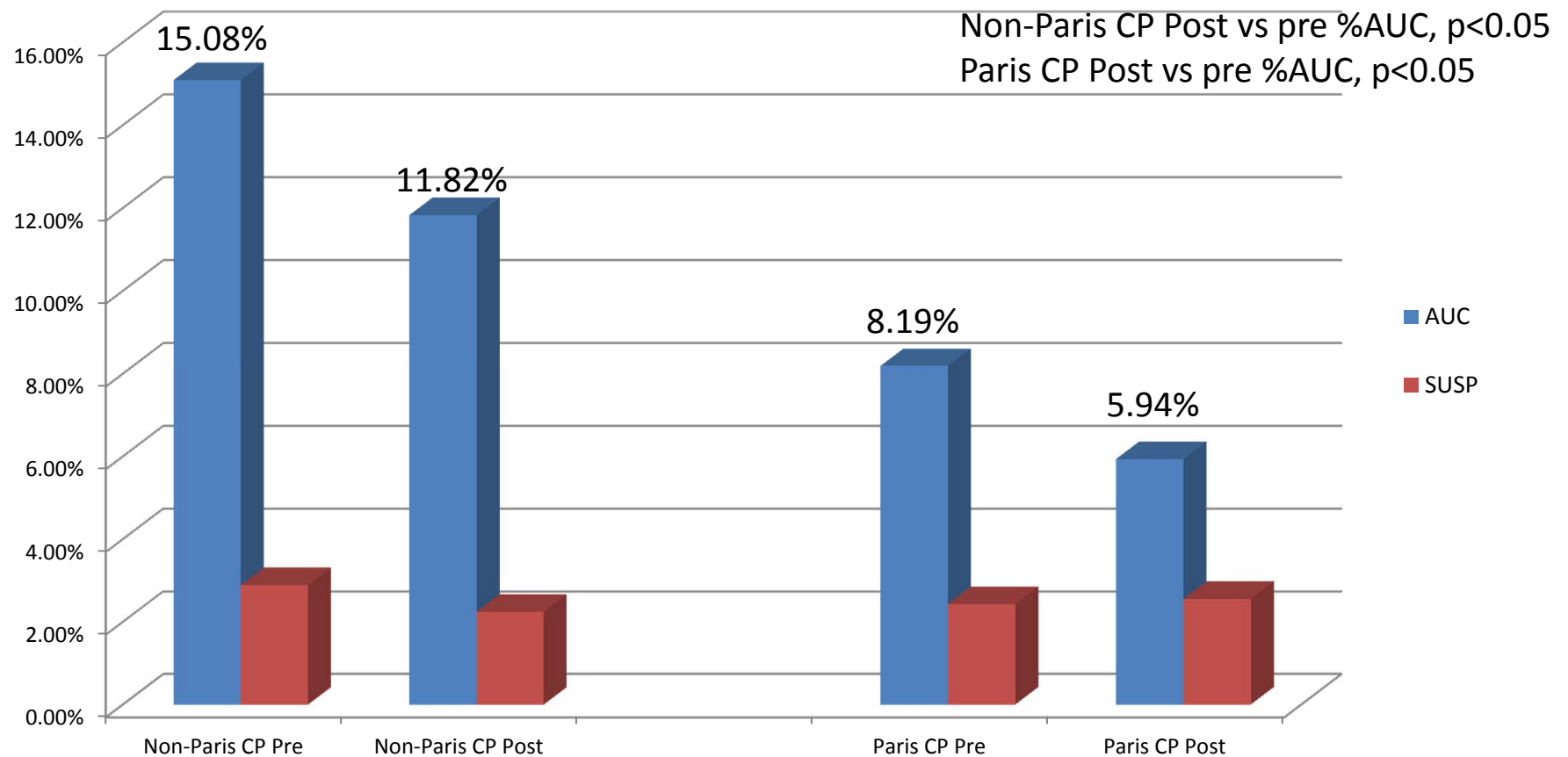
%AUC (blue) and %SUSP (red) at LUMC 2008-2016



Rate of Atypia at Loyola per pathologist



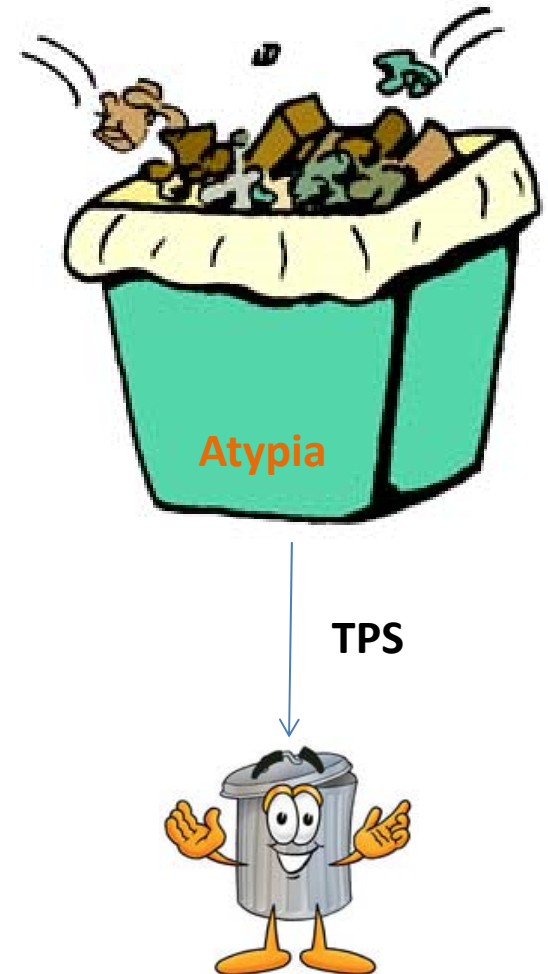
%AUC and %SUSP before and After TPS Implementation at LUMC





Final take home message

- HGUC – this is the one that matters –
Negative for HGUC
- The diagnosis “atypia” should not be used as a waste basket and dx should be based on criteria
- LGUN – new diagnostic category, based on presence of fibrovascular cores
- Not all malignant cells in urines are urothelial carcinoma
- Future studies are needed for validation of TPS





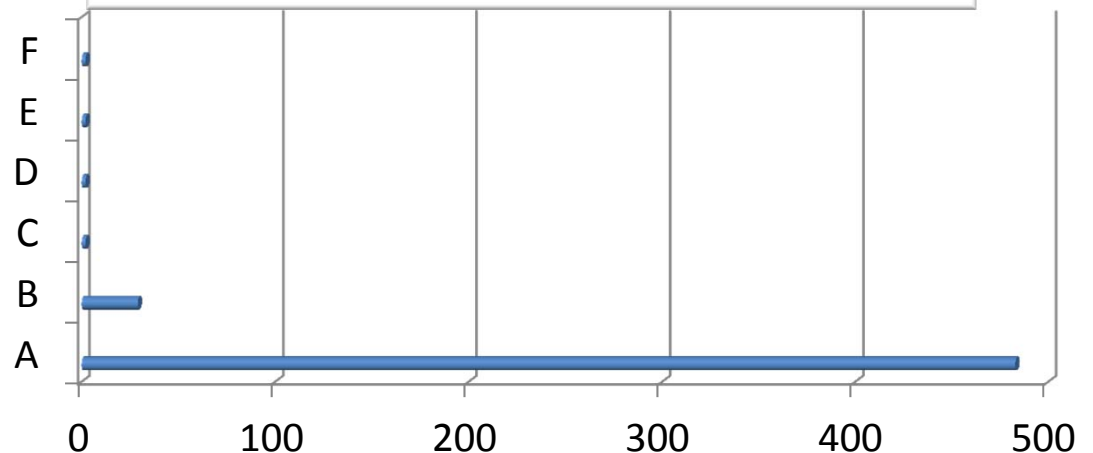
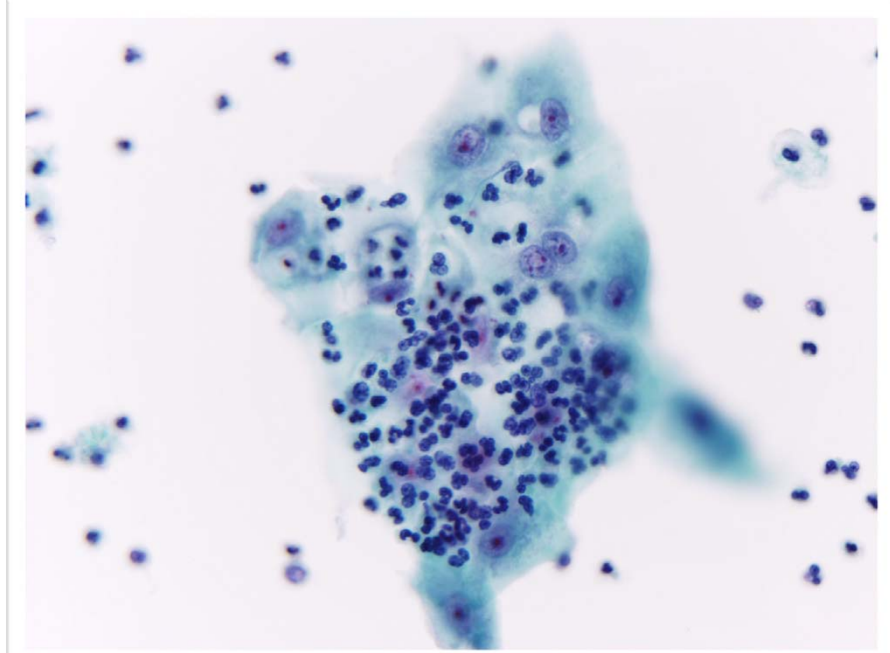
Paris System in Practice

Case 1

72-year old male with dysuria, voided urine (Washing, TP, medium mag).

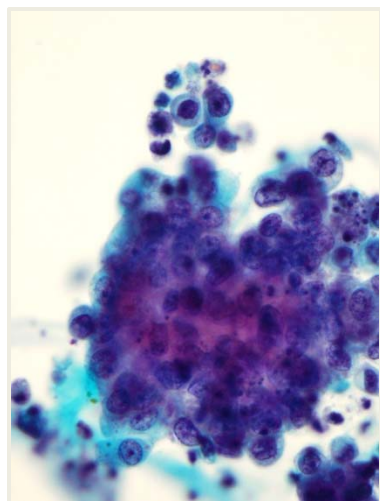
What is the best diagnosis?

- A. Negative for high grade urothelial carcinoma
- B. Atypical urothelial cells present
- C. Suspicious for high grade urothelial carcinoma
- D. High grade urothelial carcinoma
- E. Low grade urothelial neoplasm
- F. Other; positive for malignancy



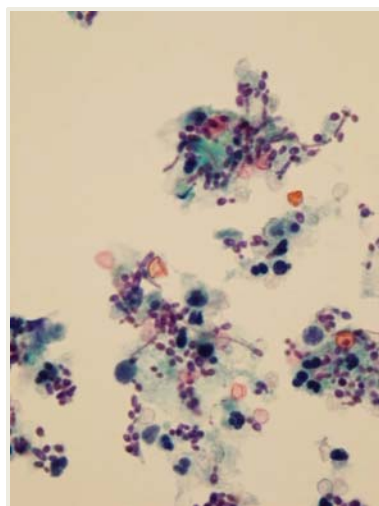
Infectious processes – Not Atypia

Acute bacterial



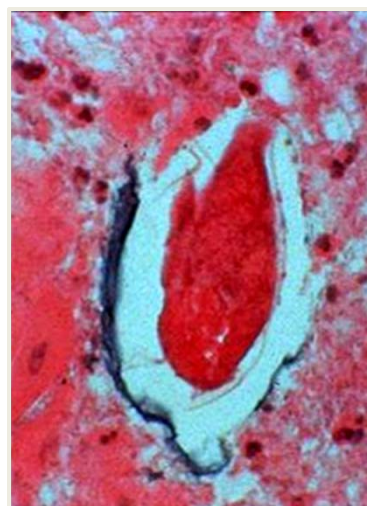
- Women
- Gram negative enteric bacilli
- Reactive atypia (Dx. Negative)

Fungal



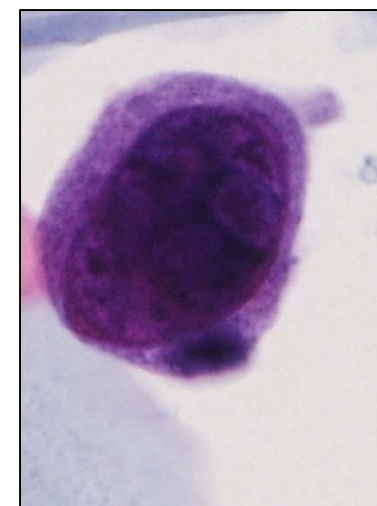
- Chronic debilitating disease (diabetes)
- Associated with acute inflammation
- Tissue damage
- Candida

Parasitic

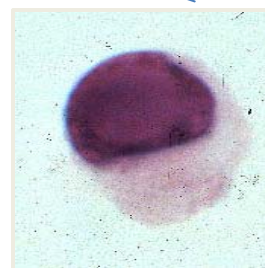


- Endemic in Africa (Egypt)
- S. Haematobium
- Squamous cell carcinoma

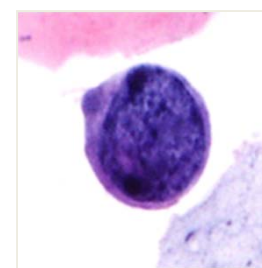
Viral



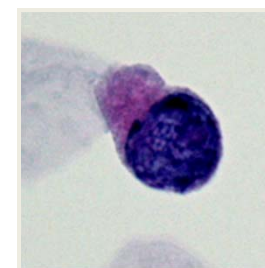
- Herpes
- Cytomegalovirus
- Adenovirus
- HPV
- Polyoma virus



Decoy cell



Net cell



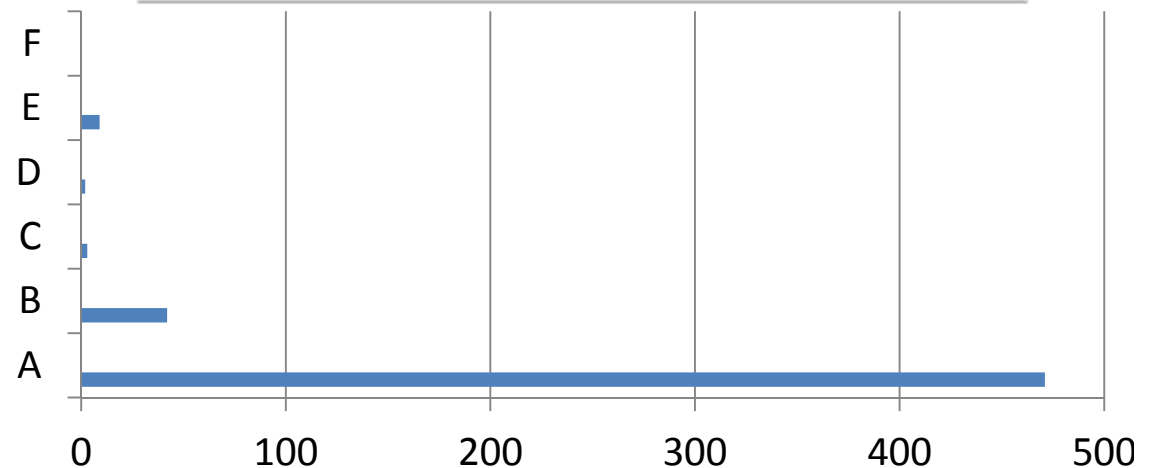
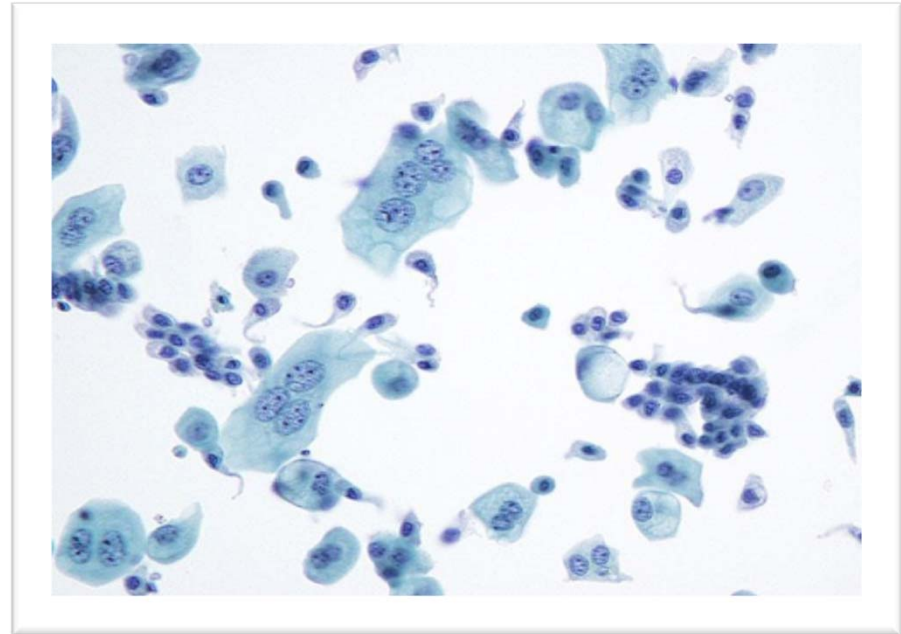
Comet cell

Case 2

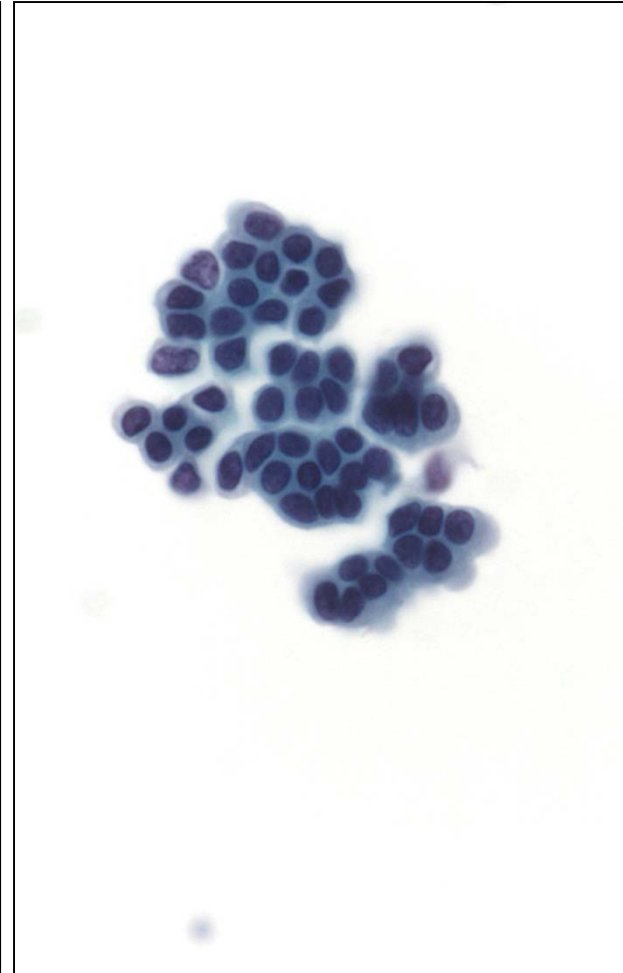
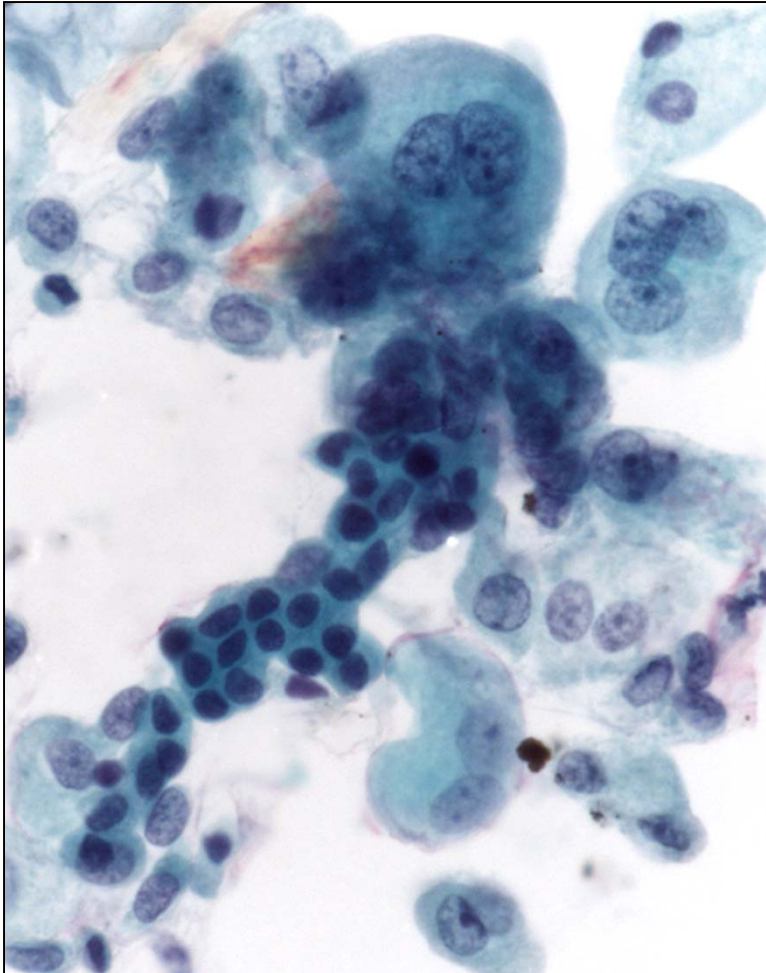
A 57-year-old man present with hematuria. Bladder barbotage.

What is the best diagnosis?

- A. Negative for high grade urothelial carcinoma
- B. Atypical urothelial cells present
- C. Suspicious for high grade urothelial carcinoma
- D. High grade urothelial carcinoma
- E. Low grade urothelial neoplasm
- F. Other; positive for malignancy



Cells from basal layer

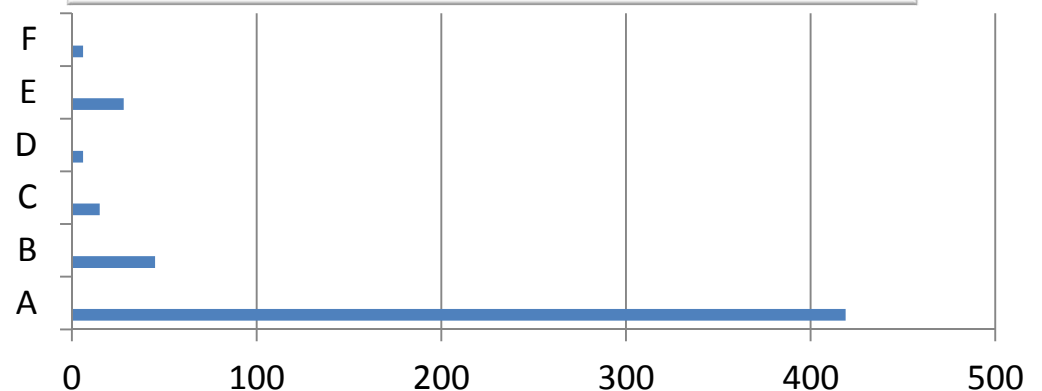
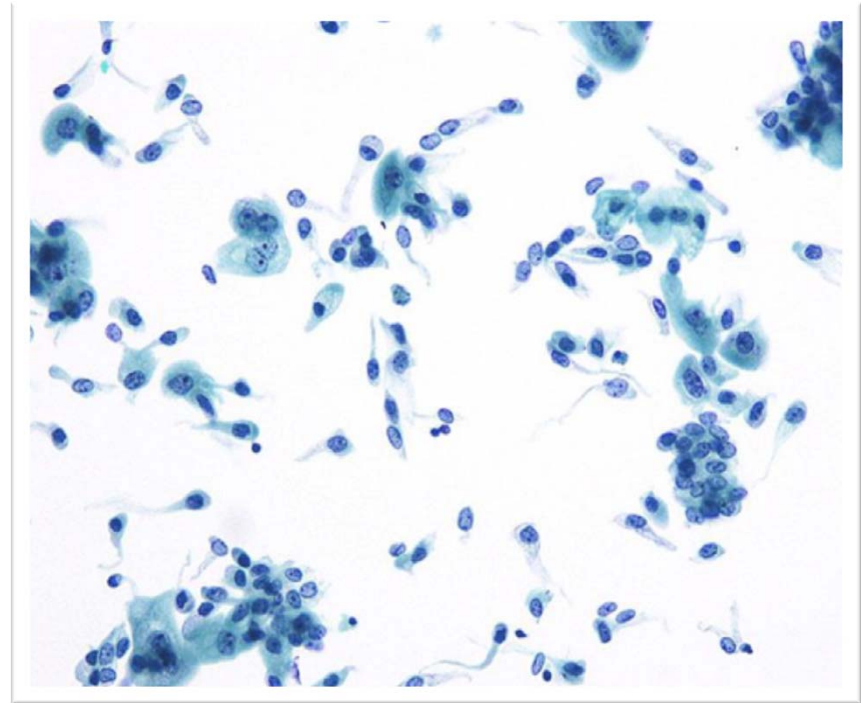


Case 3

80-year-old man present with hematuria. Bladder barbotage.

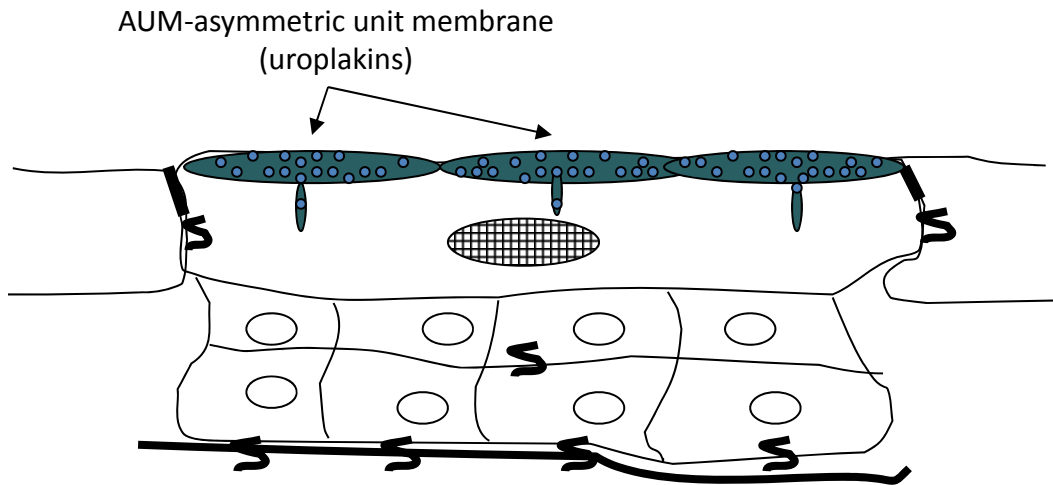
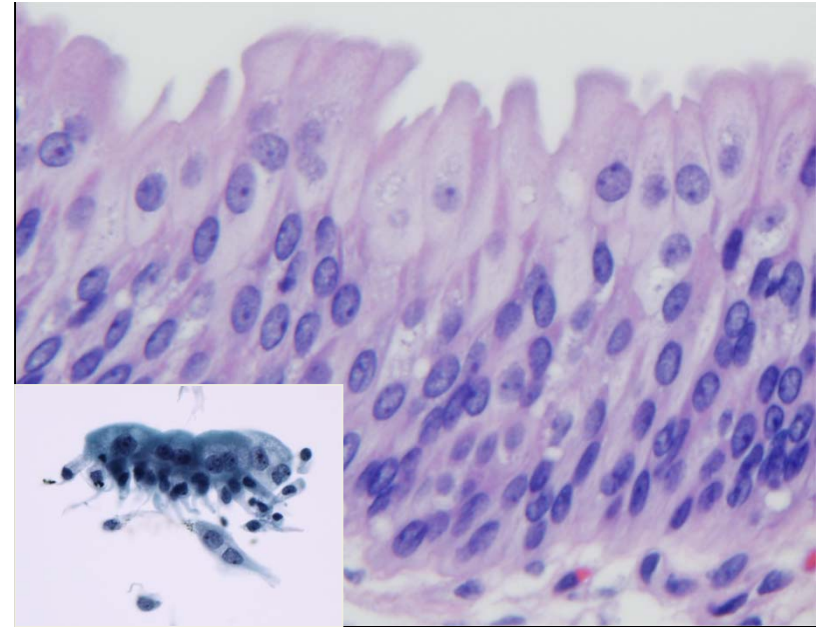
What is the best diagnosis?

- A. Negative for high grade urothelial carcinoma
- B. Atypical urothelial cells present
- C. Suspicious for high grade urothelial carcinoma
- D. High grade urothelial carcinoma
- E. Low grade urothelial neoplasm
- F. Other; positive for malignancy

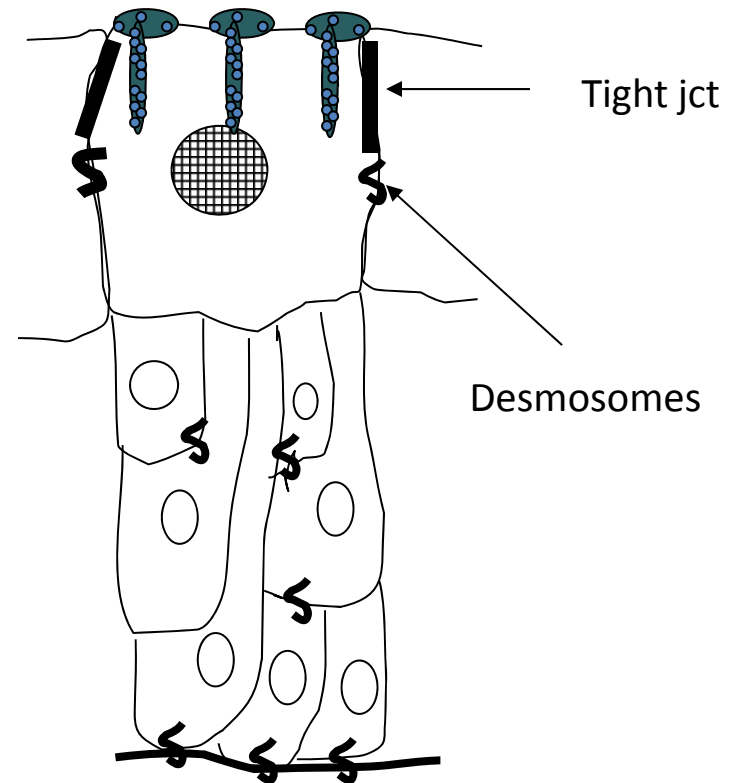


Function of the urothelium

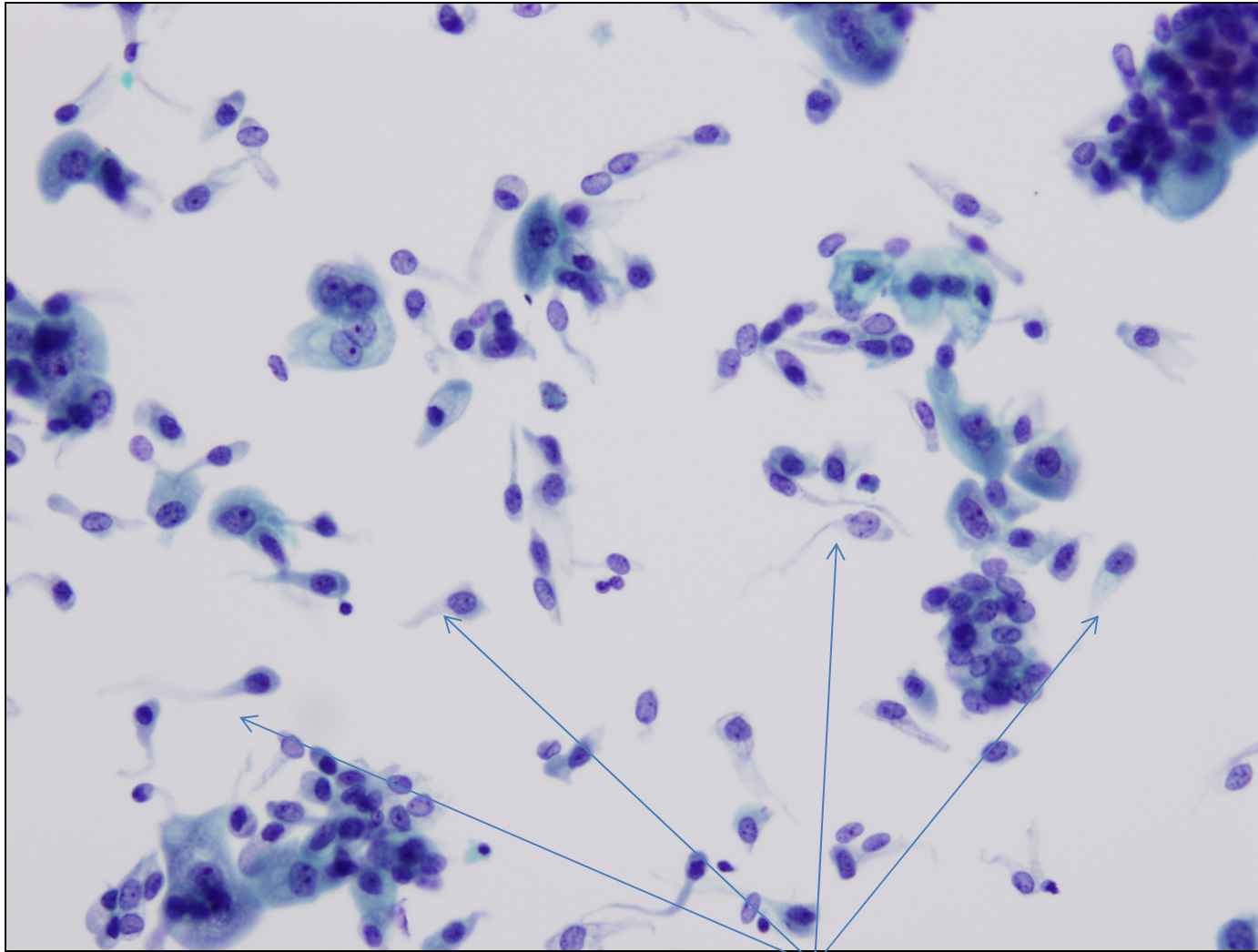
- Urine - blood barrier
- Ability to dilate and contract



Adopted from Koss



What cells to expect



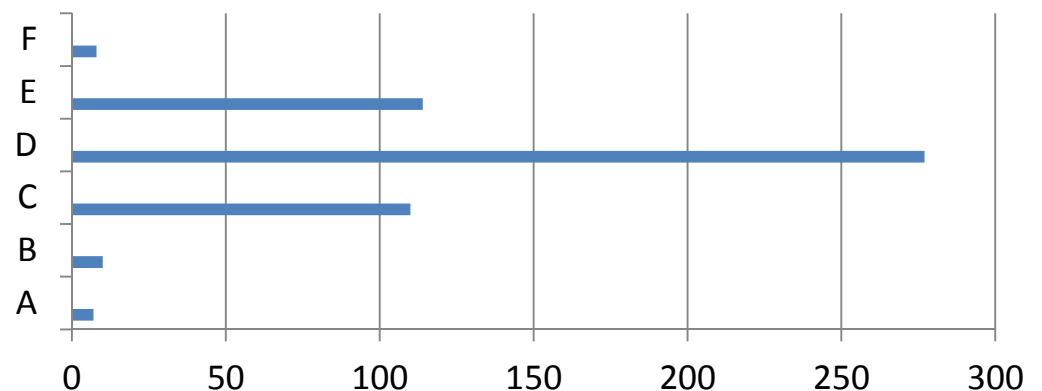
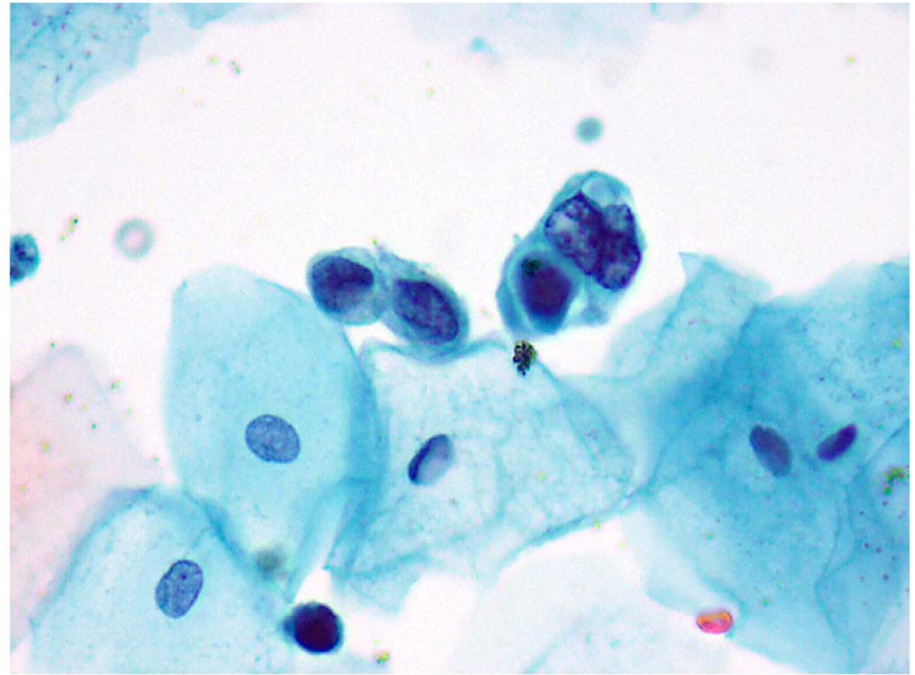
Circulariform cells

Case 4

A 73-year-old man with hematuria. Bladder barbotage.

What is the best diagnosis?

- A. Negative for high grade urothelial carcinoma
- B. Atypical urothelial cells present
- C. Suspicious for high grade urothelial carcinoma
- D. High grade urothelial carcinoma
- E. Low grade urothelial neoplasm
- F. Other; positive for malignancy



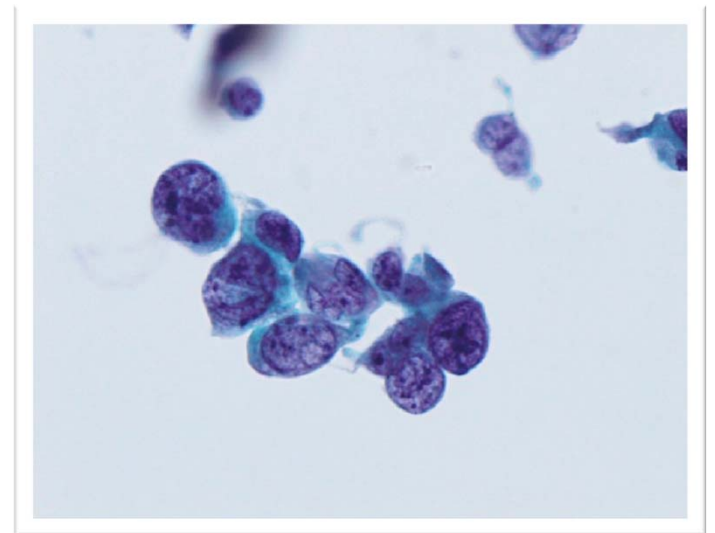
Criteria for Suspicious for HGUC

- Non-superficial and non-degenerated urothelial cells with an high **N/C ratio > 0.7** (required)
- **Hyperchromasia** (compared to the umbrella cells or the intermediate squamous cell nucleus) (required)

and one of the following:

- **Irregular clumpy chromatin**
- **Irregular nuclear membranes**

<10 cells

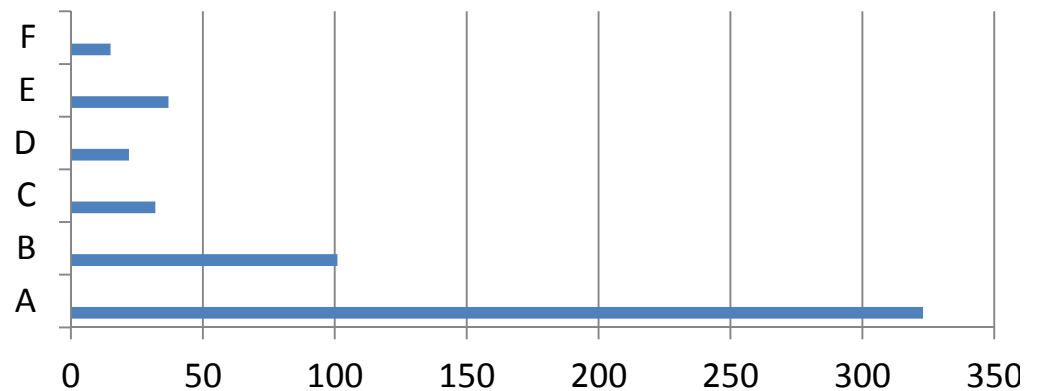
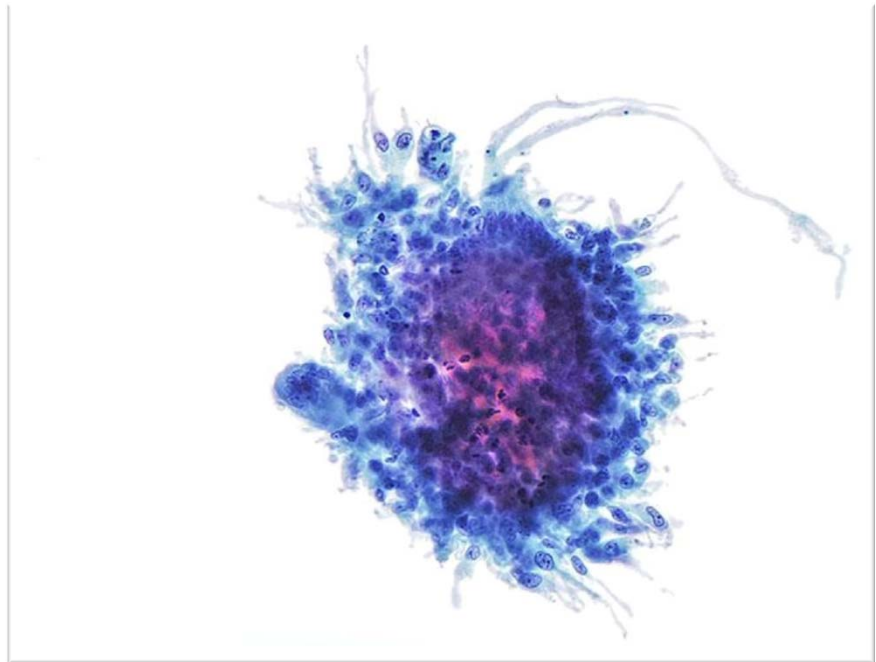


Case 5

The patient is a 63-year-old man with a history of urothelial carcinoma in situ. Bladder barbotage.

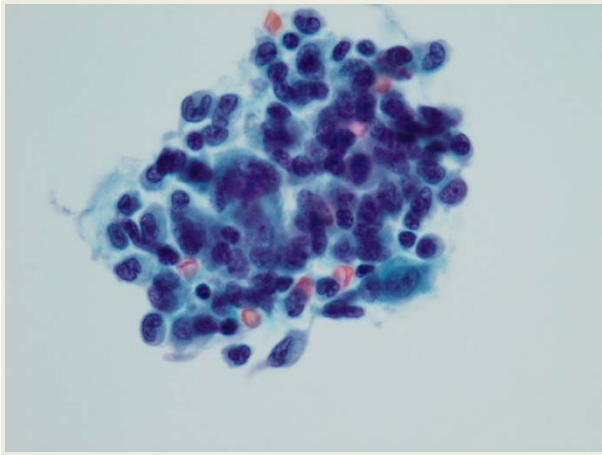
What is the best diagnosis?

- A. Negative for high grade urothelial carcinoma
- B. Atypical urothelial cells present
- C. Suspicious for high grade urothelial carcinoma
- D. High grade urothelial carcinoma
- E. Low grade urothelial neoplasm
- F. Other; positive for malignancy

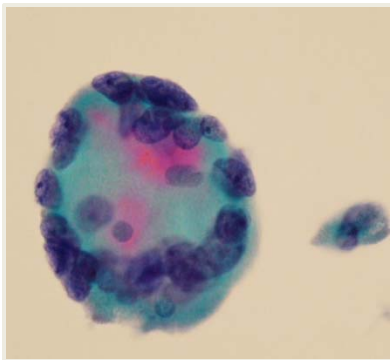


Treatment effect

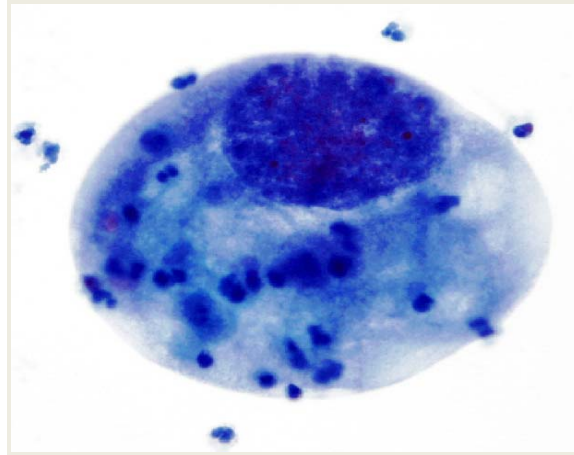
BCG



- Granulomas
- Multinucleated giant cells
- Inflammation

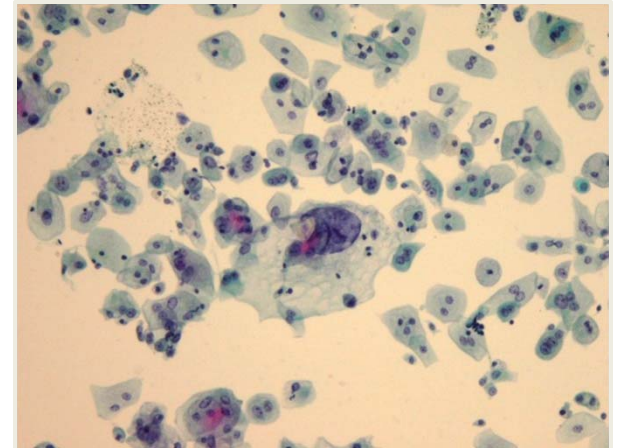


Thiotepa



- Marked nuclear enlargement
- Umbrella cells mostly affected
- Multinucleation
- Hyperchromatic, granular chromatin

XRT



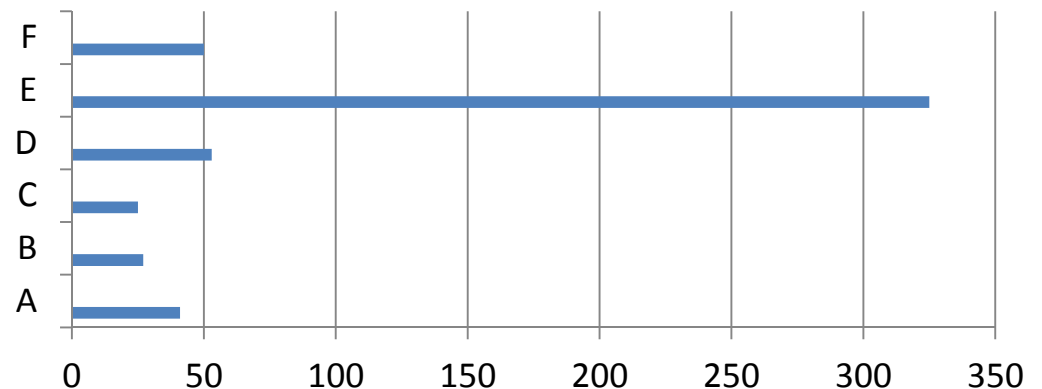
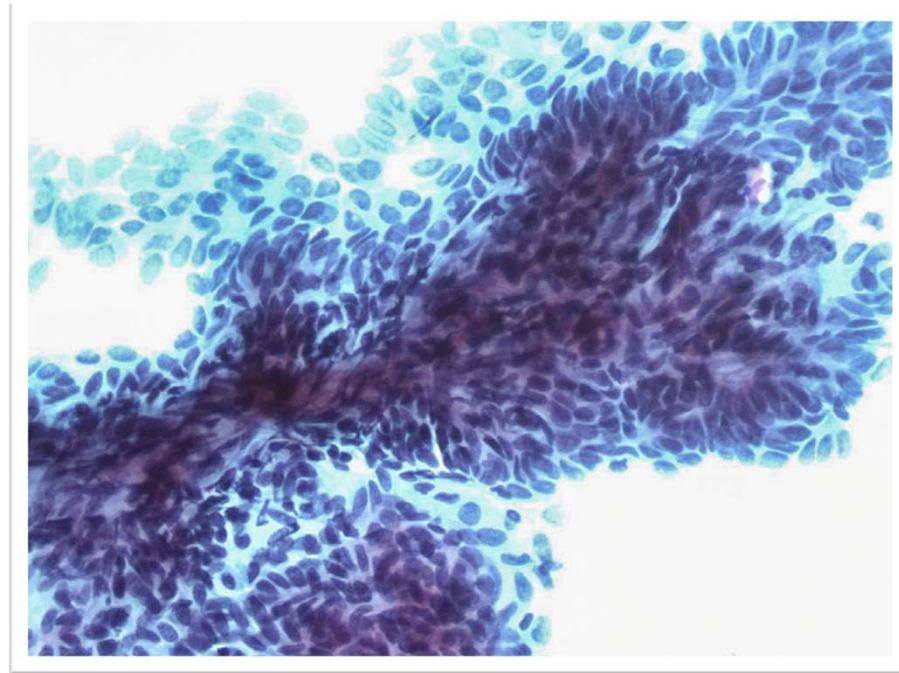
- Cytomegaly
- Nucleomegaly
- Preserved N/C ratio
- Multinucleation
- Nuclear and cytoplasmic vacuoles

Case 6

55-year-old man present with hematuria. CT shows vague thickening/nodular area in the pelvicalyceal system. Renal pelvis brushing.

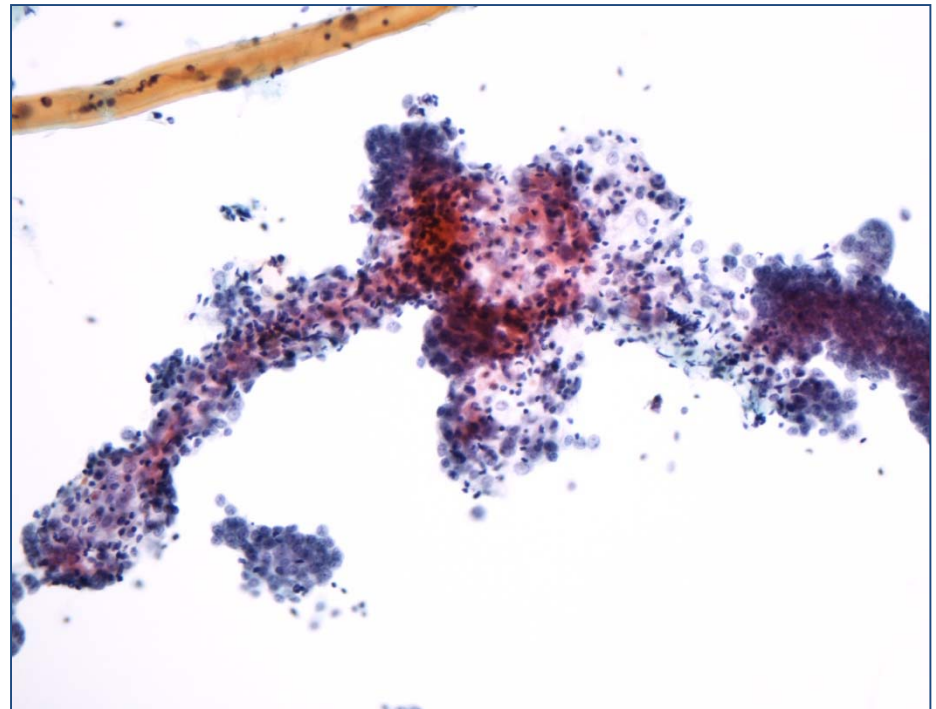
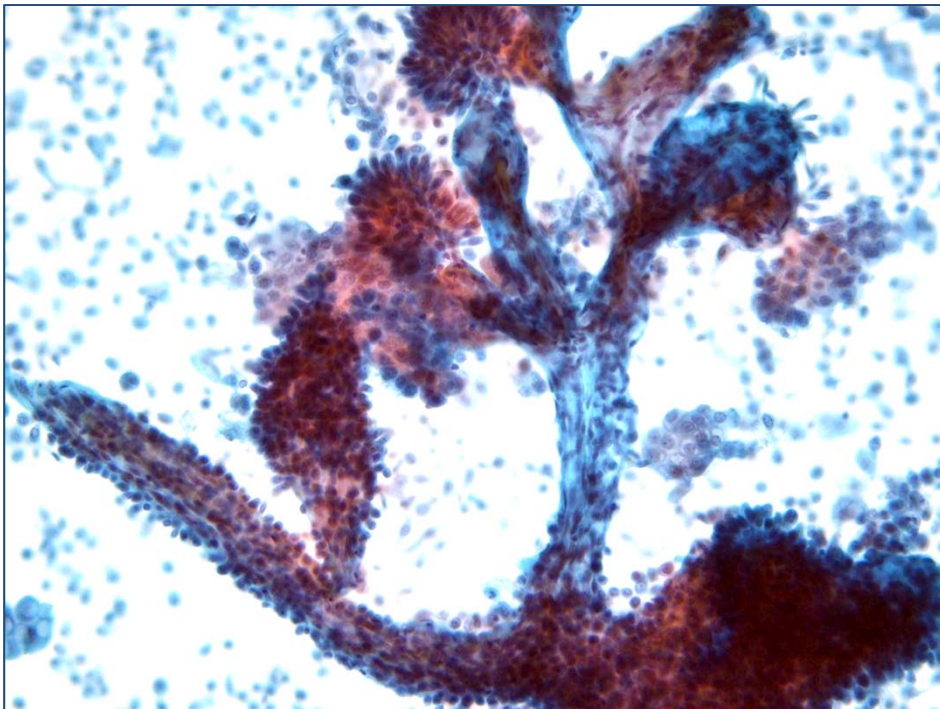
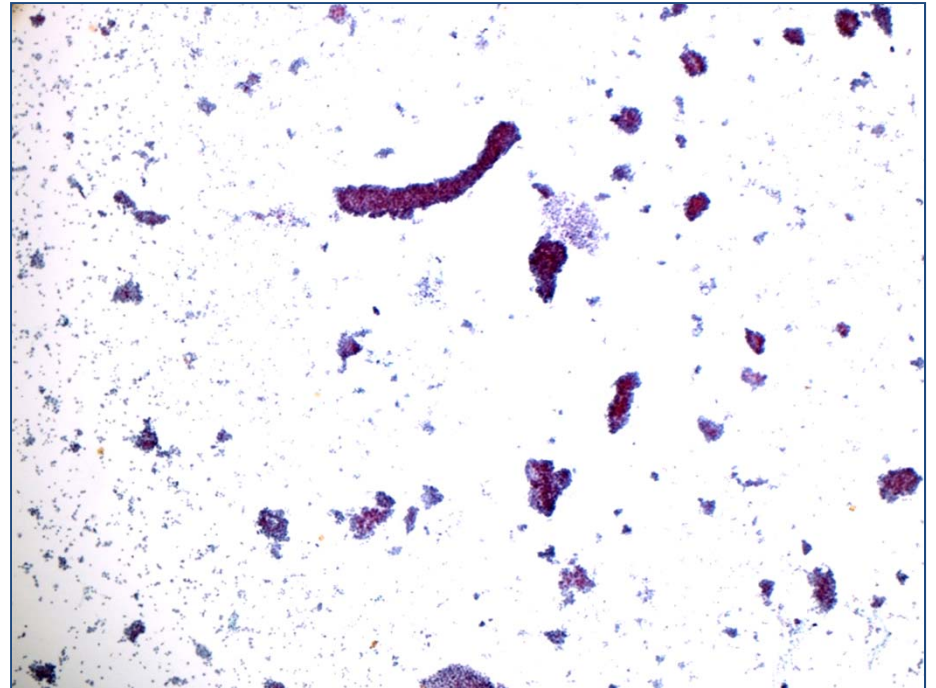
What is the best diagnosis?

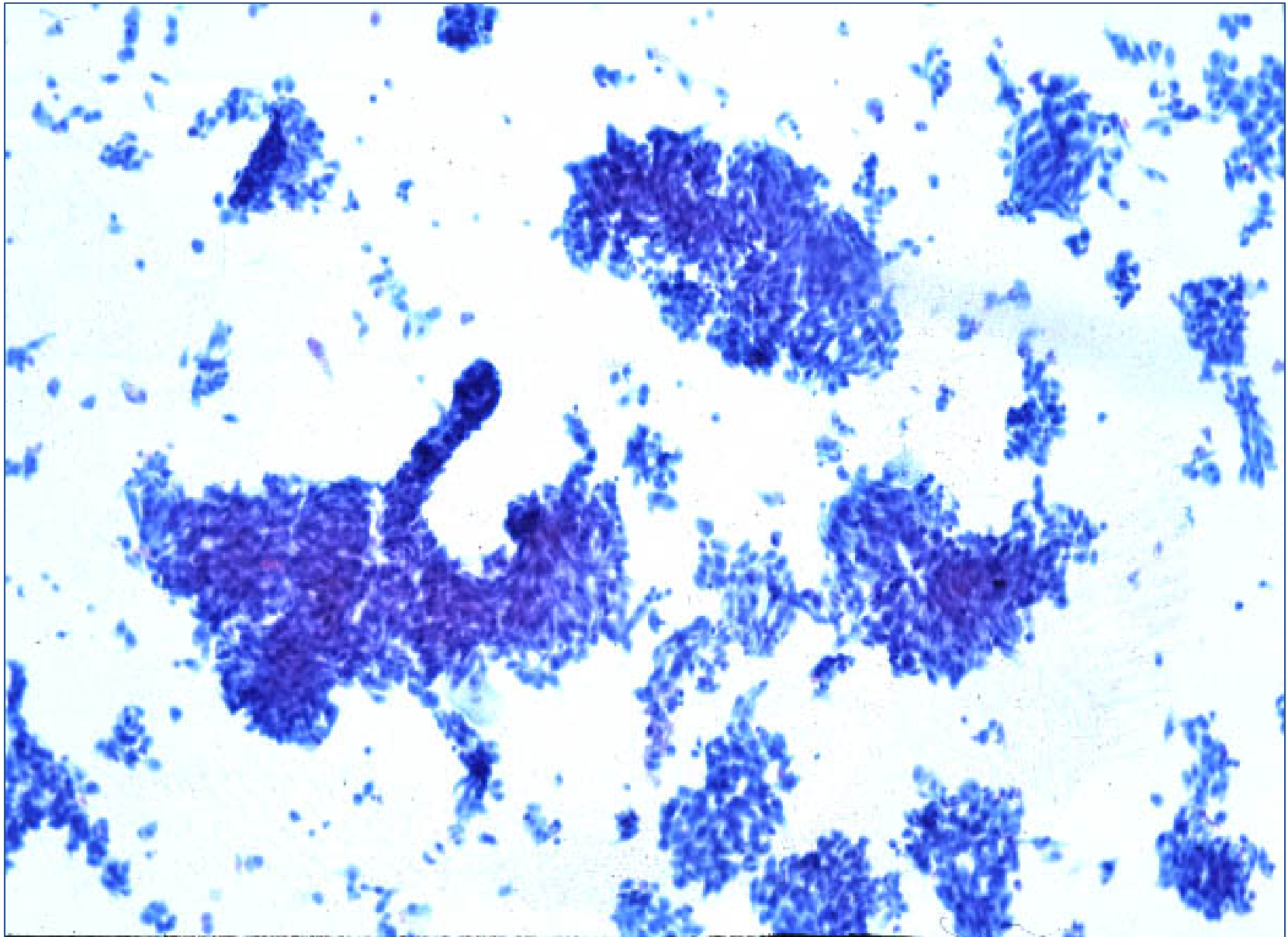
- A. Negative for high grade urothelial carcinoma
- B. Atypical urothelial cells present
- C. Suspicious for high grade urothelial carcinoma
- D. High grade urothelial carcinoma
- E. Low grade urothelial neoplasm
- F. Other; positive for malignancy



LGUN

- Fibrovascular cores
- Central capillary vessel





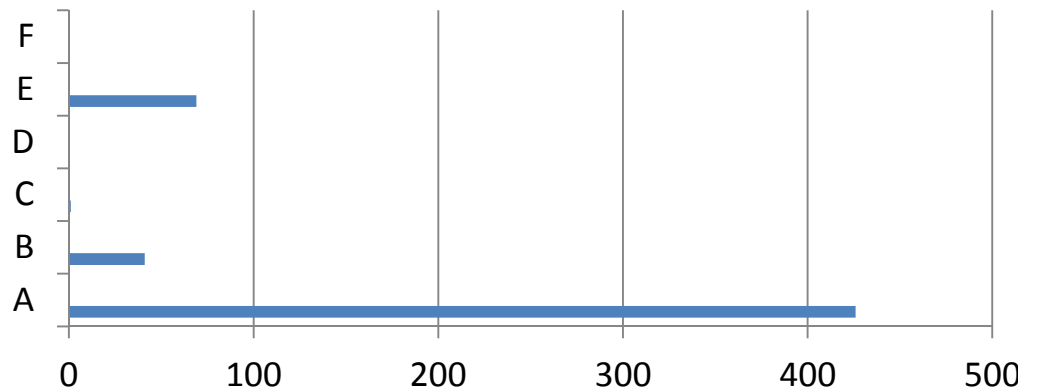
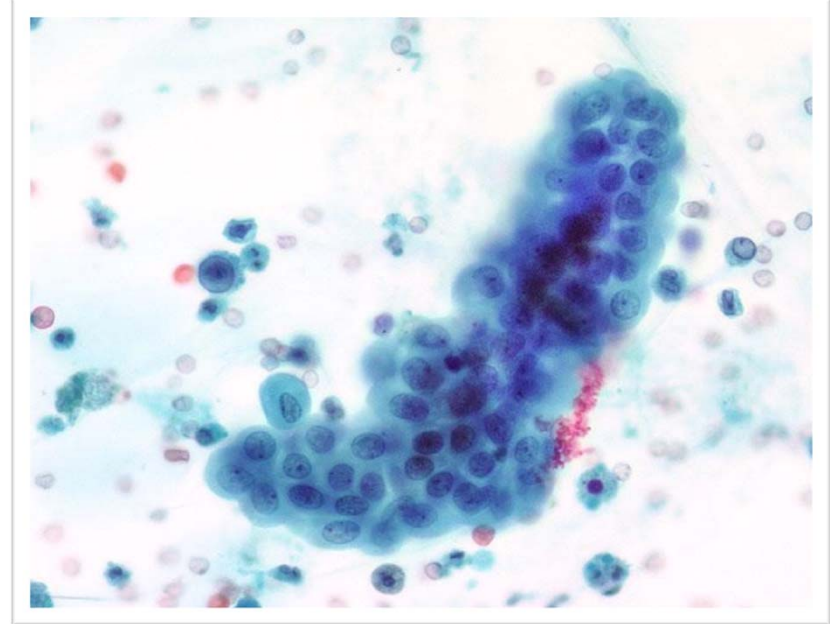
"A secure diagnosis of a LG UC can be established when tumor fragments with a clearly identified connective tissue stalk or a central capillary vessel are present in the sediment" *Koss*

Case 7

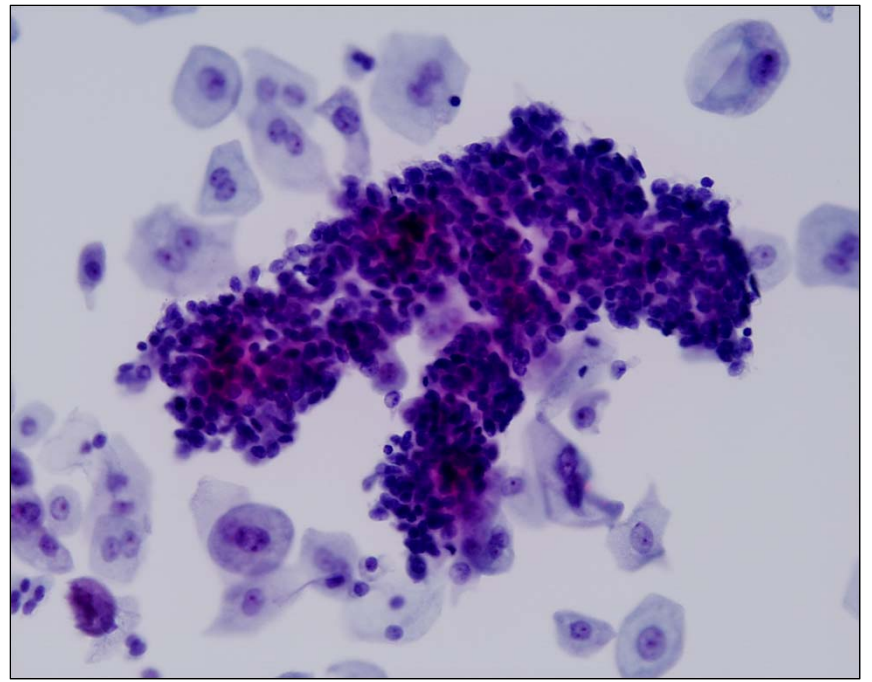
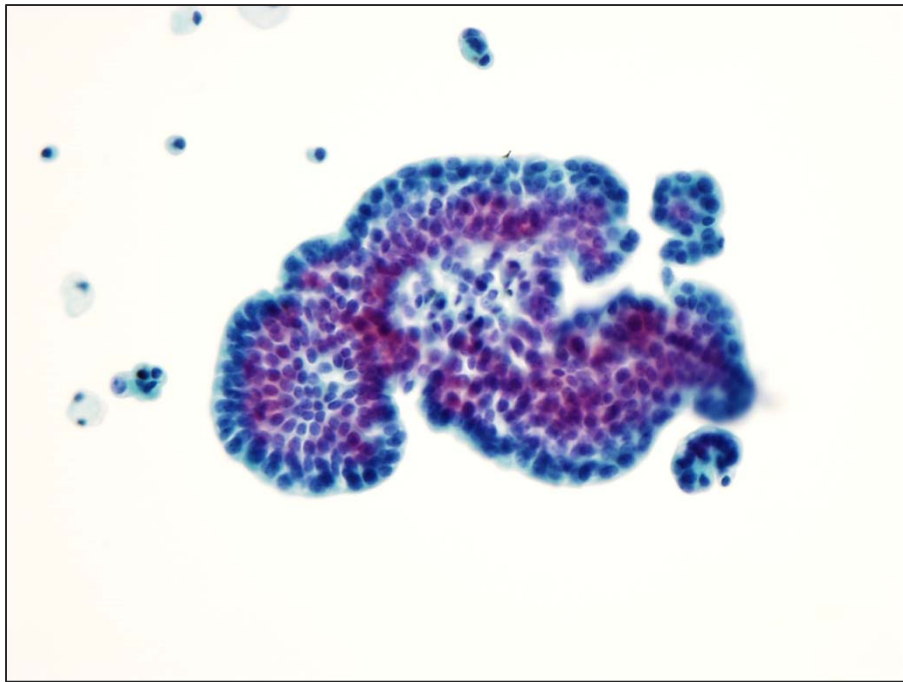
The patient is a 55-year-old woman with recurrent urolithiasis, and no history of urothelial carcinoma. Bladder barbotage.

What is the best diagnosis?

- A. Negative for high grade urothelial carcinoma
- B. Atypical urothelial cells present
- C. Suspicious for high grade urothelial carcinoma
- D. High grade urothelial carcinoma
- E. Low grade urothelial neoplasm
- F. Other; positive for malignancy



Instrumentation - Not Atypia

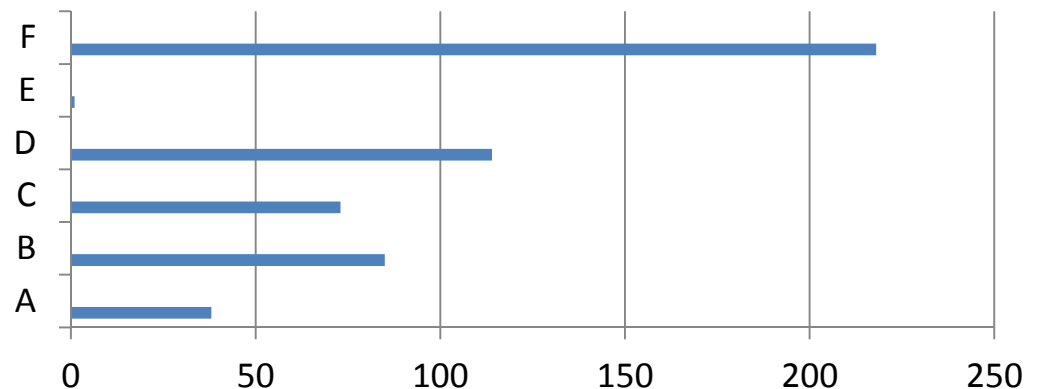
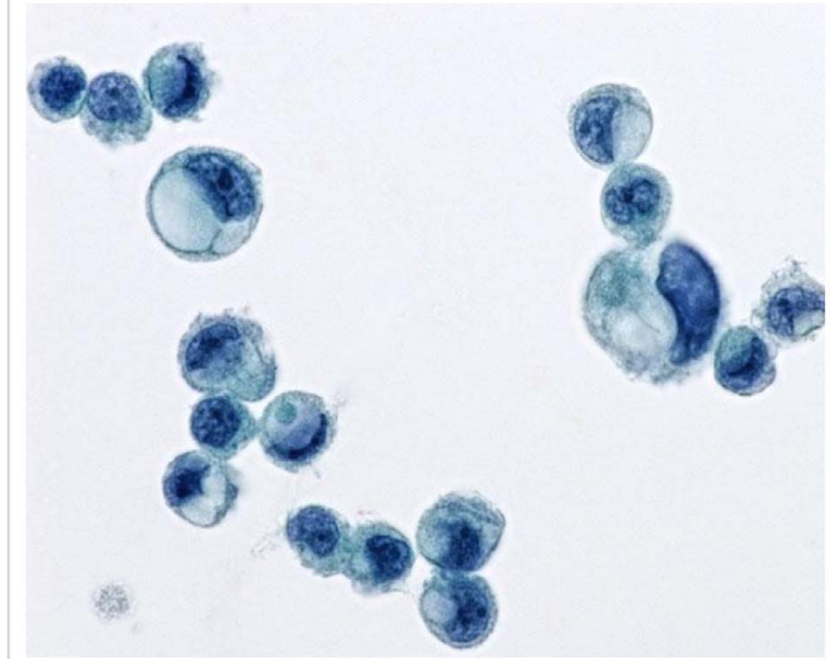


Case 8

A 77-year-old man presents with hematuria. Normal serum PSA.

What is the best diagnosis?

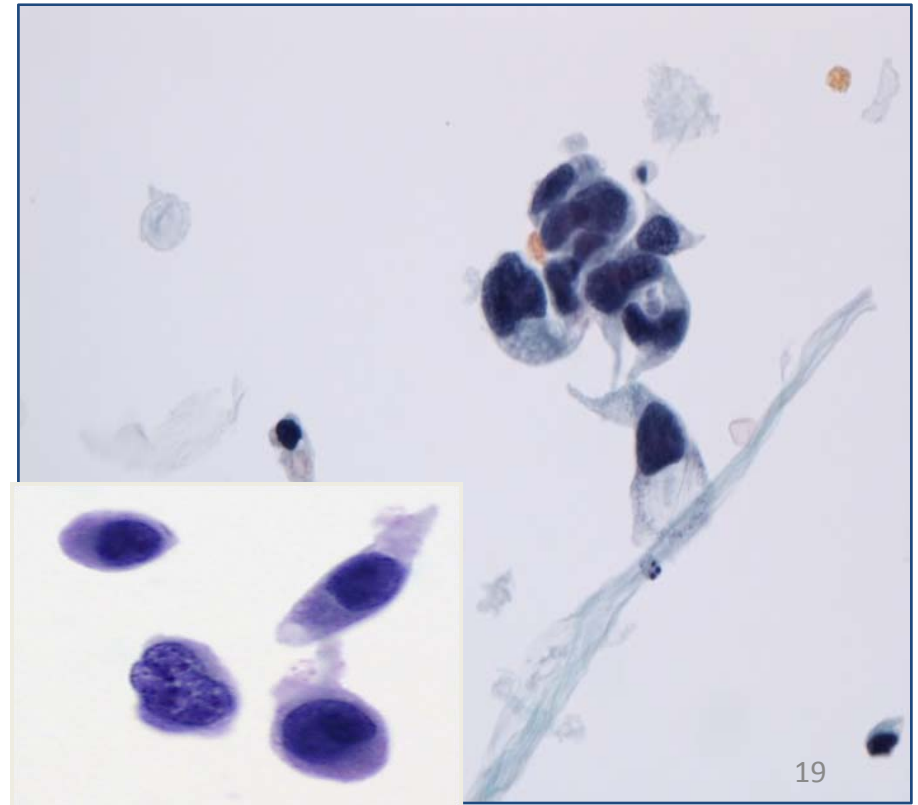
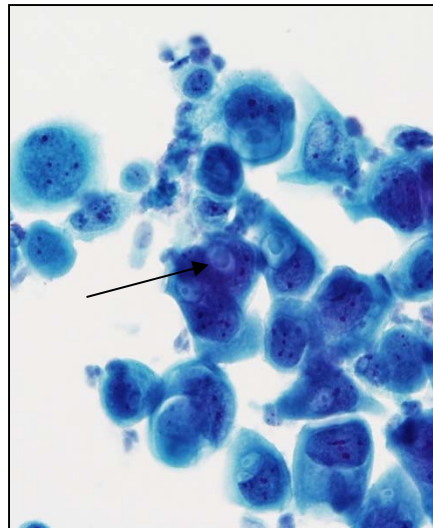
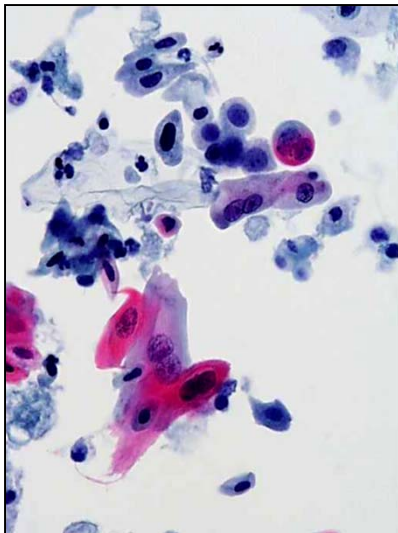
- A. Negative for high grade urothelial carcinoma
- B. Atypical urothelial cells present
- C. Suspicious for high grade urothelial carcinoma
- D. High grade urothelial carcinoma
- E. Low grade urothelial neoplasm
- F. Other; positive for malignancy



High grade urothelial carcinoma

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

- **High nuclear cytoplasmic ratio**
- **Nuclear hyperchromasia**
- **Coarse, clumped chromatin**
- **Irregular nuclear membranes**



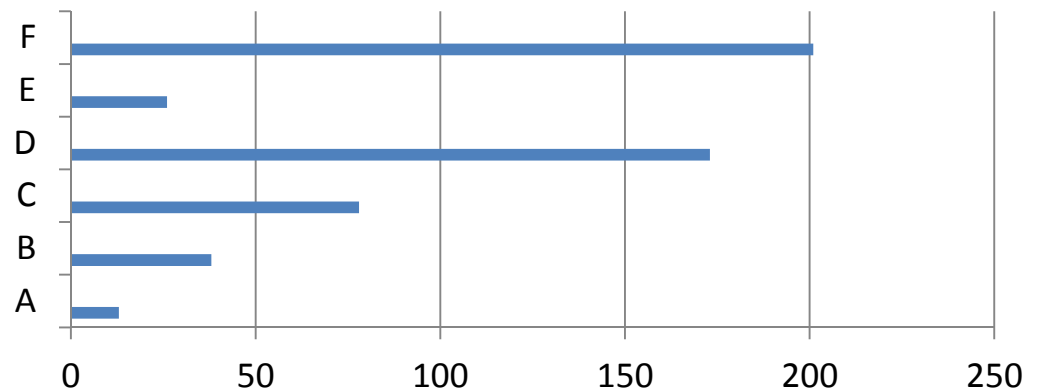
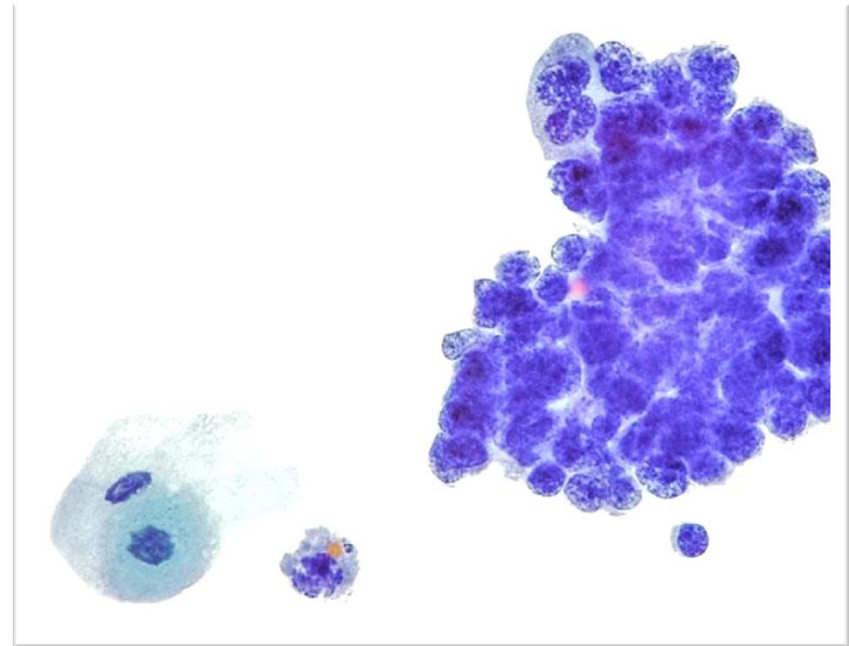
Case 9

A 68-year-old man present with
painless hematuria.

Bladder barbotage.

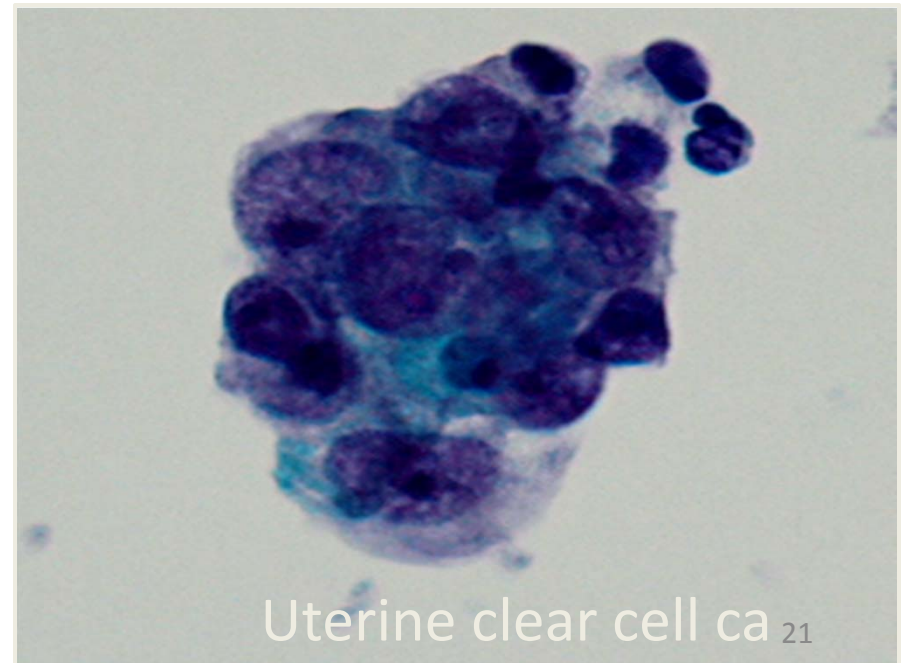
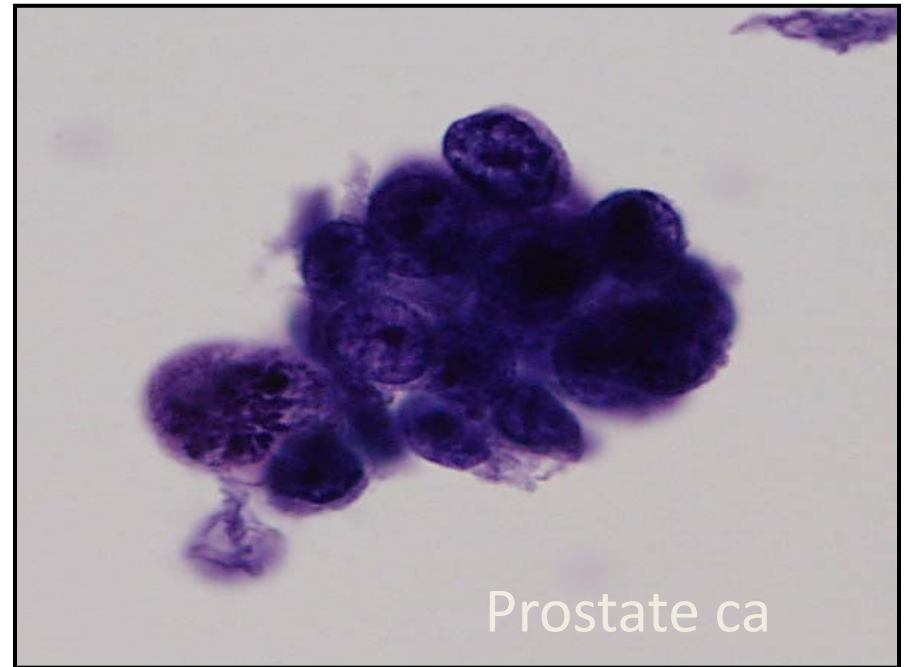
What is the best diagnosis?

- A. Negative for high grade urothelial carcinoma
- B. Atypical urothelial cells present
- C. Suspicious for high grade urothelial carcinoma
- D. High grade urothelial carcinoma
- E. Low grade urothelial neoplasm
- F. Other; positive for malignancy

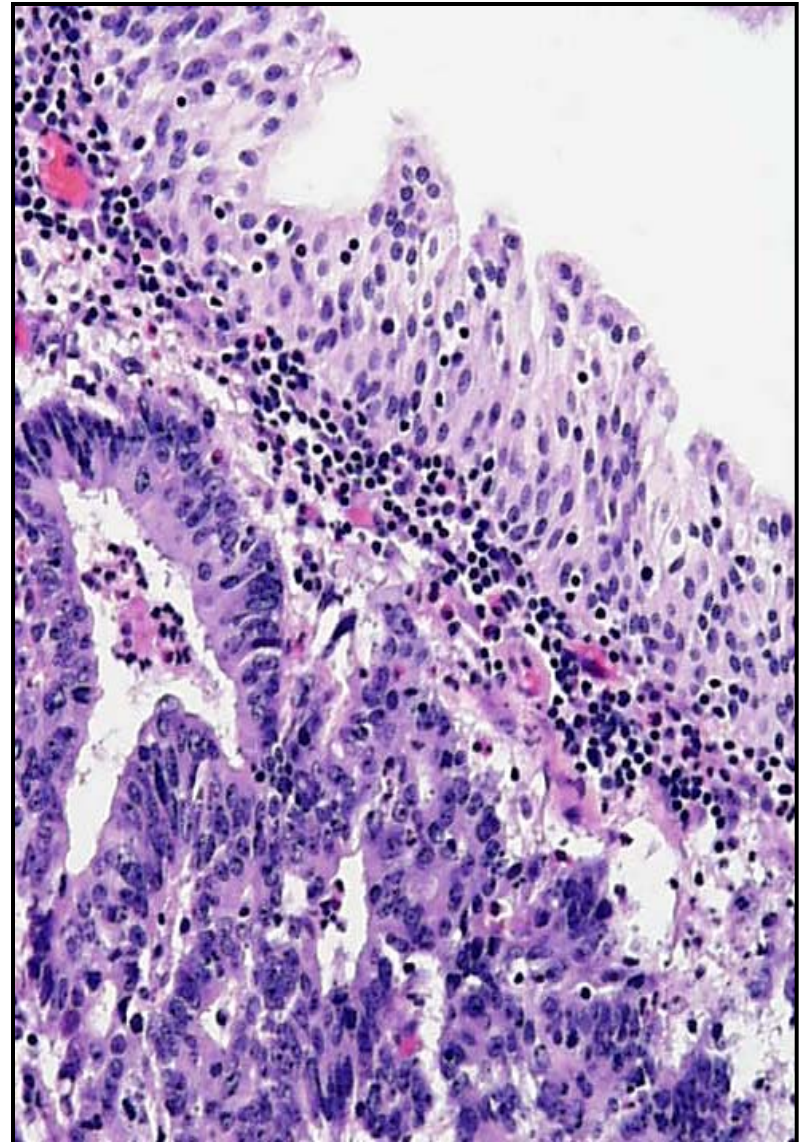
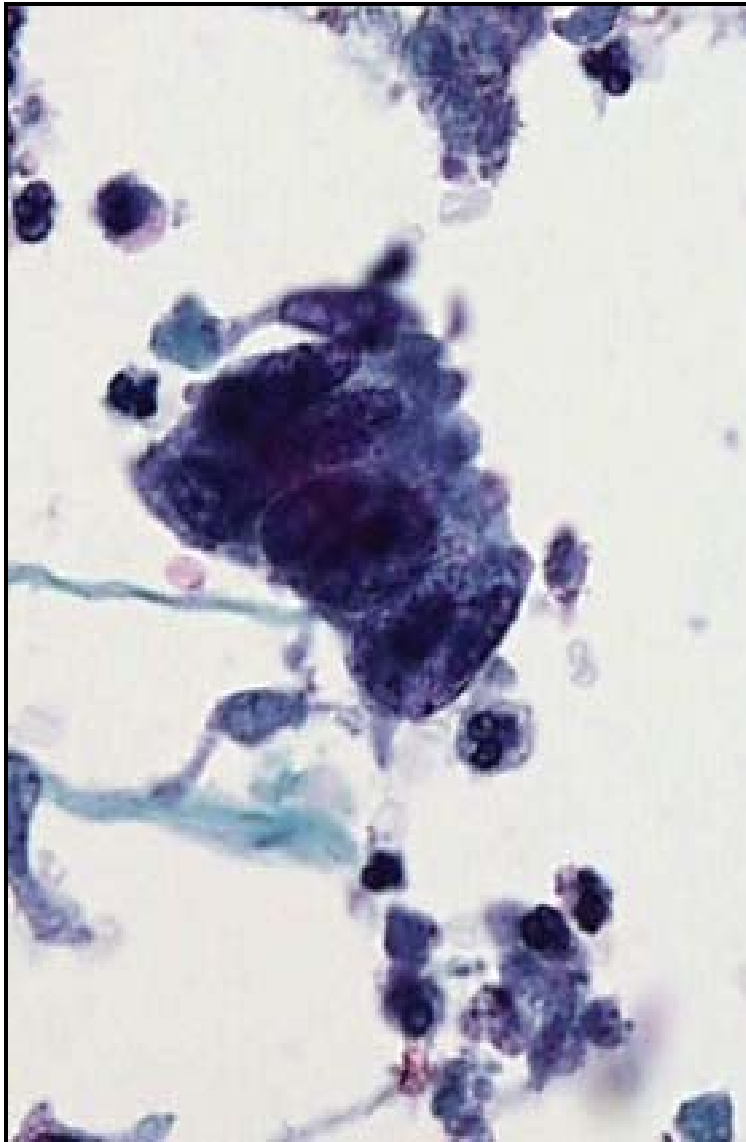


Other bladder neoplasms

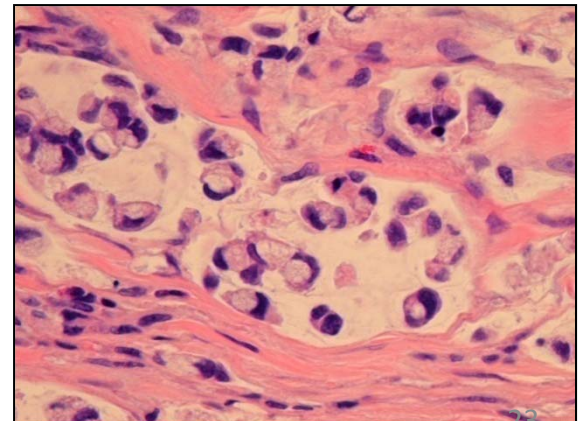
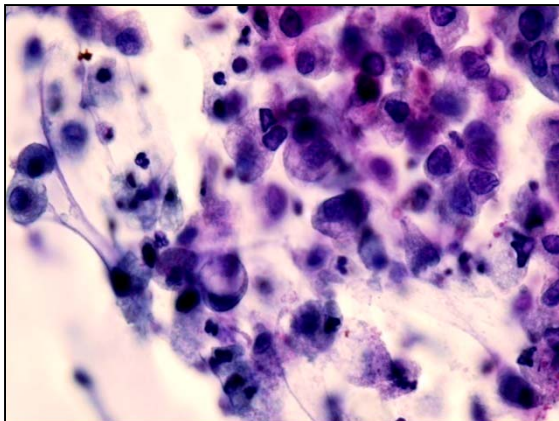
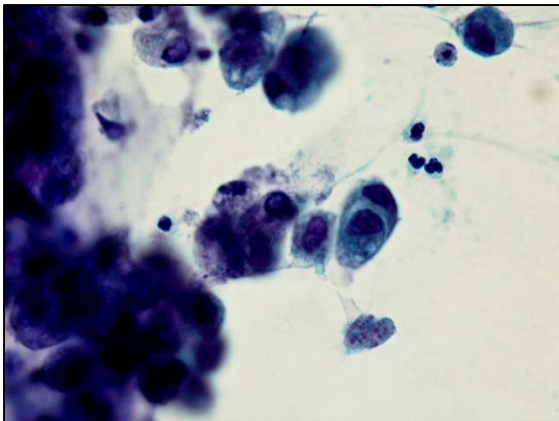
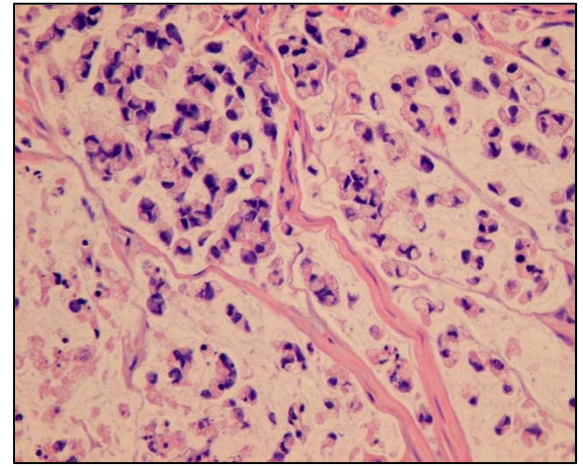
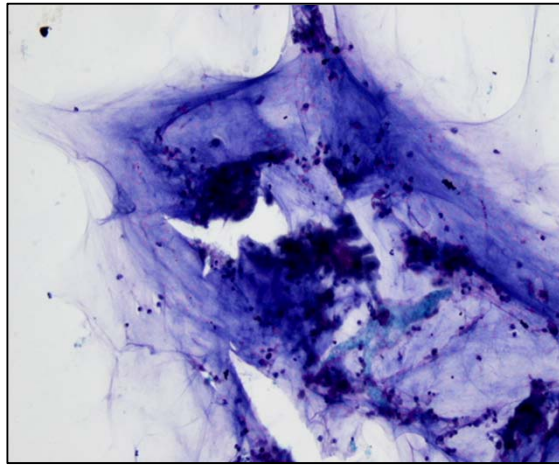
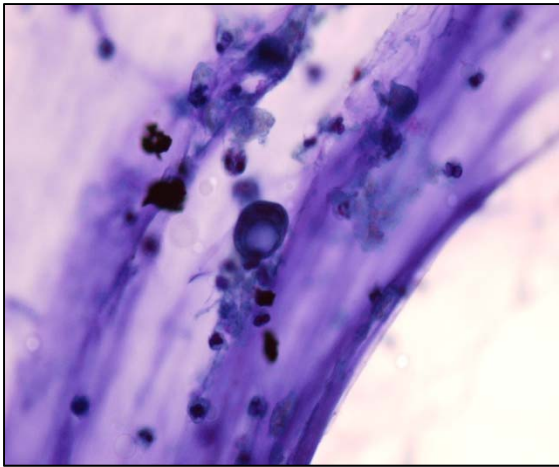
- PRIMARY
 - Squamous cell carcinoma
 - Adenocarcinoma
 - Small cell carcinoma
 - Carcinosarcoma
- SECONDARY
 - Majority (~70%) – direct invasion: prostate, cervix, uterus, GI tract
 - Distant metastases – malignant melanoma, carcinomas of stomach, breast, kidney and lung



Bladder washing - colonic adenocarcinoma



Mucinous adenocarcinoma urachal origin

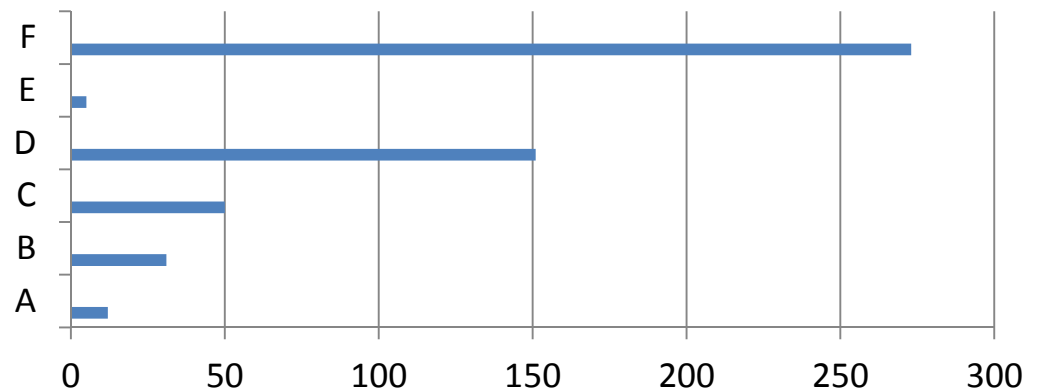
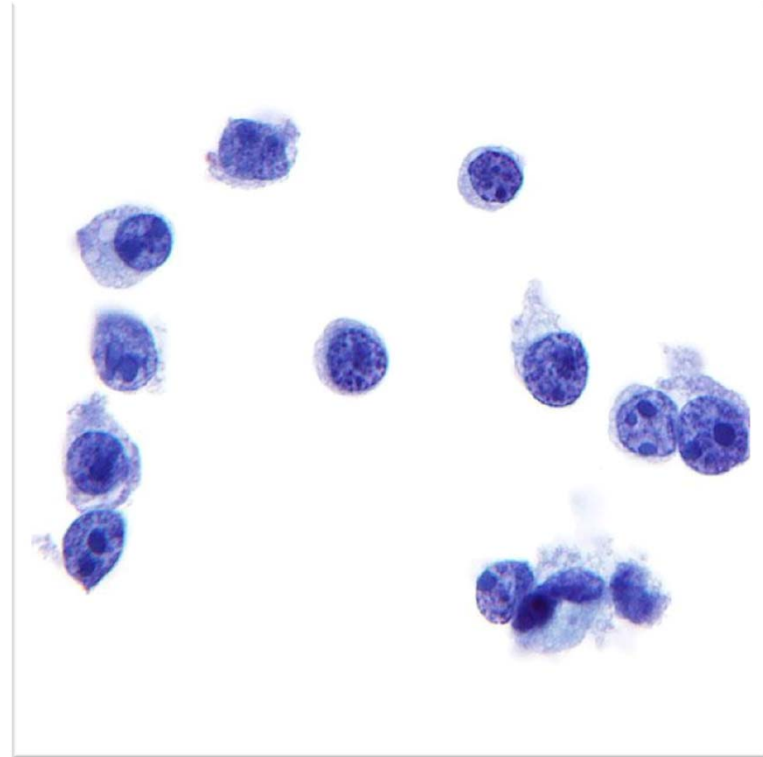


Case 10

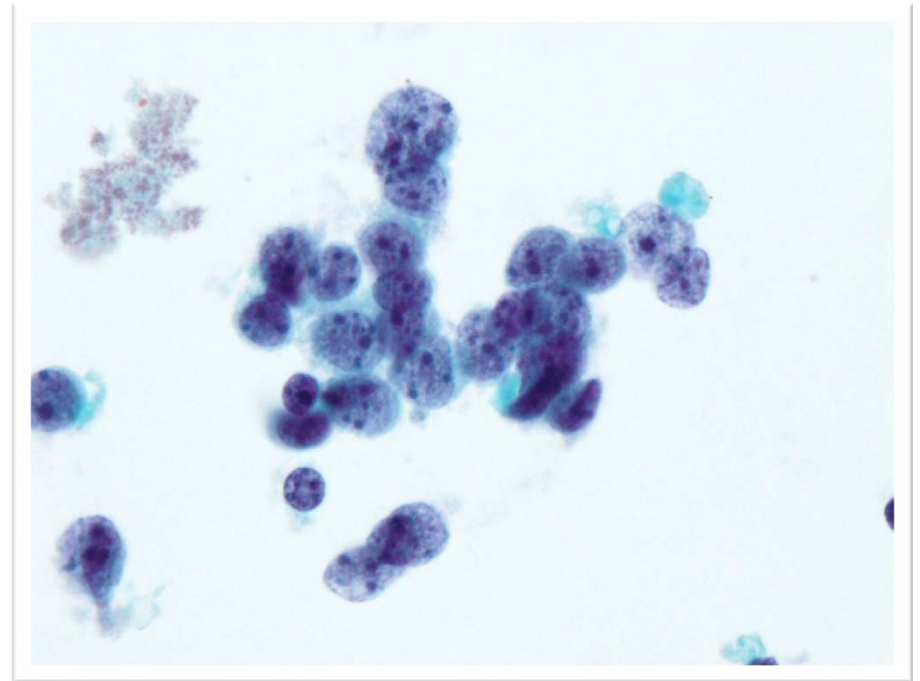
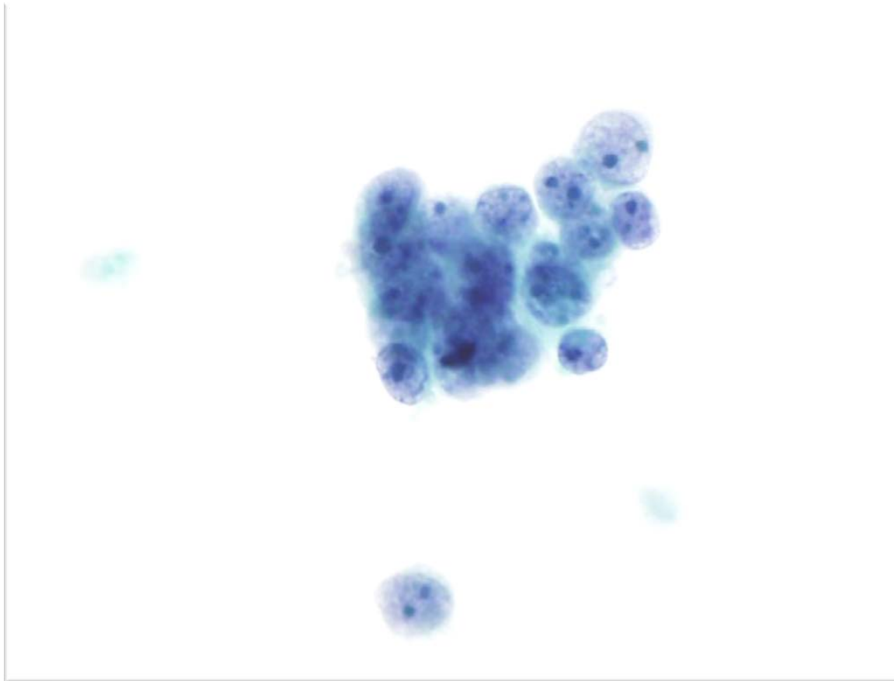
A 72-year-old man presents with post-void dribbling and suprapubic discomfort.

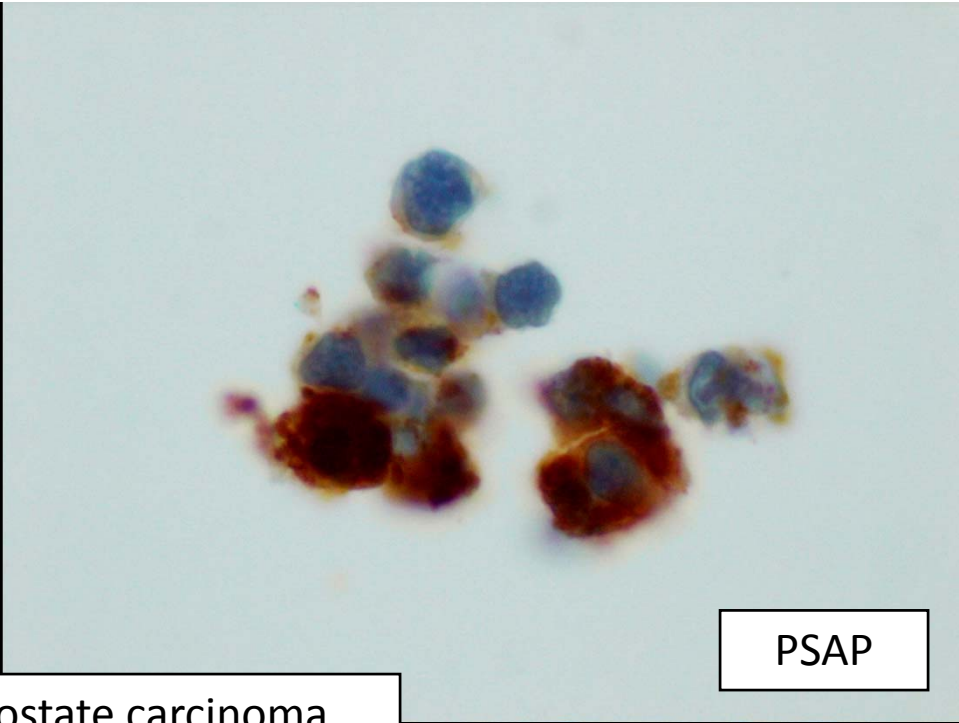
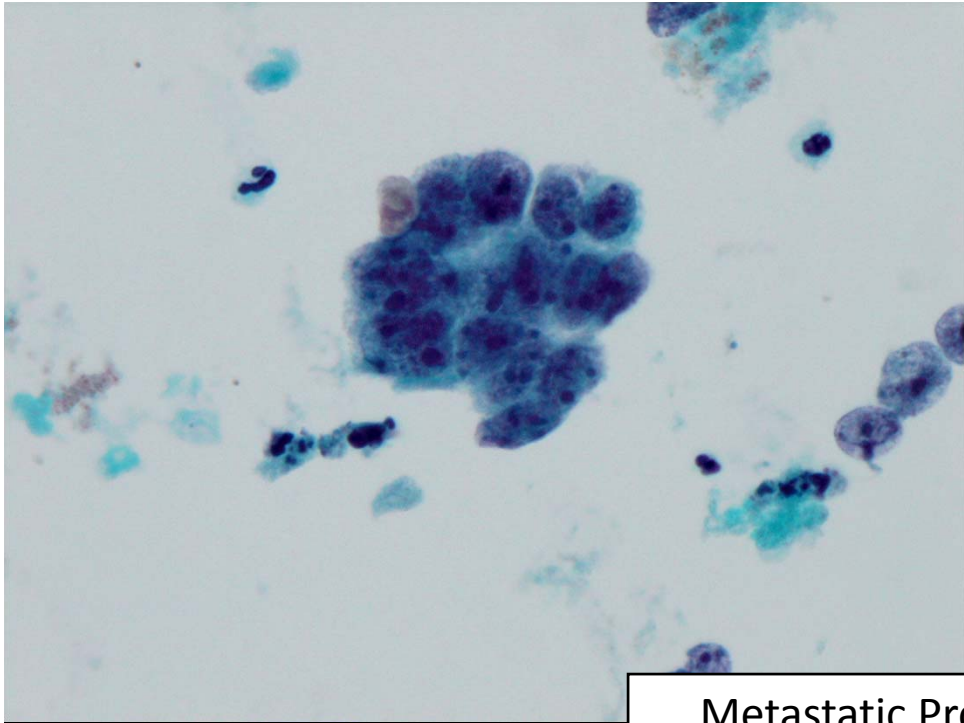
What is the best diagnosis?

- A. Negative for high grade urothelial carcinoma
- B. Atypical urothelial cells present
- C. Suspicious for high grade urothelial carcinoma
- D. High grade urothelial carcinoma
- E. Low grade urothelial neoplasm
- F. Other; positive for malignancy



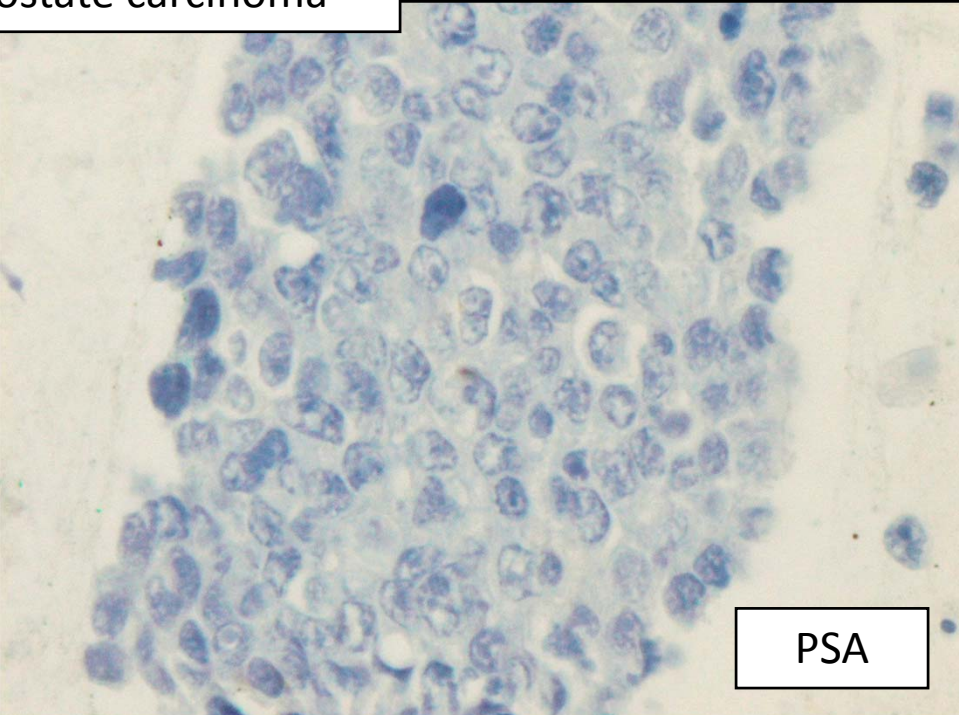
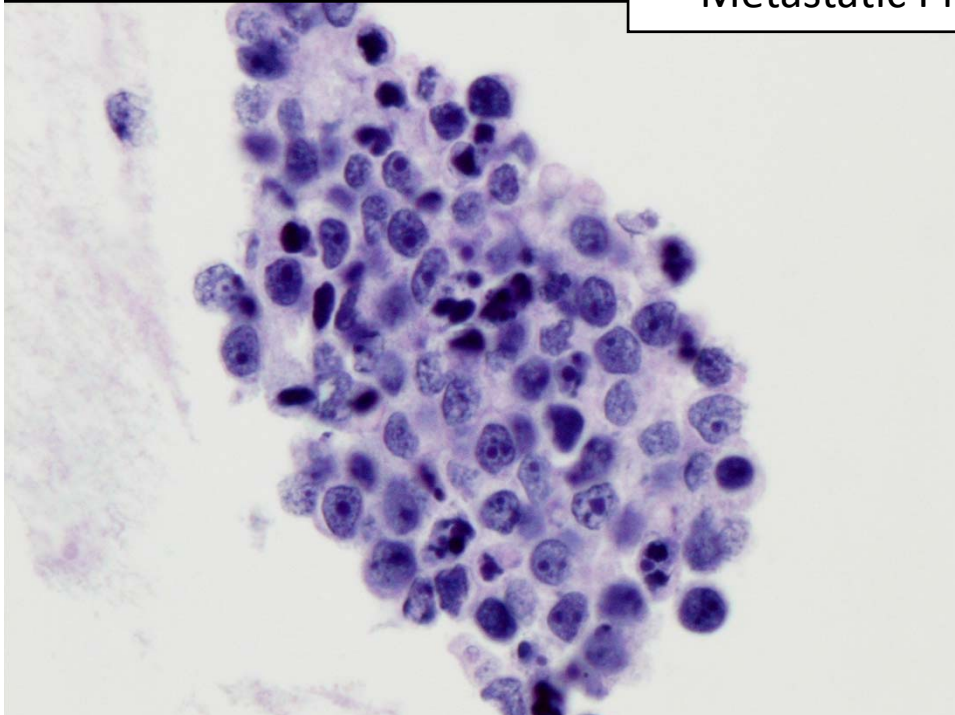
Similar cases





PSAP

Metastatic Prostate carcinoma



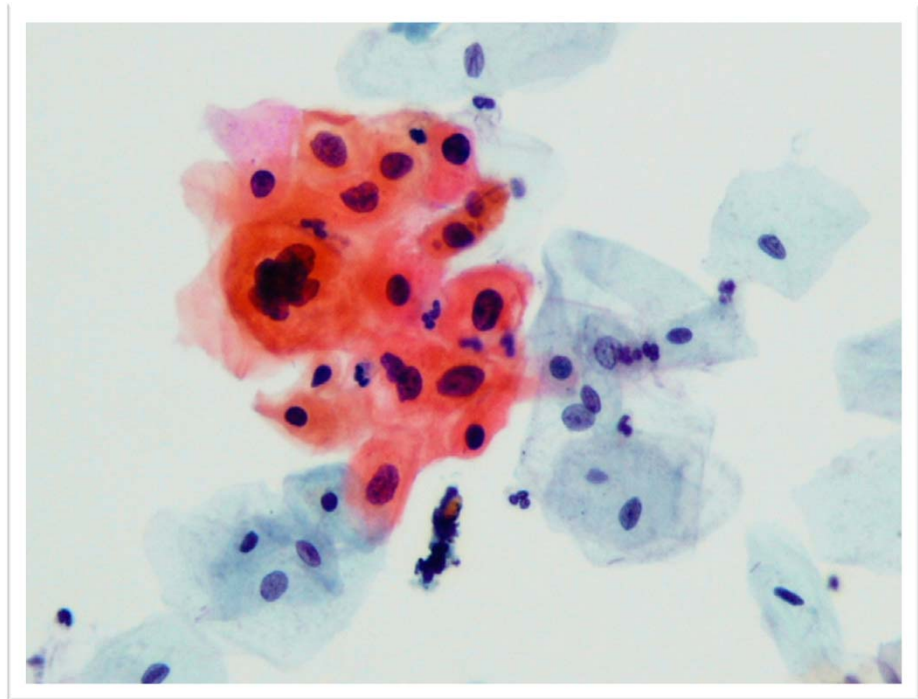
PSA

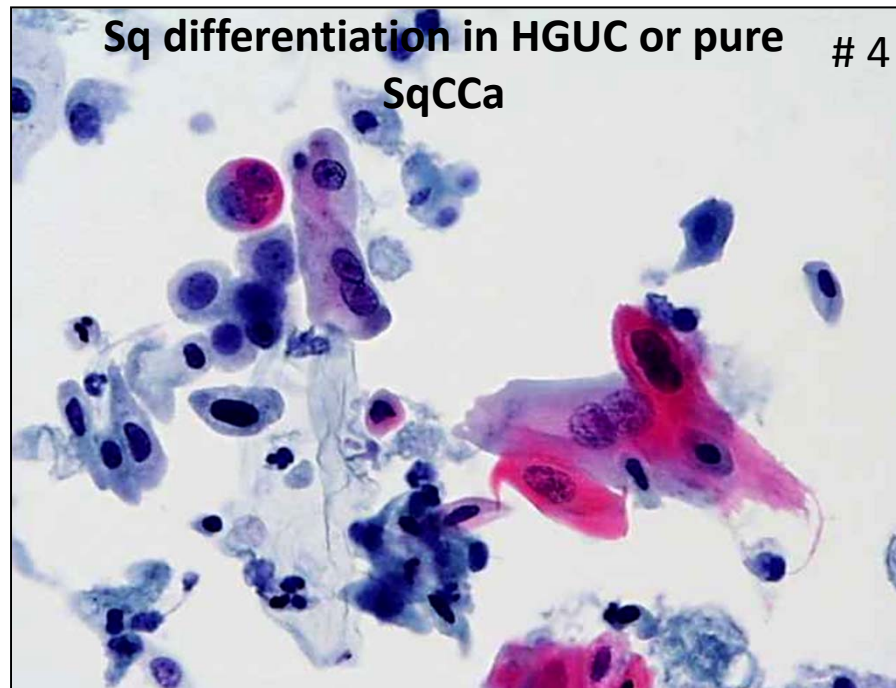
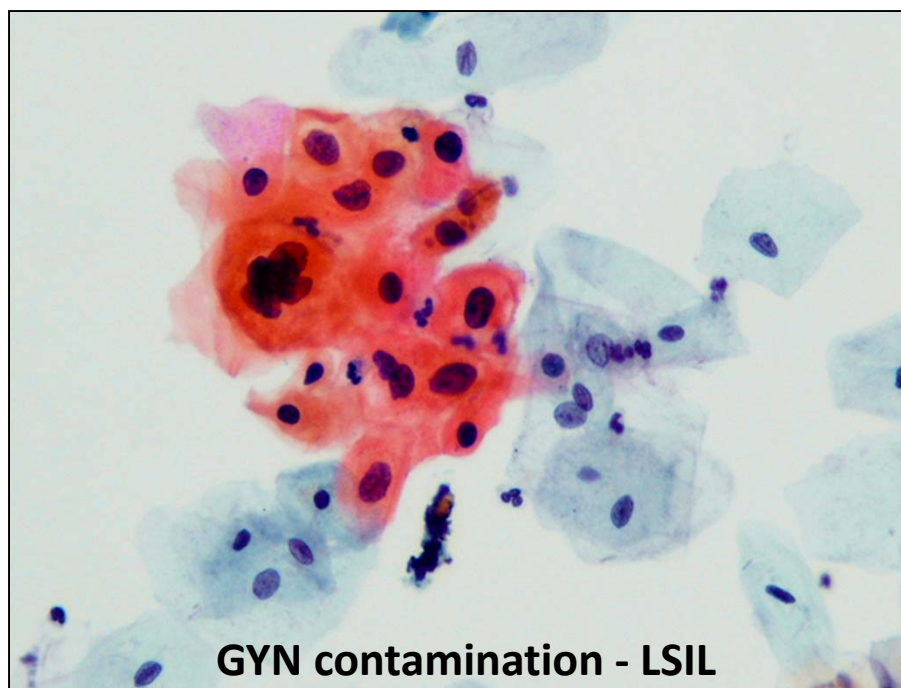
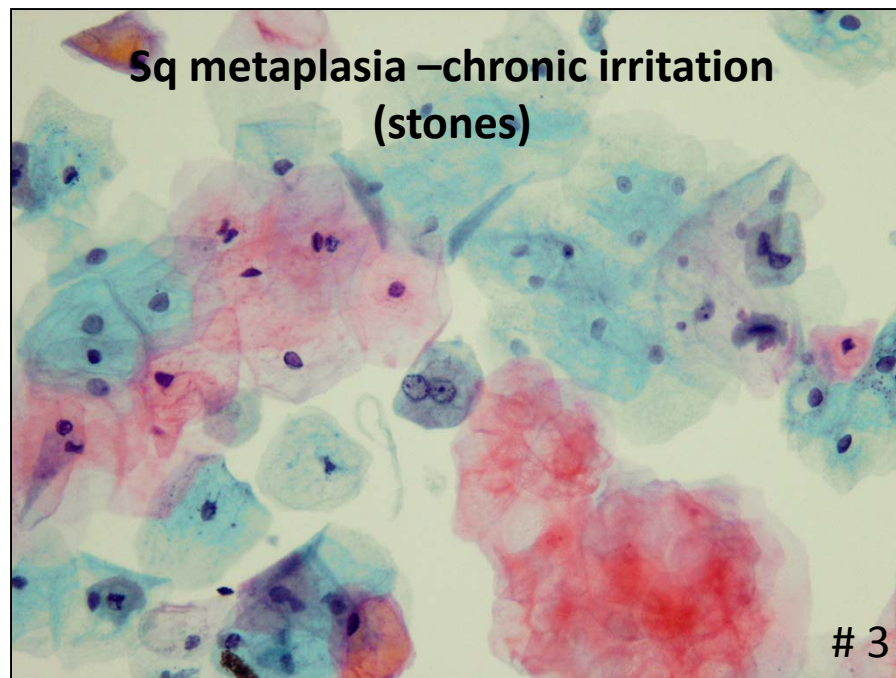
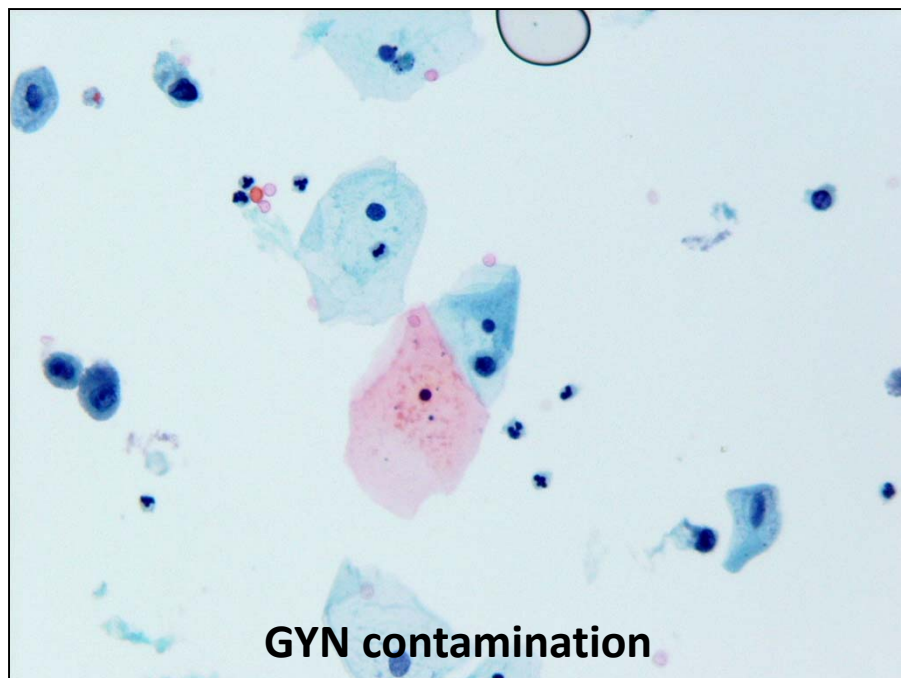
Case 11

A 28-year-old woman presents with hematuria and dysuria. Voided urine.

What is the best diagnosis?

- A. Negative for high grade urothelial carcinoma
- B. Atypical urothelial cells present
- C. Suspicious for high grade urothelial carcinoma
- D. High grade urothelial carcinoma
- E. Low grade urothelial neoplasm
- F. Other; positive for malignancy





Squamous cells

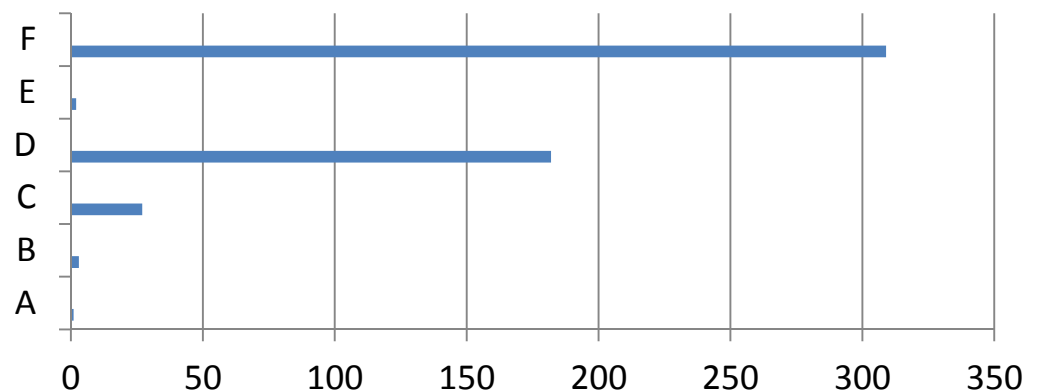
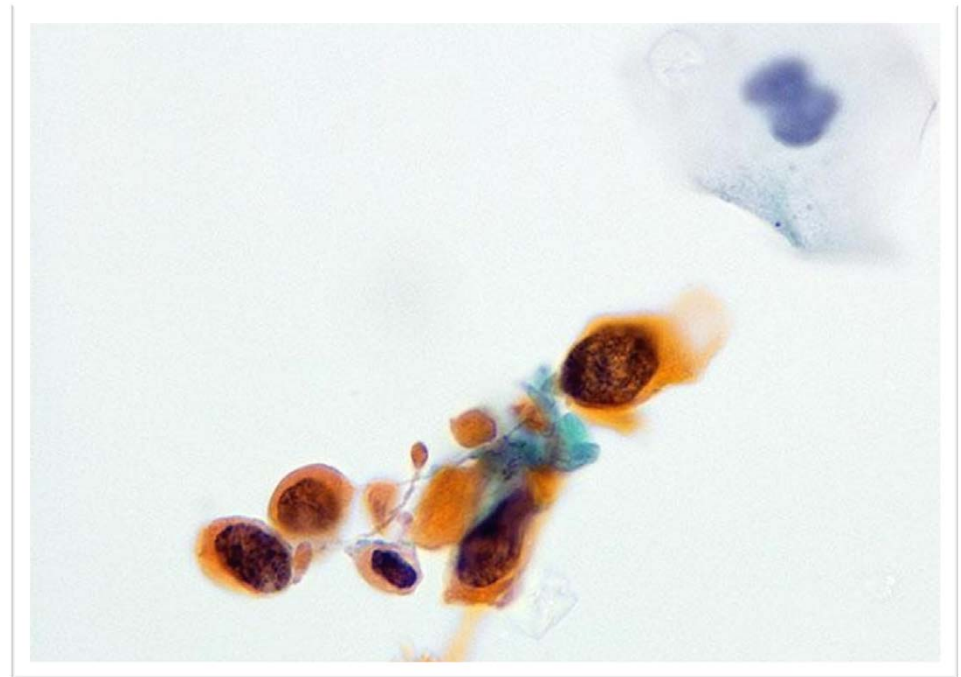
- Benign squamous cells
 - Females - GYN contamination
 - Males – squamous metaplasia – chronic irritations
- Dysplastic squamous cells
 - Females – GYN origin
 - Males – distal urethra
 - Older females and males – “tip of an iceberg” - ?HG UC with squamous differentiation
- Malignant squamous cells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

Case 12

A 65-year-old man with previous abnormal urine. Abnormal cystoscopy

What is the best diagnosis?

- A. Negative for high grade urothelial carcinoma
- B. Atypical urothelial cells present
- C. Suspicious for high grade urothelial carcinoma
- D. High grade urothelial carcinoma
- E. Low grade urothelial neoplasm
- F. Other; positive for malignancy

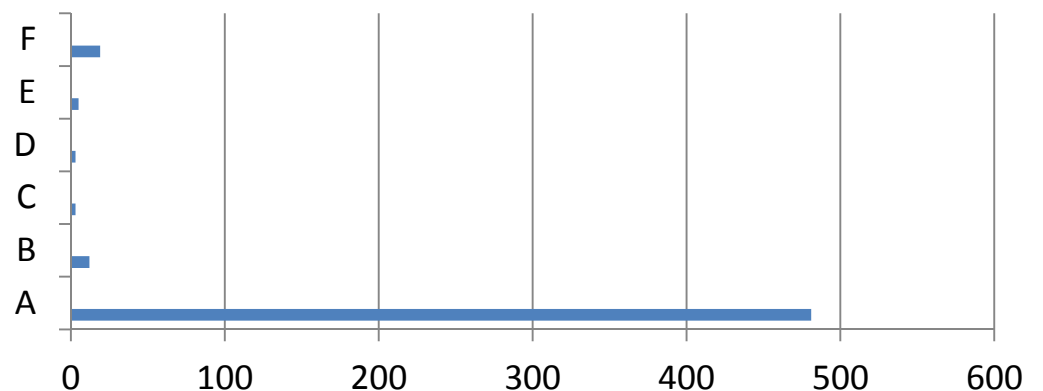
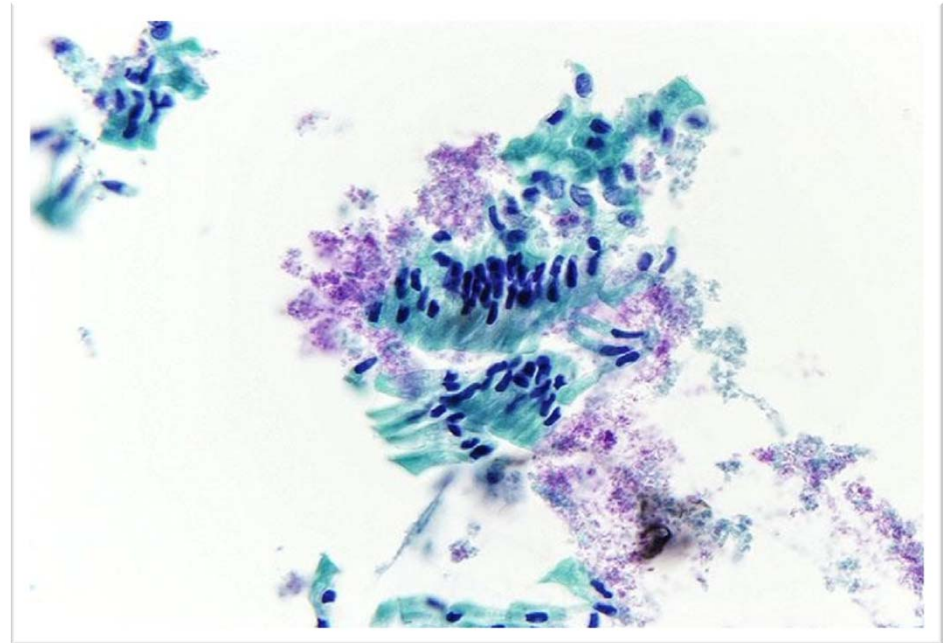


Case 13

A 92-year-old man presents with a history of bladder cancer. Iliac conduit urine.

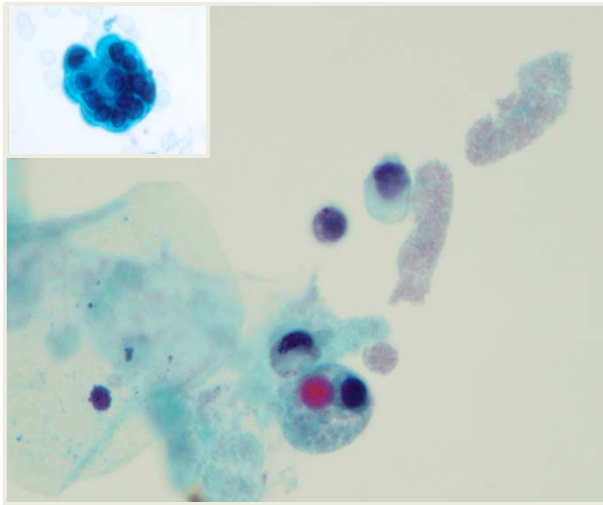
What is the best diagnosis?

- A. Negative for high grade urothelial carcinoma
- B. Atypical urothelial cells present
- C. Suspicious for high grade urothelial carcinoma
- D. High grade urothelial carcinoma
- E. Low grade urothelial neoplasm
- F. Other; positive for malignancy



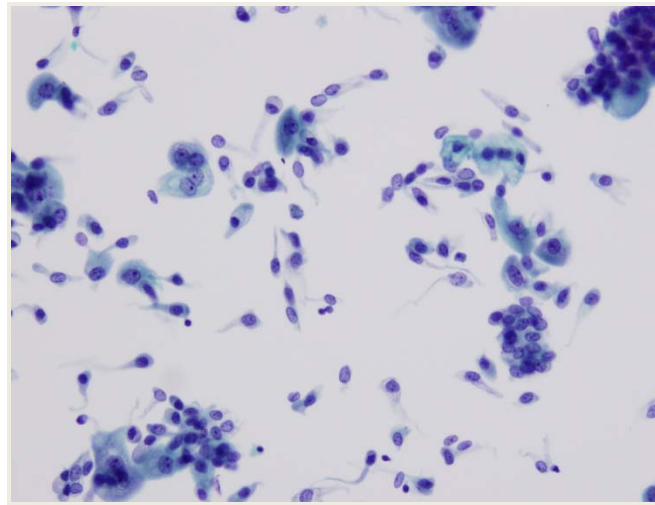
Type of urine specimens

Voided urine



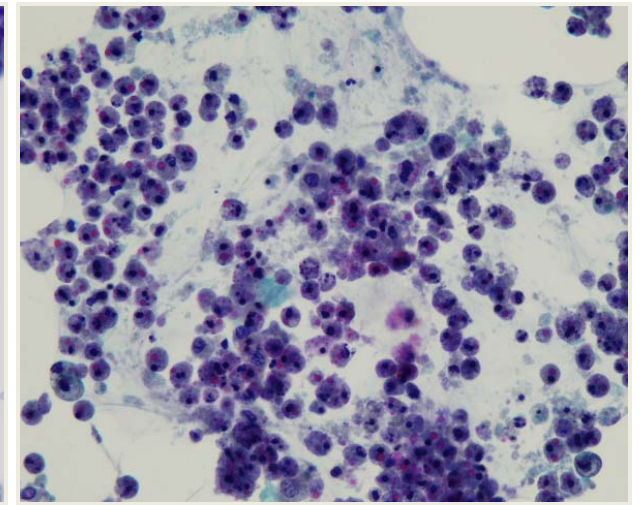
- 2nd morning midstream
- Low cellularity – umbrella cells, few intermediate cells, squamous cells (women)
- Rare cell clusters
- Eosinophilic cytoplasmic inclusions - degeneration

Instrumented urine



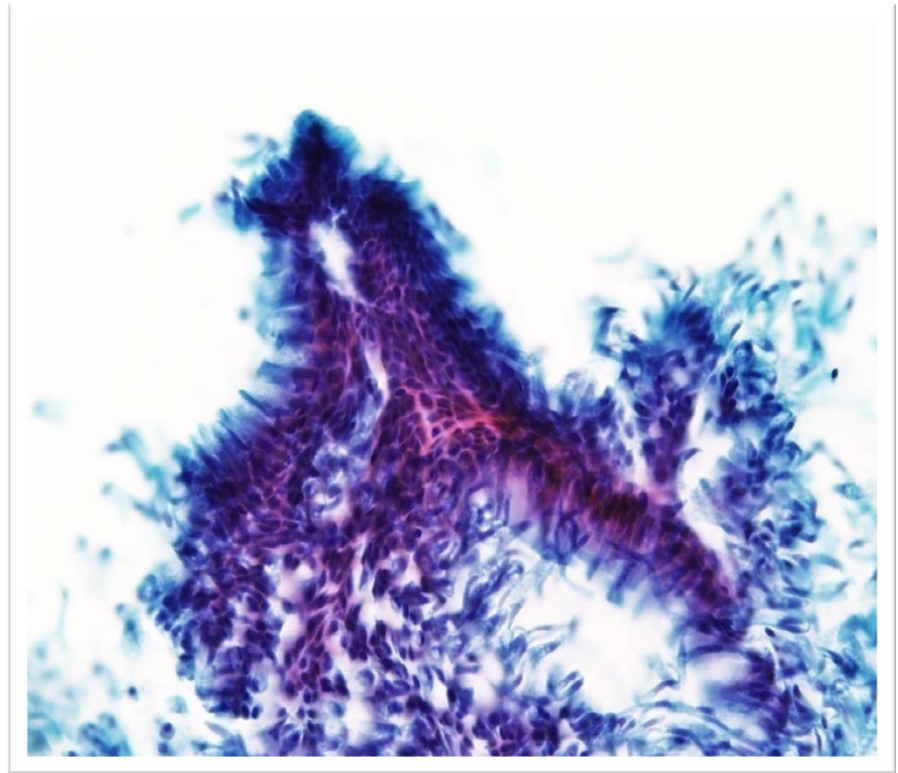
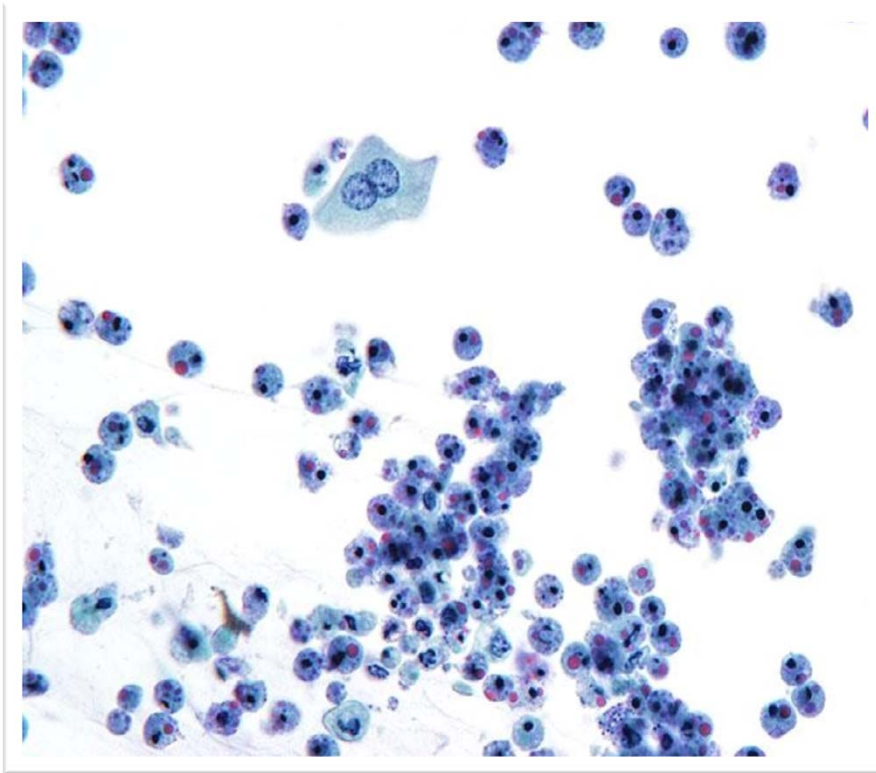
- High cellularity – umbrella cells and intermediate/basal cells
- Better cellular preservation
- Numerous cell clusters
- Similar findings in urolithiasis and low grade carcinomas

Urinary diversion urine



- Ileal conduit, Indiana pouch, neobladder
- To monitor upper urinary tract
- Numerous poorly preserved glandular cells

Urinary Diversion Urine – Not Atypia

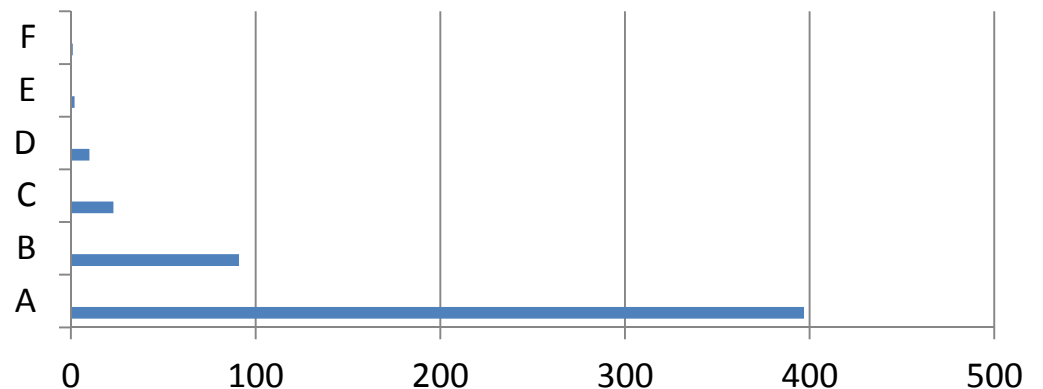
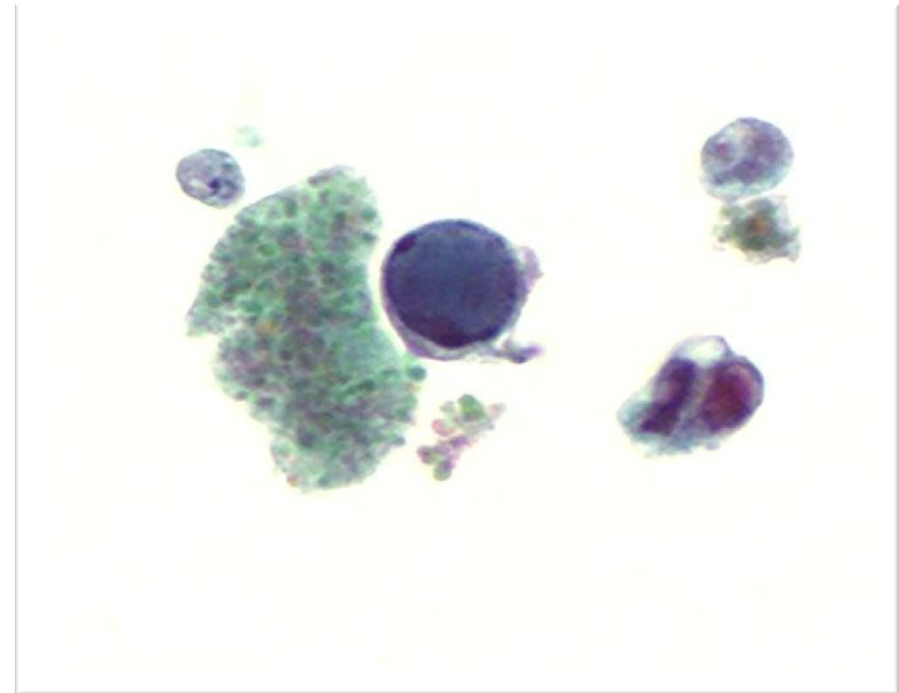


Case 14

A 58-year-old man presents with hematuria.

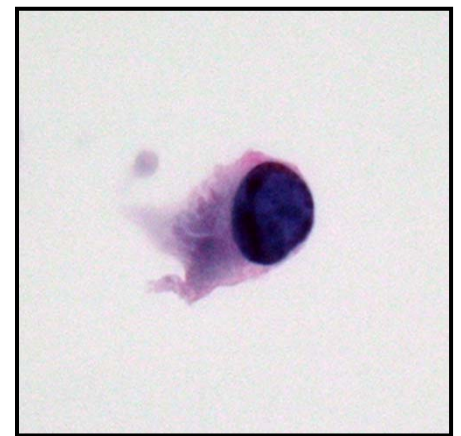
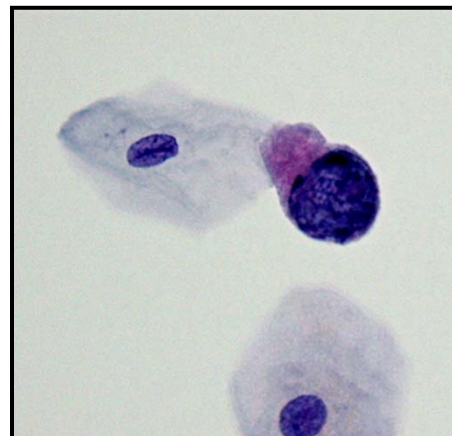
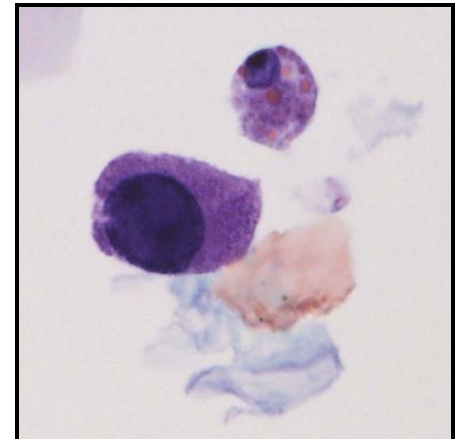
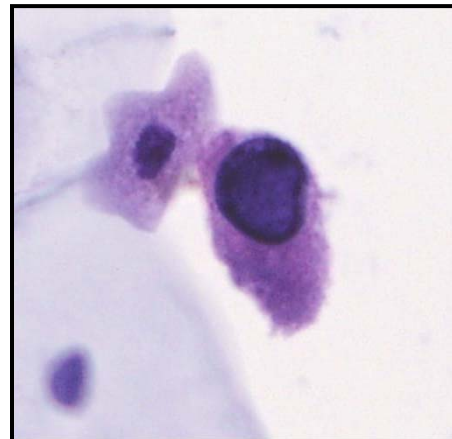
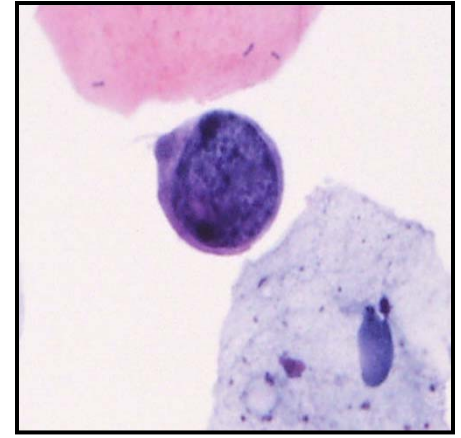
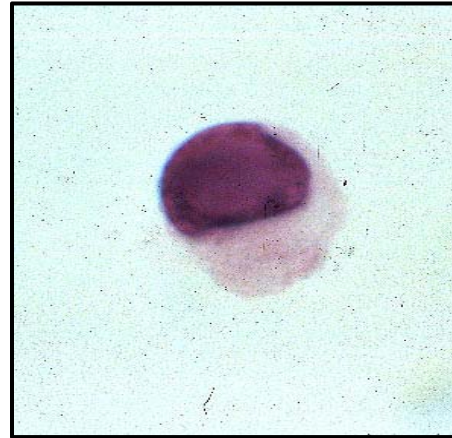
What is the best diagnosis?

- A. Negative for high grade urothelial carcinoma
- B. Atypical urothelial cells present
- C. Suspicious for high grade urothelial carcinoma
- D. High grade urothelial carcinoma
- E. Low grade urothelial neoplasm
- F. Other; positive for malignancy



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

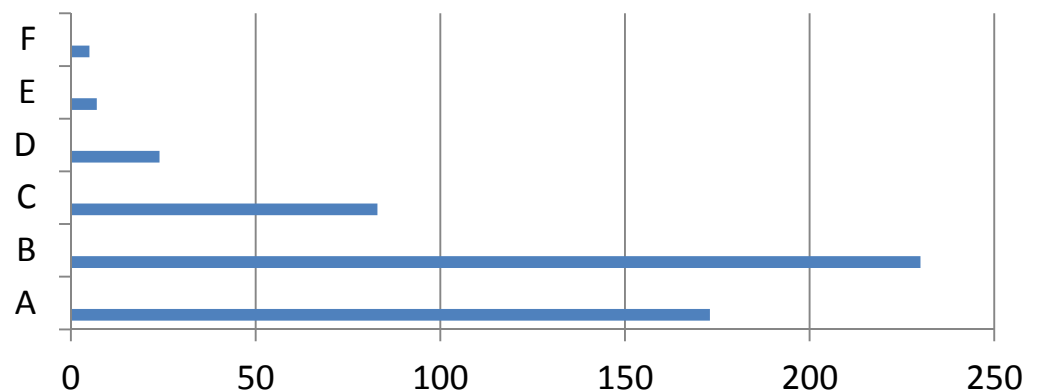
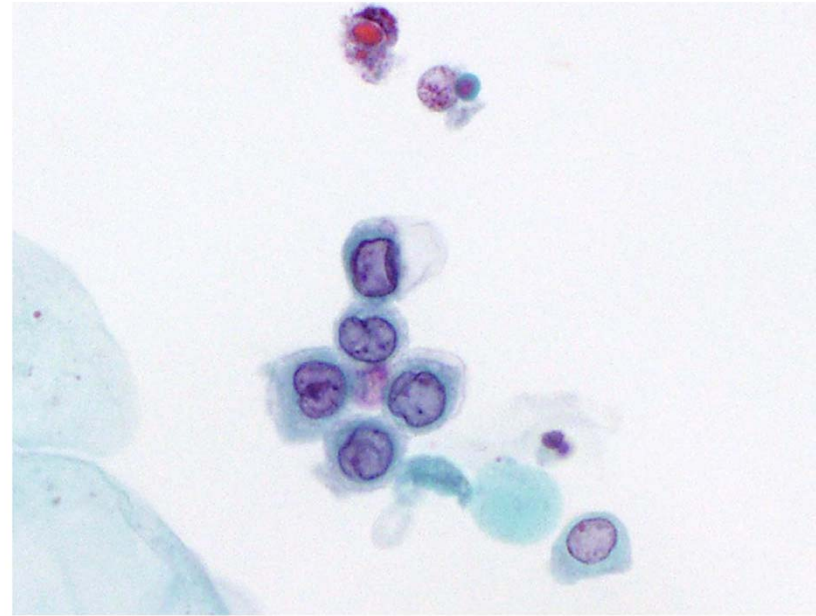


Case 15

A 50-year-old man presents with hematuria.

What is the best diagnosis?

- A. Negative for high grade urothelial carcinoma
- B. Atypical urothelial cells present
- C. Suspicious for high grade urothelial carcinoma
- D. High grade urothelial carcinoma
- E. Low grade urothelial neoplasm
- F. Other; positive for malignancy

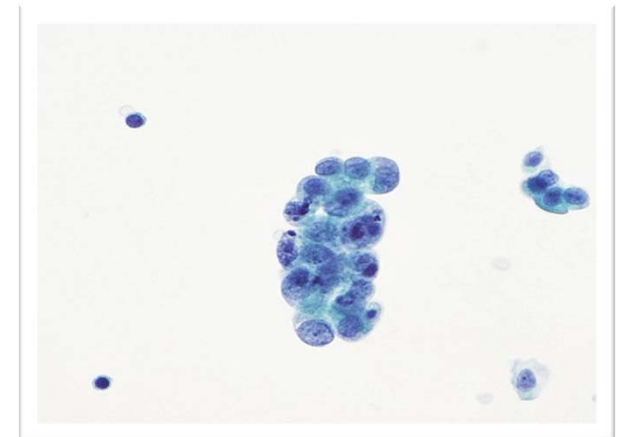


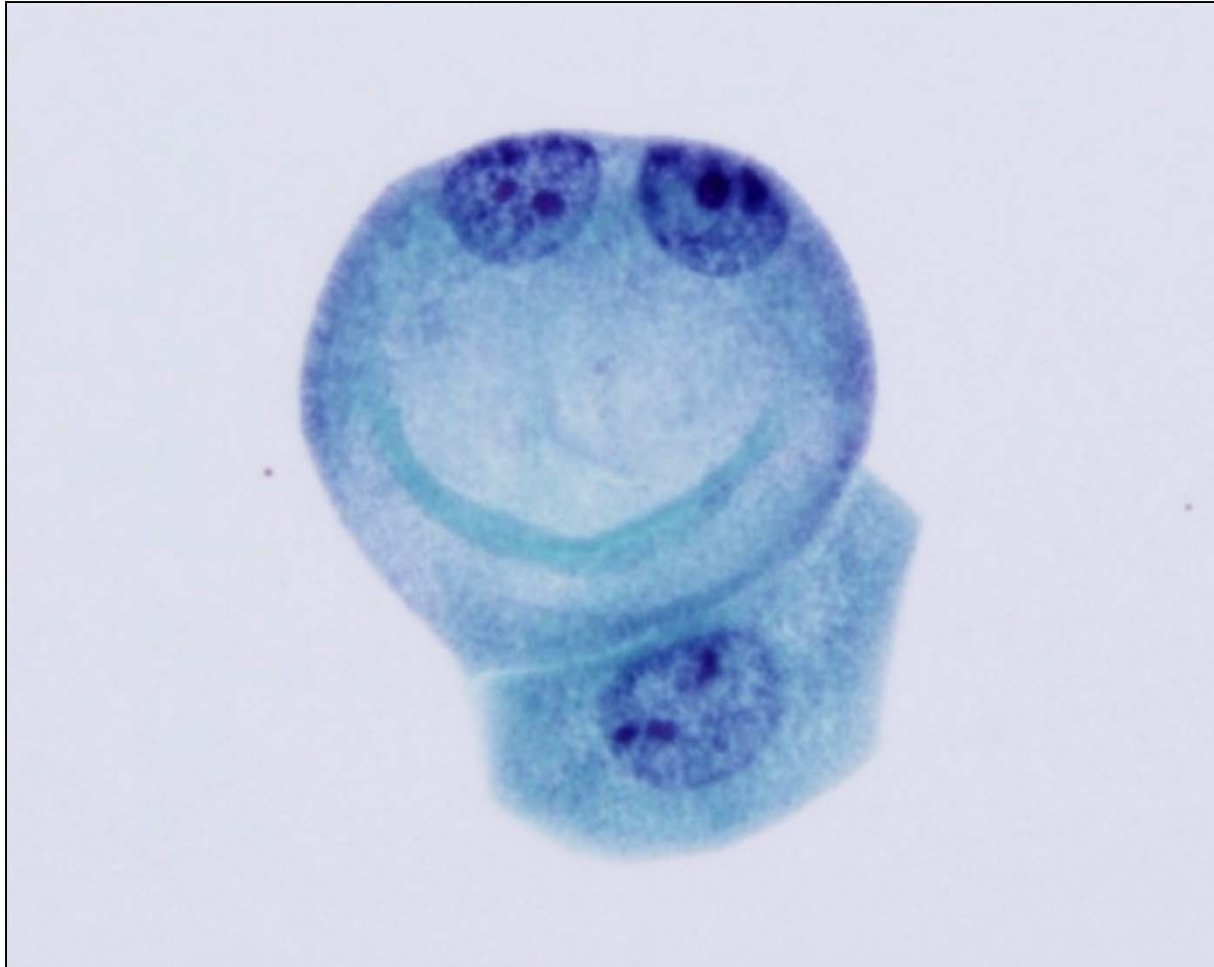
Criteria for “Atypical Urothelial Cells”

- Non-superficial and non-degenerated urothelial cells with an **high N/C ratio > 0.5**
(required)

and one of the following:

- **Hyperchromasia** (compared to the umbrella cells or the intermediate squamous cell nucleus)
- **Irregular clumpy chromatin**
- **Irregular nuclear membranes**





Thank You!