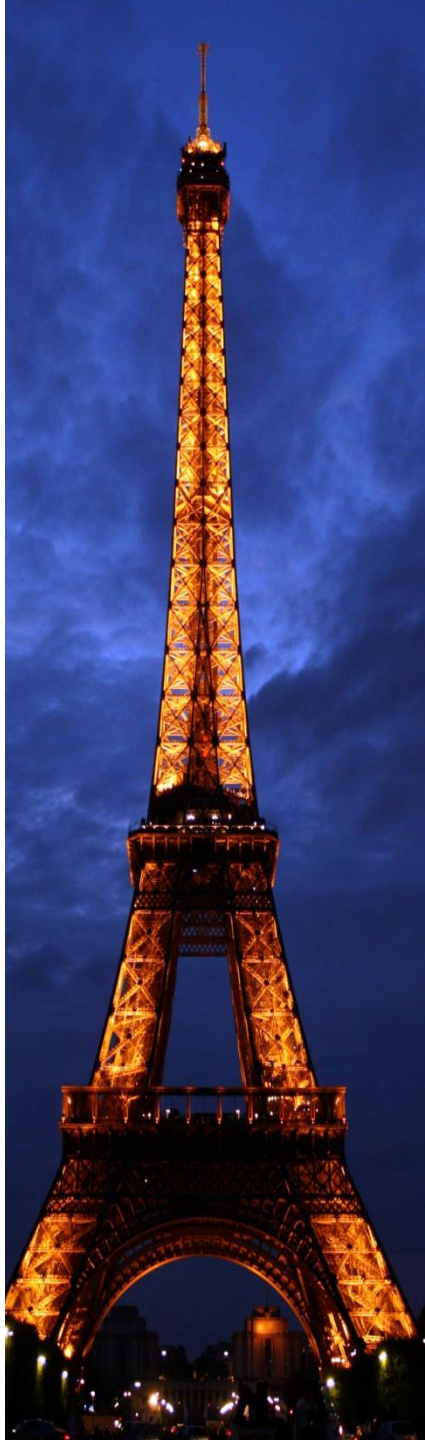
50th anniversary of
the French Society of Clinical Cytology
Looking at the Past and into the Future
of Cytopathology
22th November 2017
Convention Centre "Palais des Congrès", Paris, France

The Paris System (TPS) 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

What led to Paris?

- Rate of atypia – range from 2% to >50%
- Wide intraobserver variability
- No reproducibility
- Dwindling credibility
- Simultaneous publications on atypia
- Better understanding of the bladder cancer

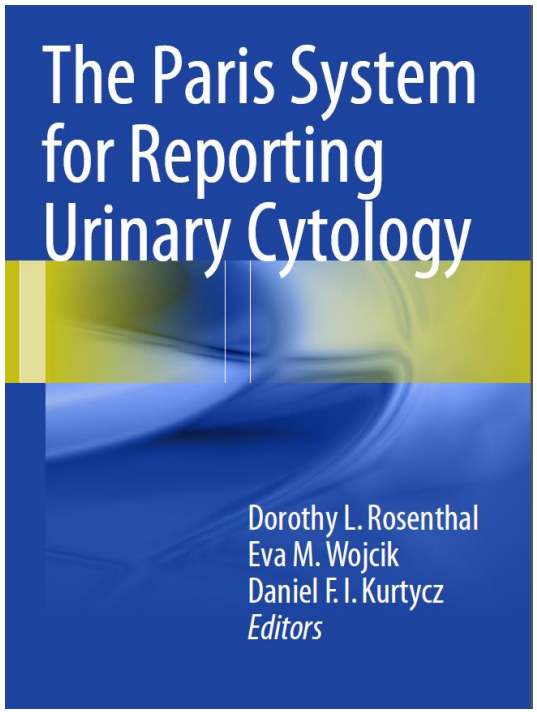


Where did we start?

- 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**

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.

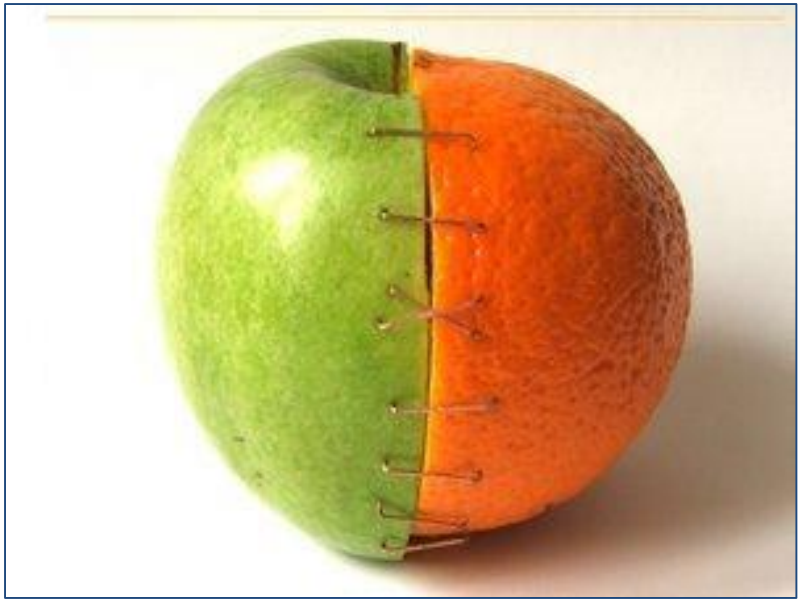


I. Pathogenesis of Urothelial Carcinoma
II. Adequacy
III. Negative for High Grade Urothelial Carcinoma
IV. Atypical Urothelial Cells
V. Suspicious for High Grade Urothelial Carcinoma
VI. High Grade Urothelial Carcinoma
VII. Low Grade Urothelial Neoplasm
VIII. Other malignancies, both primary and secondary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

System has to be build based on:

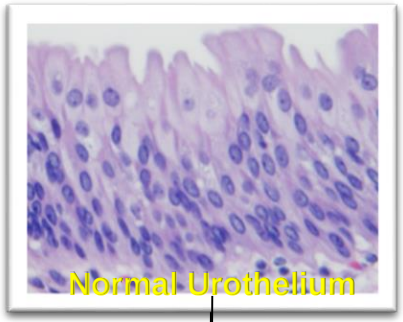
- Consensus
- Evidence
- Inclusion
- Acceptance
- Understanding



Urothelial Carcinoma

Pathogenesis of Urothelial Carcinoma

Eva M. Wojcik and Stefan E. Pambuccian



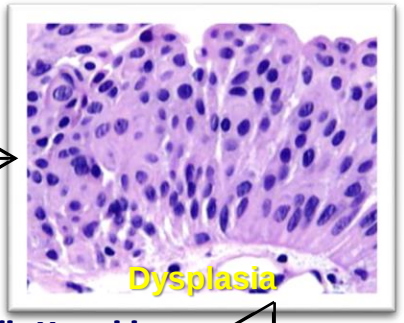
Papillary Pathway

80%

9p-, 9q-
p16

Non-Papillary Pathway

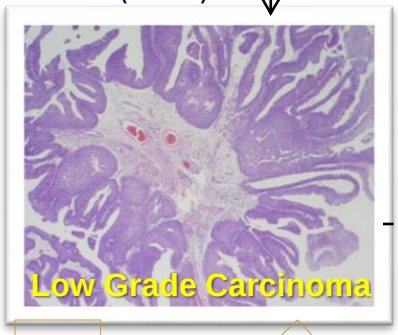
20%



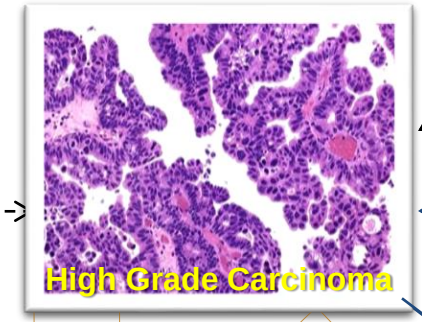
Genetically Stable
FGFR3 (~85%)

Genetically Unstable
p53 (~60%)

<10%

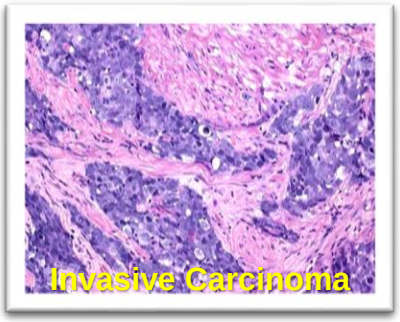


RAS (?)

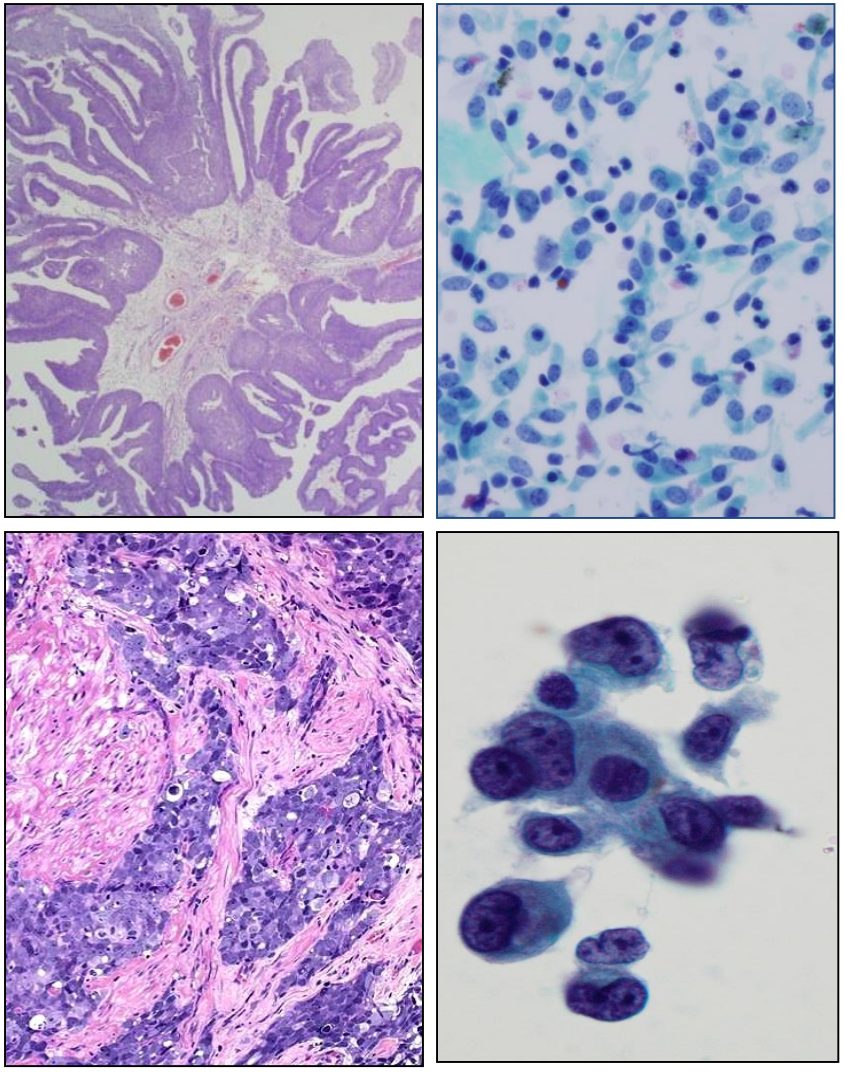


Recurrence

Recurrence



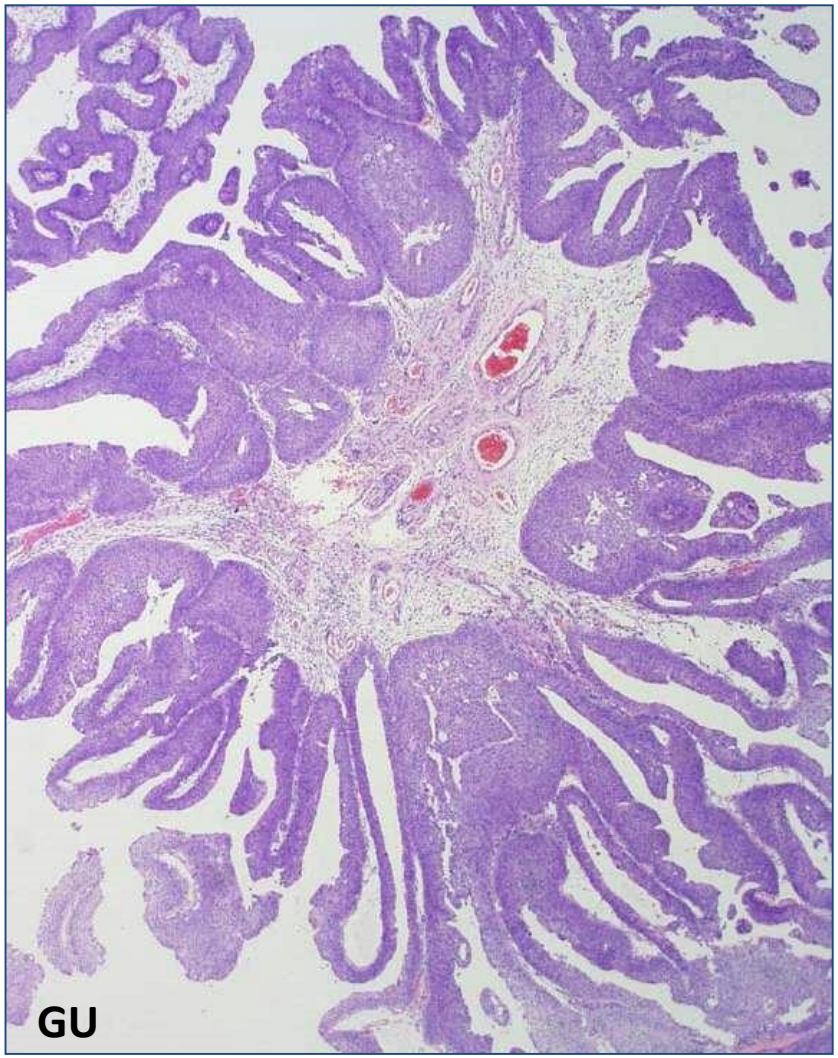
Bladder cancer – more then one disease?



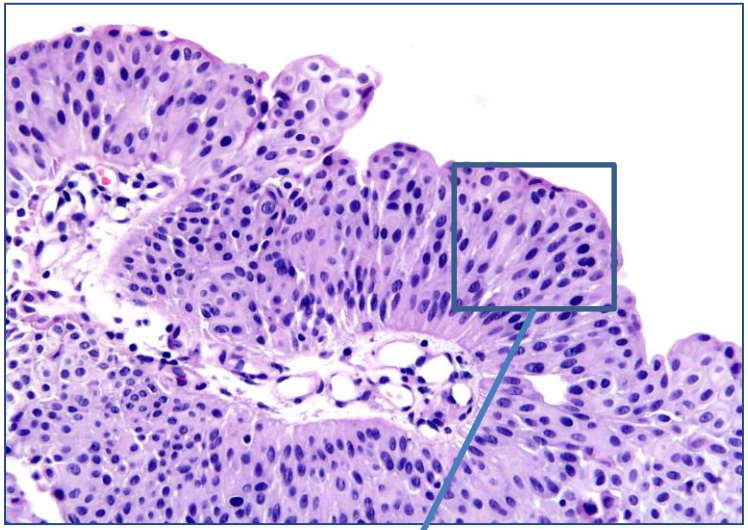
- ~ 75 % Non-Muscle-Invasive (Ta/T1)
  - Good prognosis
  - Recurrence
  - 10%-15% progression (LG Ta - <1%)*
- ~ 25 % Muscle-Invasive (≥ T2)
  - >60% overall survival

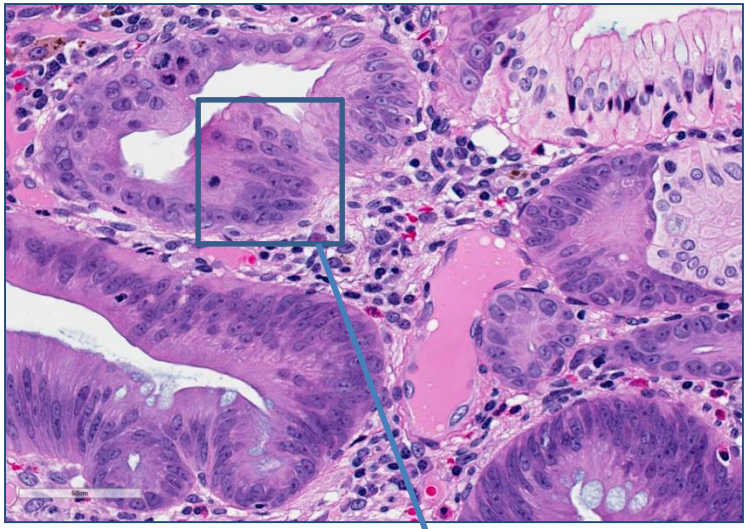
*Nielsen ME et al. Trends in Stage-Specific Incidence Rates for Urothelial Carcinoma of the Bladder In the United States: 1998-2006. Cancer 2014:120:86

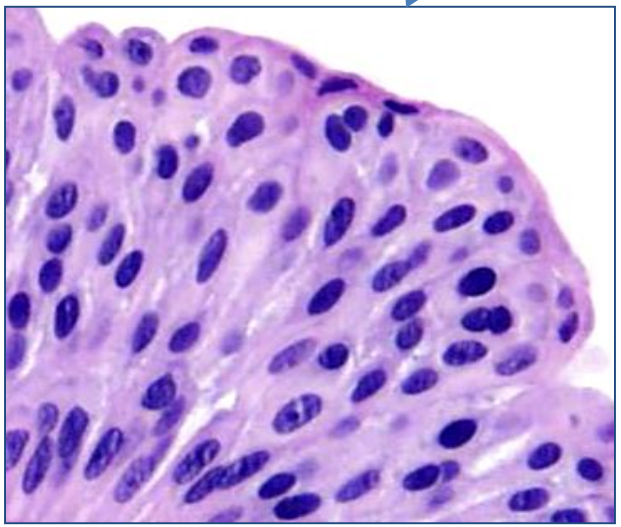
Question…. “Carcinoma”?



Question…. “Carcinoma”?

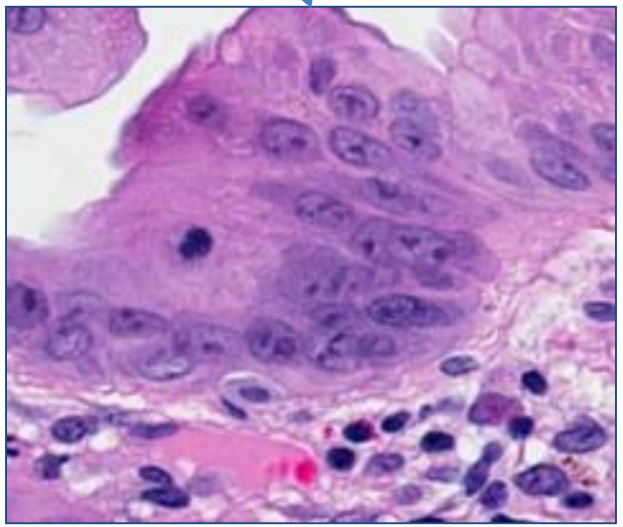




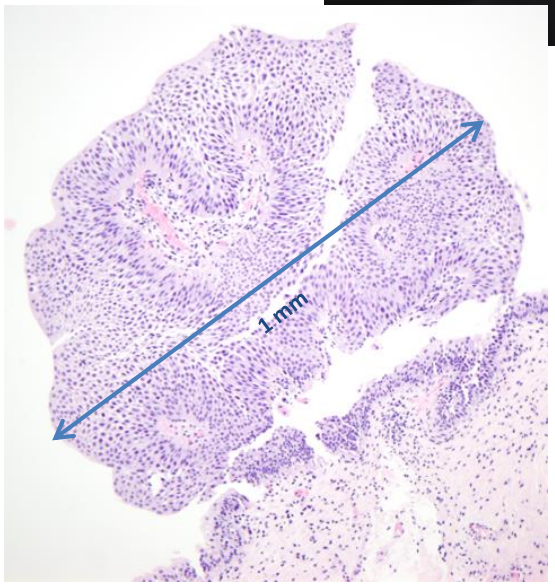


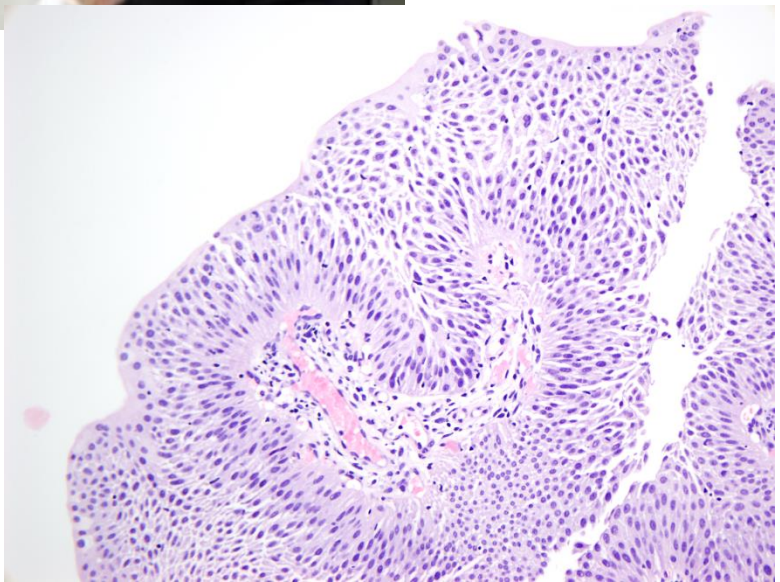
CARCINOMA

ADENOMA

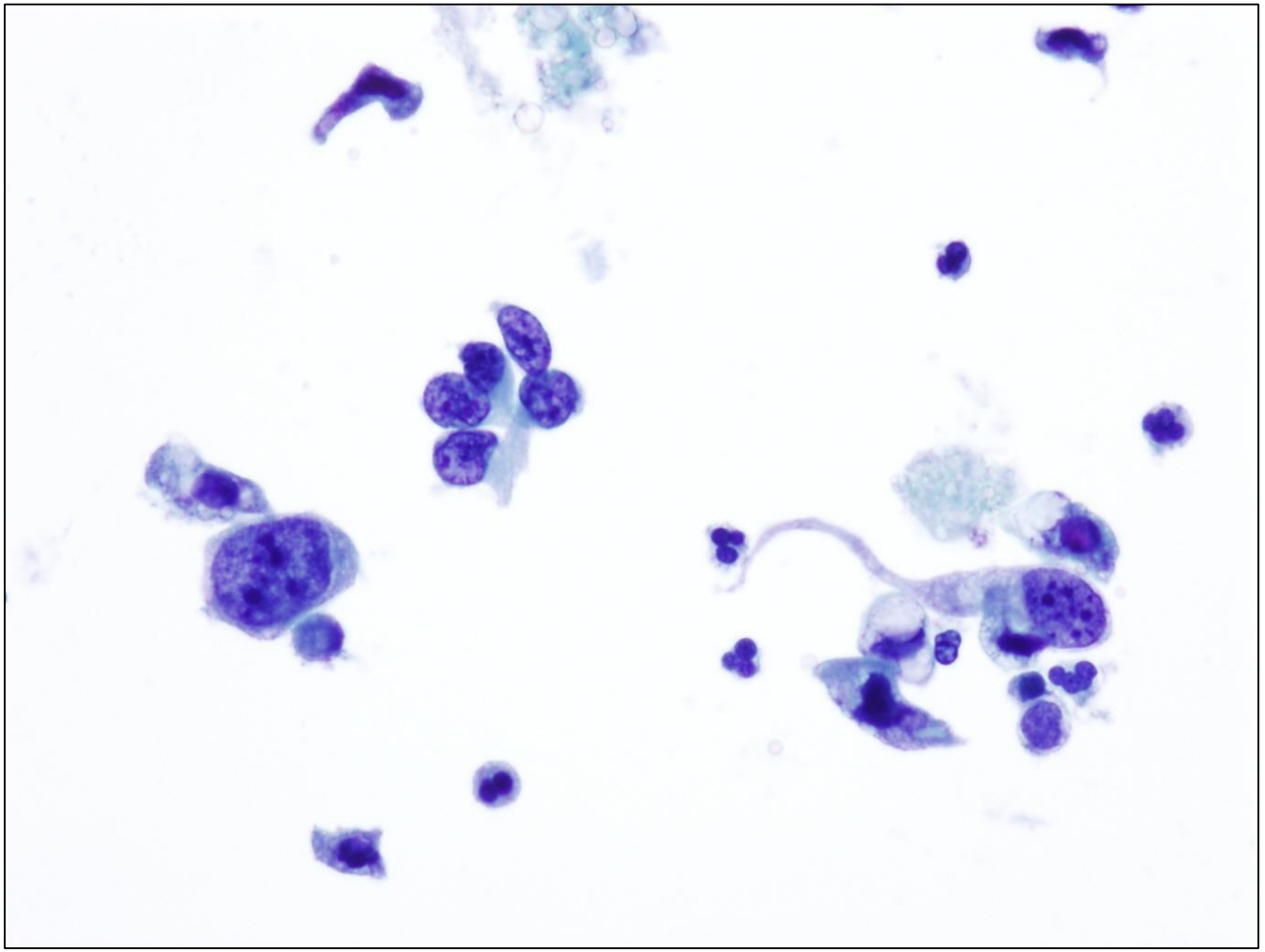


Mr. Smith - You have a bladder cancer





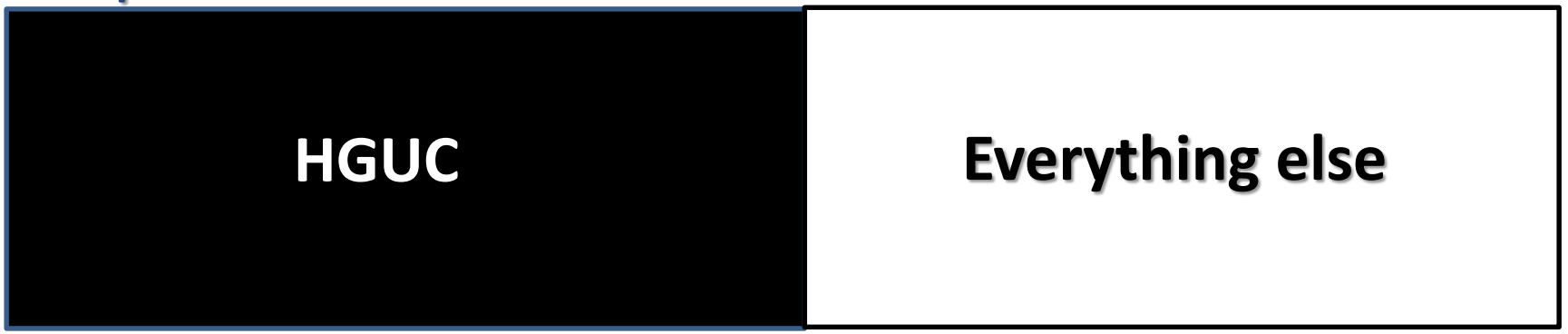
What really matters?



High Grade Urothelial Carcinoma

Diagnostic Categories

Hope



Reality

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")	Epstein 1998[14] (WHO/ISUP)
I II	Benign cells, ATY 1 cells, few clusters	Negative	Negative	Negative	NUAM	Papilloma TCC, grade 1	Papilloma PUNLMP LGUC
III	Clusters, nuclear elongation, few ATY 2 cells	Dysplastic cells	Atypical, significance uncertain	Atypical urothelial cells	AUC-US	TCC, grade 2	
		Suspicious	Suspicious		AUC-H		
IV V	Malignant tumor cells, many ATY 2 cells	Malignant cells	Neoplastic cells present	Urothelial carcinoma	Urothelial carcinoma	TCC, grade 3	HGUC

?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

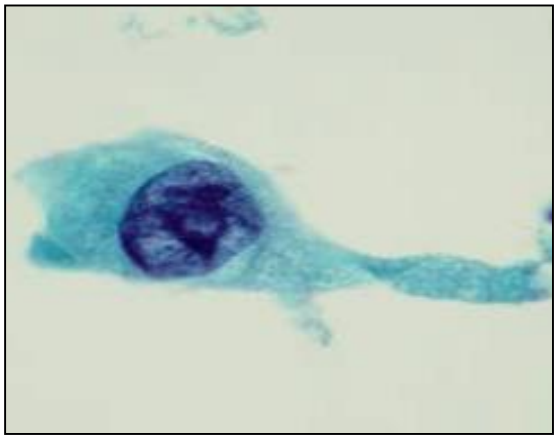
NEW paradigm

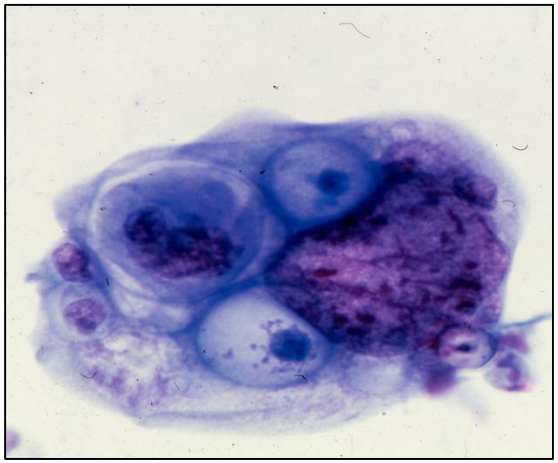
- It is all about High Grade Urothelial Carcinoma

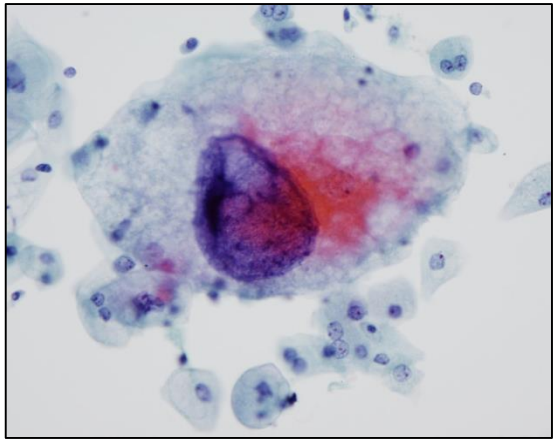
- Negative for High Grade Urothelial Carcinoma
- AUC —Quality and Quantity→ SHGUC —Quantity→ HGUC

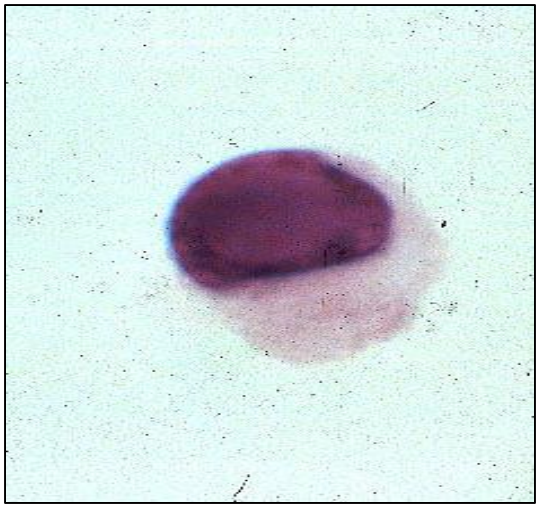
- LGUN – Low Grade Urothelial Neoplasm

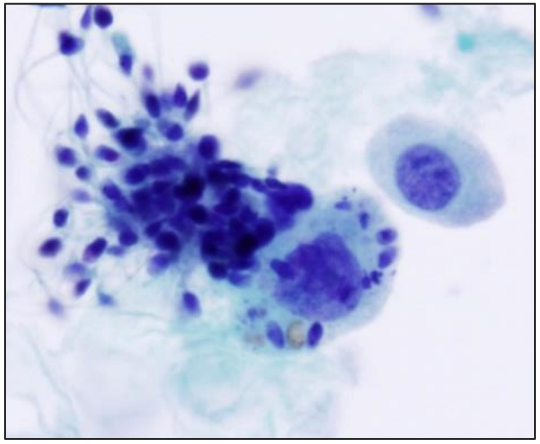
“Negative, NOT atypia”

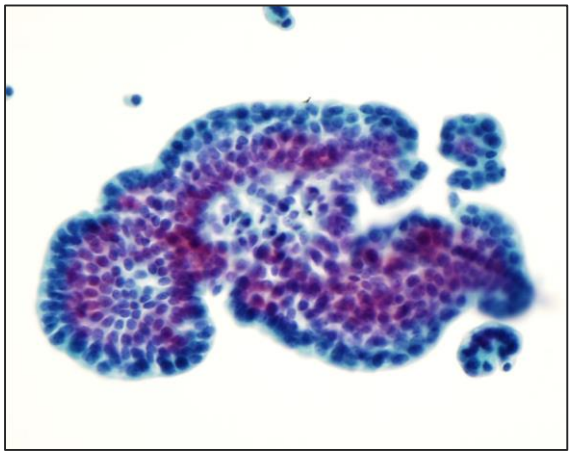


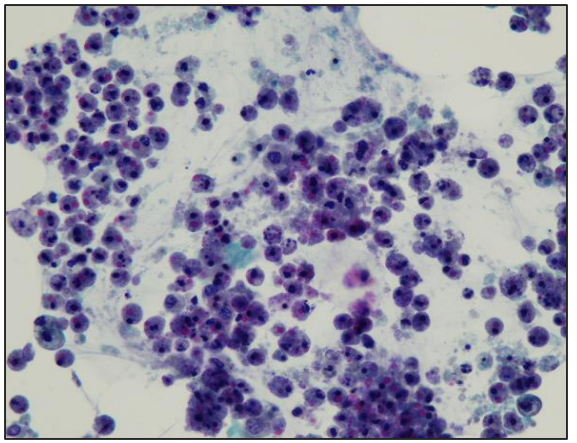


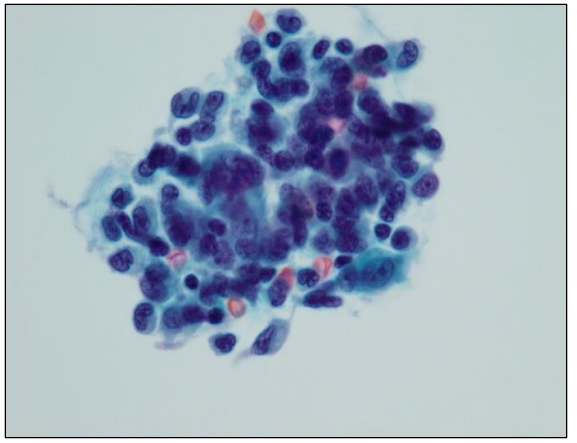












Wojcik EM: What should not be reported as atypia in urine cytology: JASC 2015;4;3;30-36

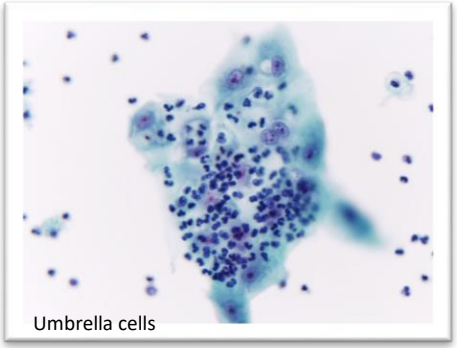
Negative for High-Grade Urothelial Carcinoma (Negative)

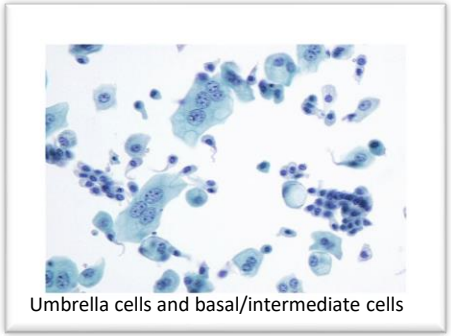
Dorothy L. Rosenthal, Michael B. Cohen, Hui Guan, Christopher L. Owens, Yuji Tokuda, and Eva M. Wojcik

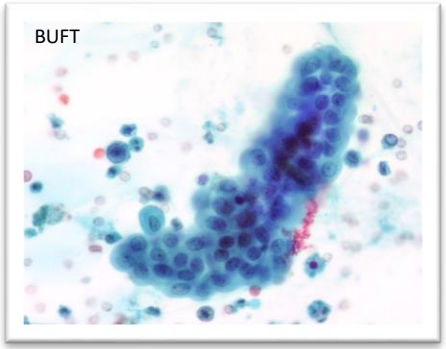
Definition of Negative for High-Grade Urothelial Carcinoma

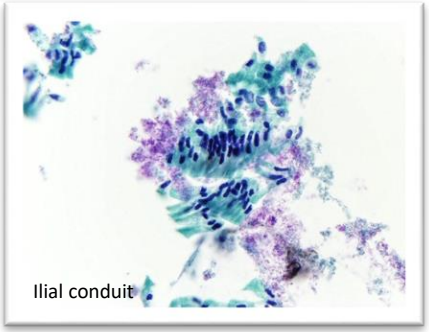
- A sample of urine, either voided or instrumented, may be considered benign, i.e., NHGUC, if any of the following components are present in the specimen:
  - Benign urothelial, glandular, and squamous cells
  - Benign urothelial tissue fragments (BUTF) and urothelial sheets or clusters
  - Changes associated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

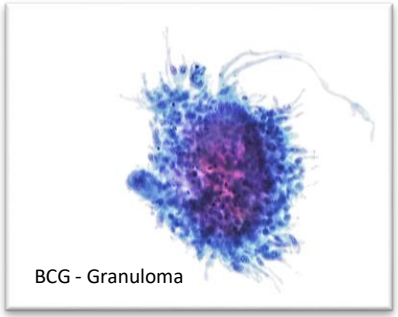

Polyoma virus


Umbrella cells

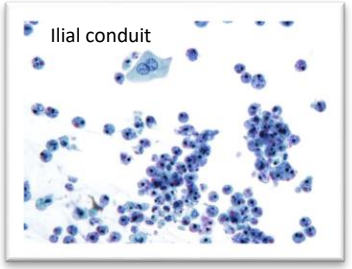

Umbrella cells and basal/intermediate cells


BUFT


Ilial conduit


BCG - Granuloma

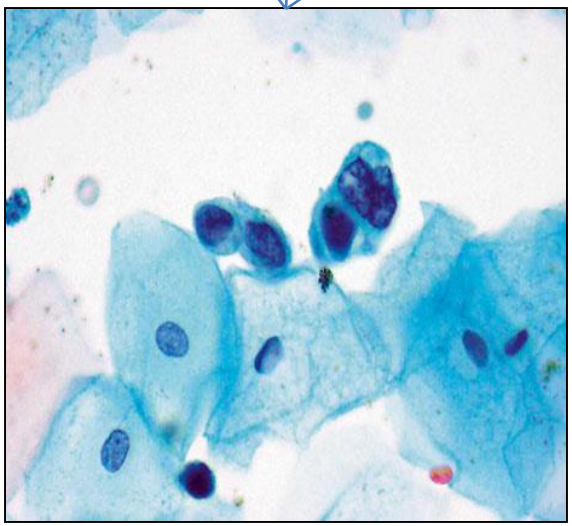

LSIL – GYN contamination

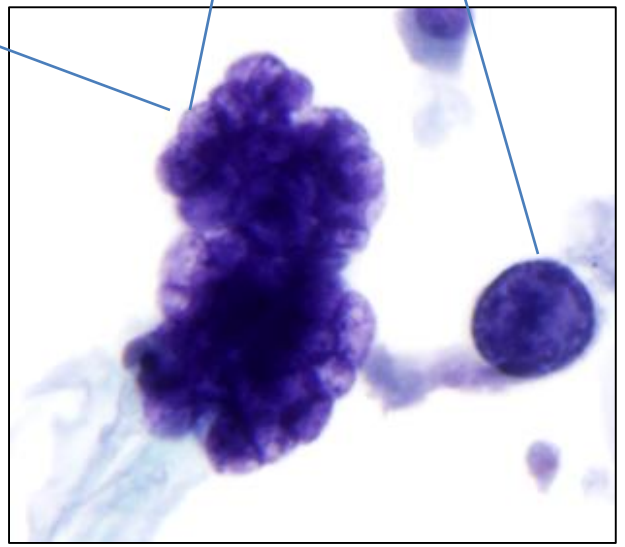

Ilial conduit

What is Atypia ?

Positive Suspicious Atypical

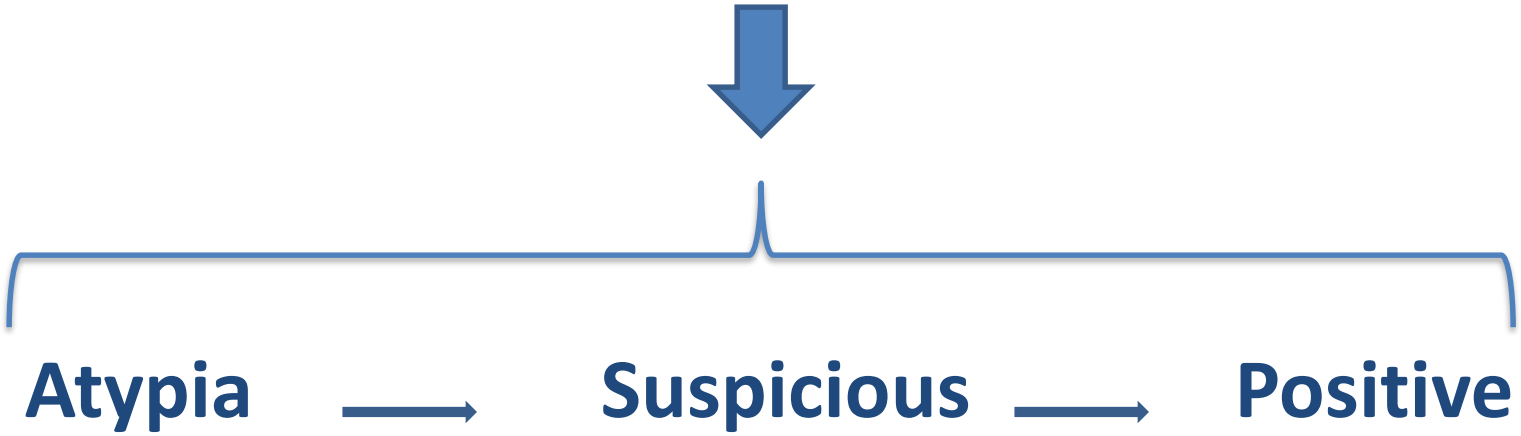
Negative

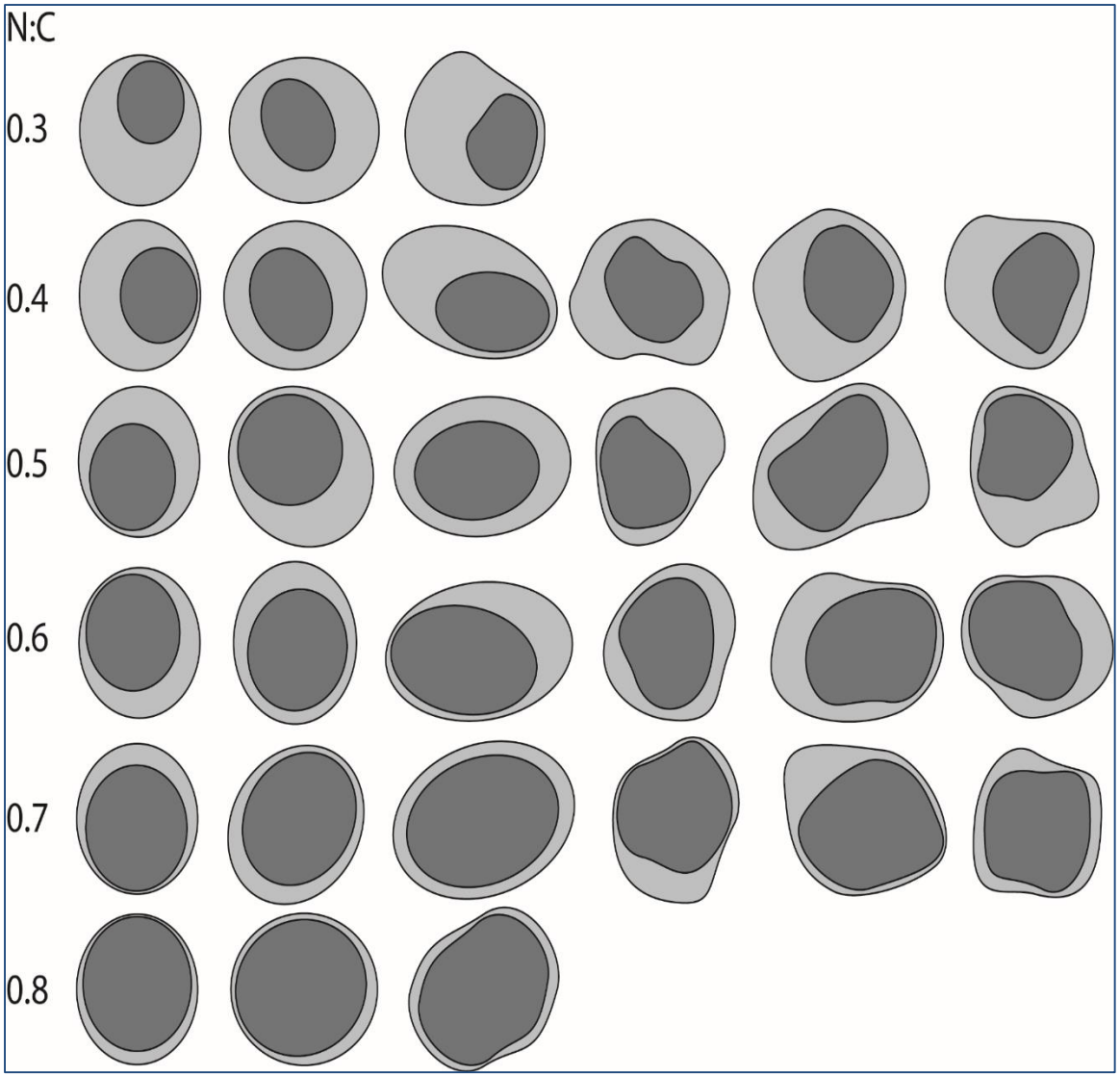




Findings in literature

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





SHGUC
+ HGUC

AUC

Zhang ML et al. Cancer Cytopathol 2016;124(9):669-677

Atypical Urothelial Cells (AUC)

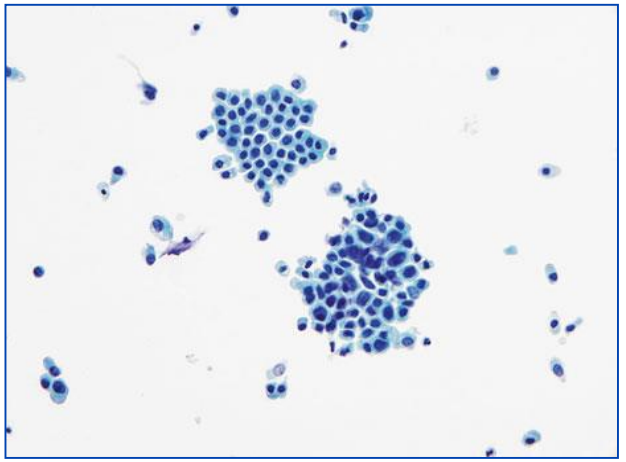
Güliz A. Barkan , Tarik M. Elsheikh , Daniel F. I. Kurtycz , Sachiko Minamiguchi , Hiroshi Ohtani , Eric Piaton , Spasenija Savic Prince , Z. Laura Tabatabai , and Christopher J. VandenBussche

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**



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

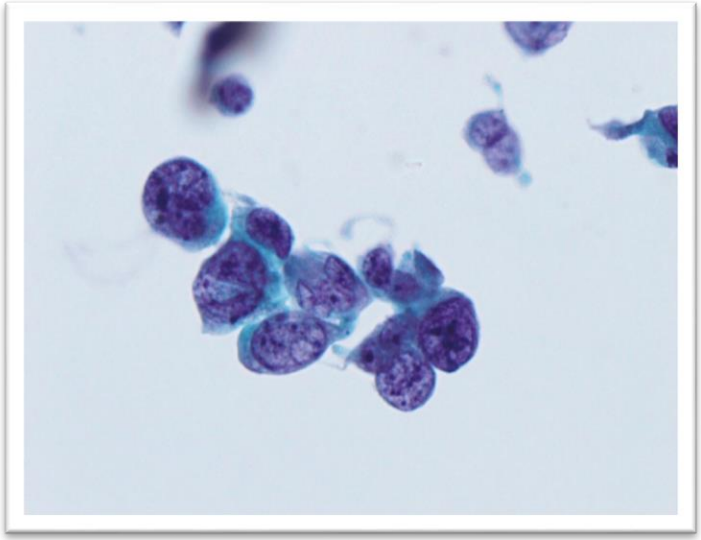
Criteria for SHGUC

- 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]

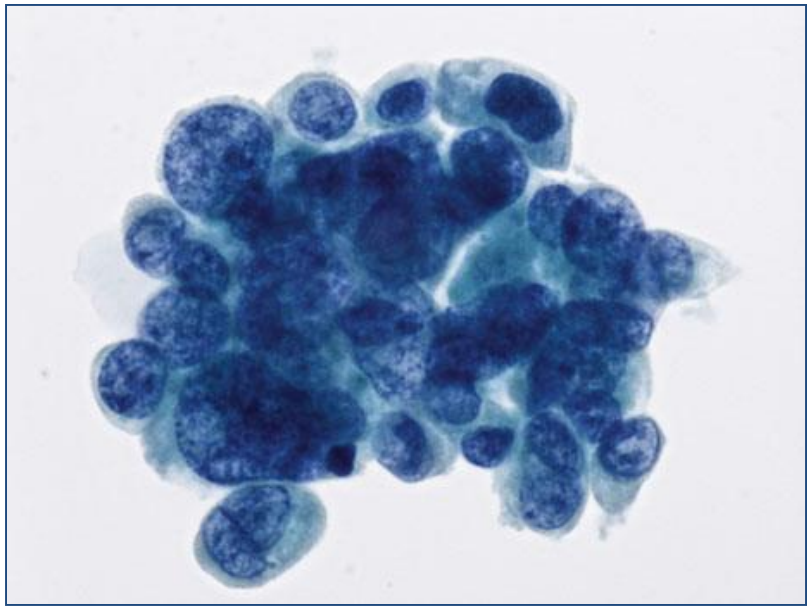
JASC 2015;4(4)232–238

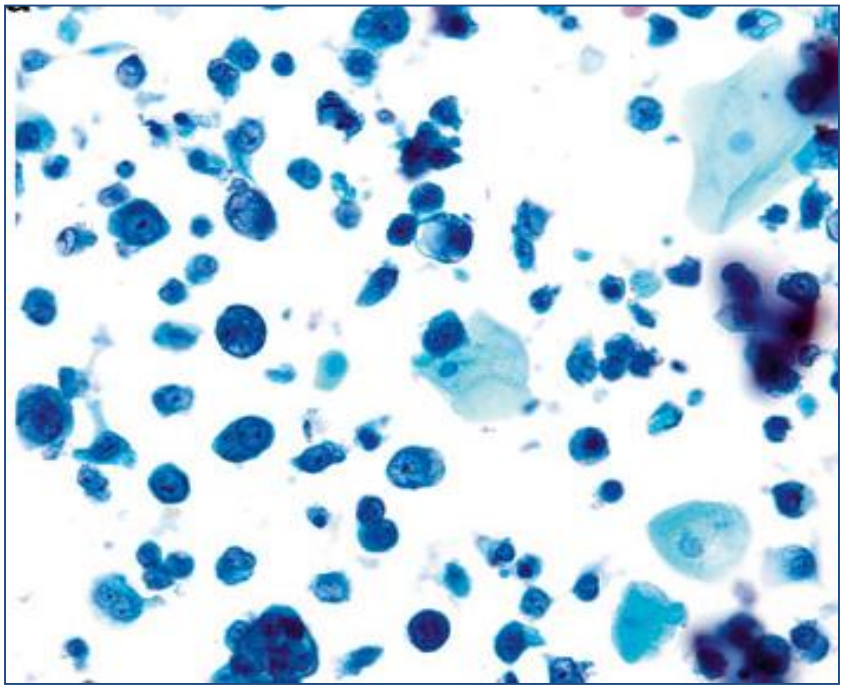
5 – 10 cells – gray zone, based on experience, history, individual threshold, etc

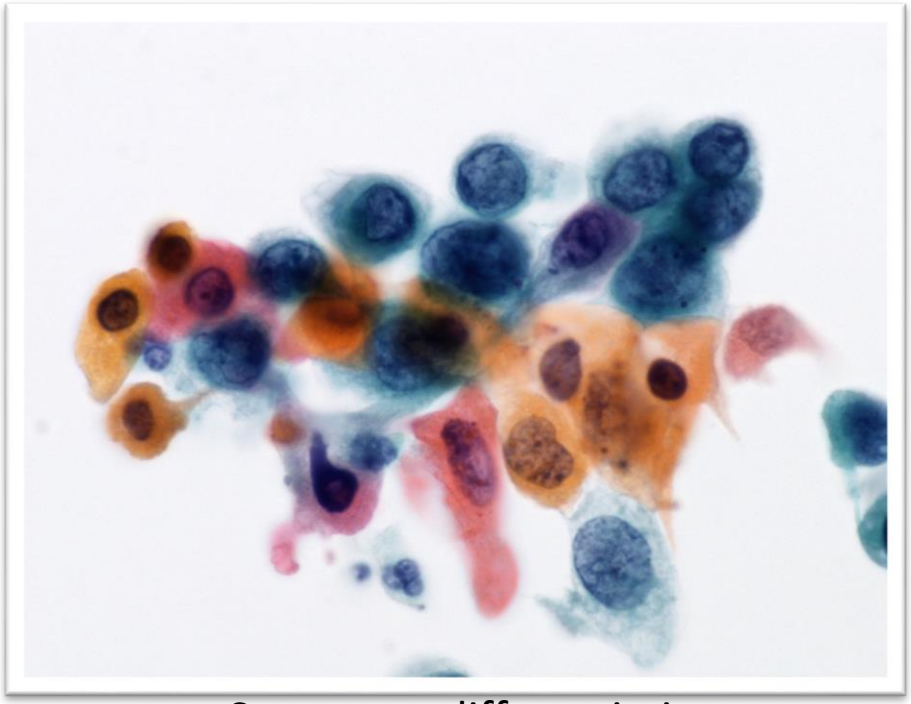
High-Grade Urothelial Carcinoma (HGUC)

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

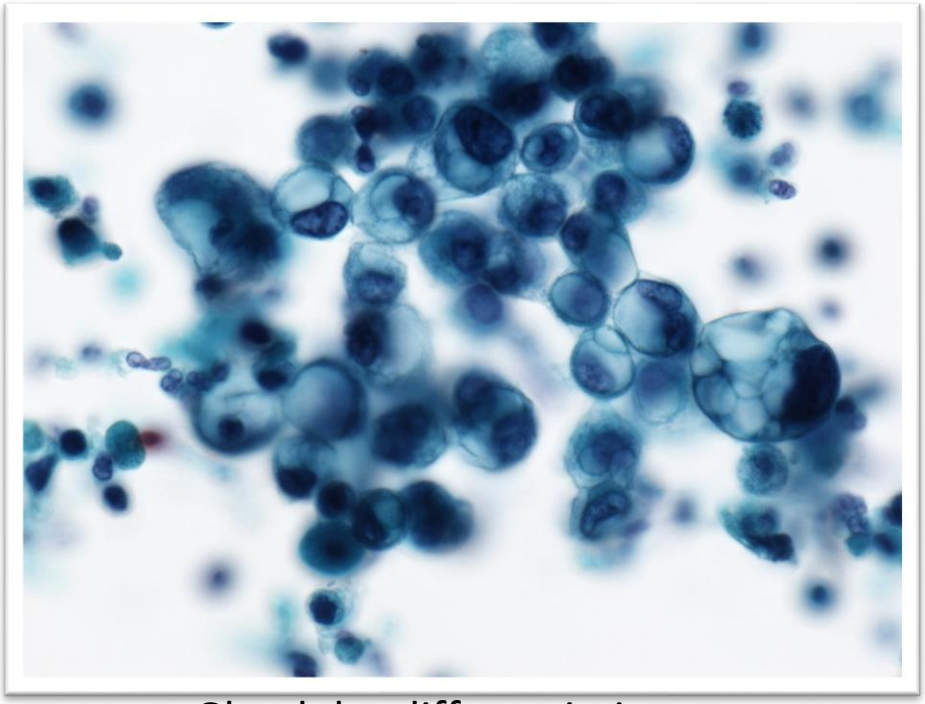
- Cellularity: At least 5–10 abnormal cells
- N/C ratio: 0.7 or greater
- Nucleus: Moderate to severe hyperchromasia
- Nuclear membrane: Markedly irregular
- Chromatin: Coarse/clumped



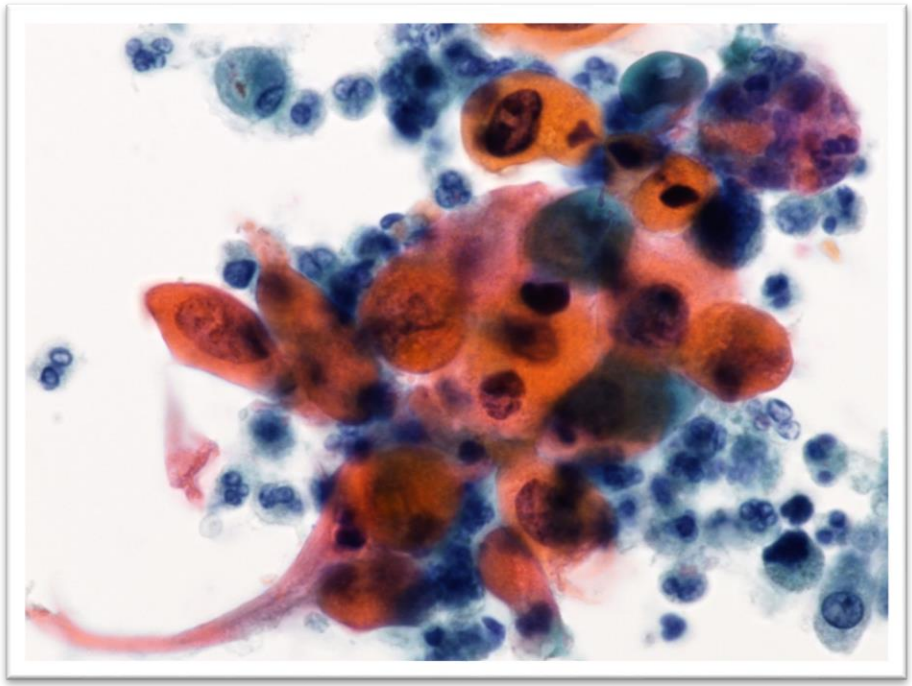


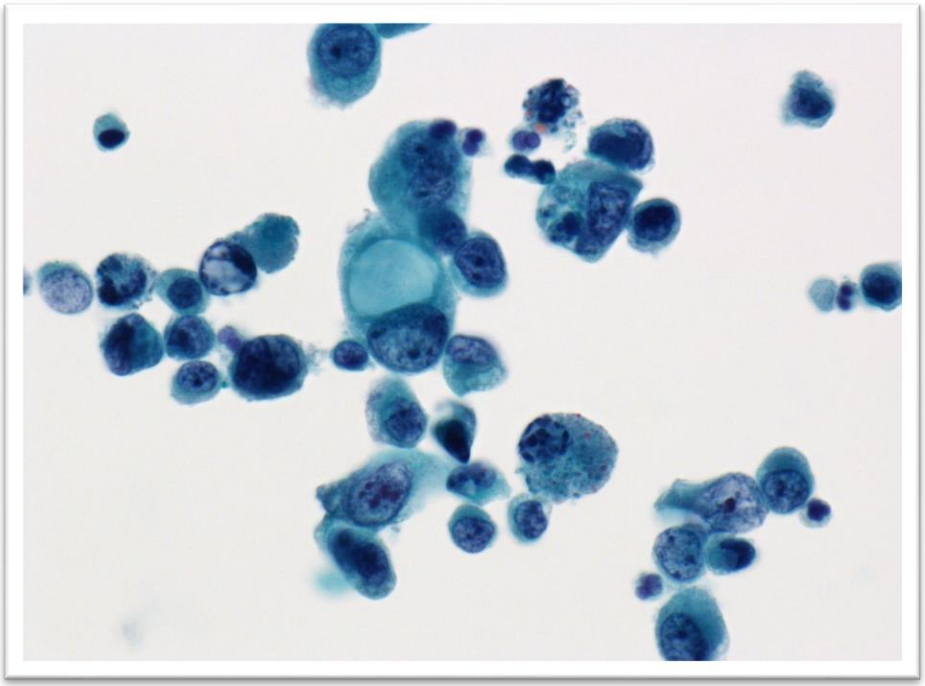


Squamous differentiation



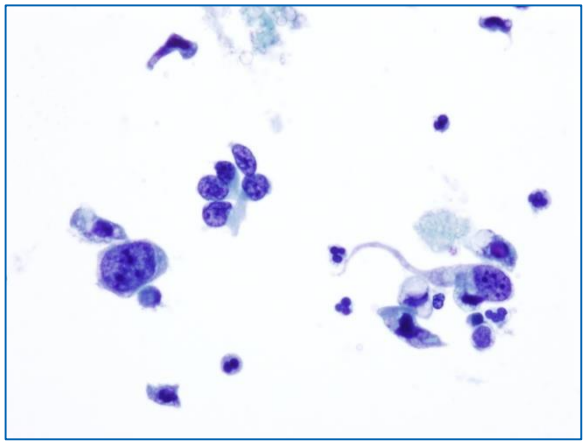
Glandular differentiation

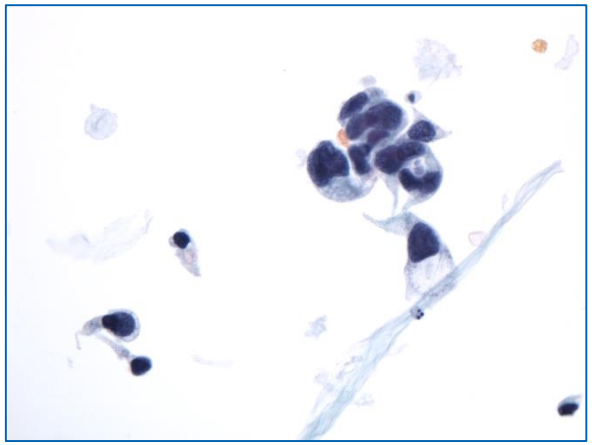


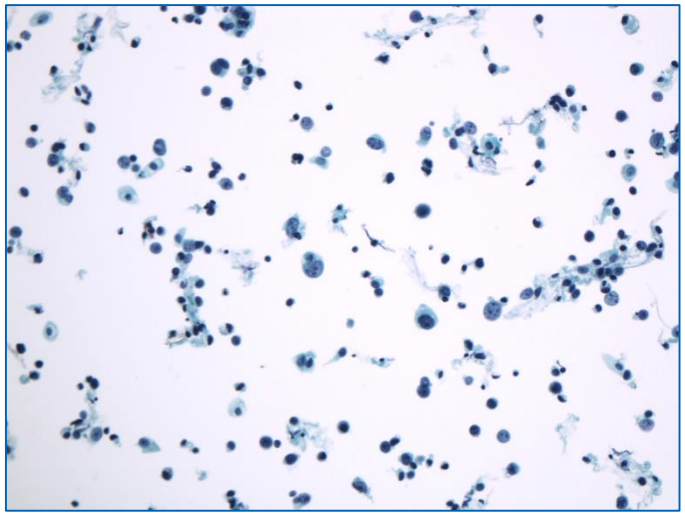


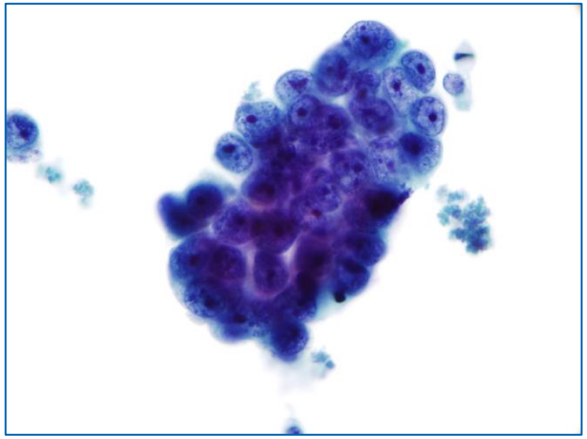
Other Notable Cytomorphologic Features

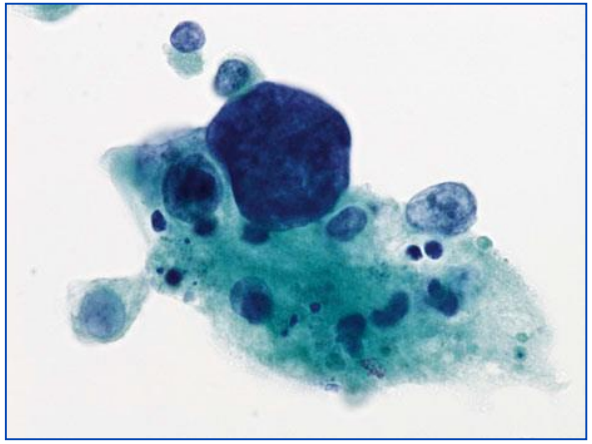
- Cellular pleomorphism
- Marked variation in cellular size and shapes, i.e., oval, rounded, elongated, or plasmacytoid (Comet cells)
- Scant, pale, or dense cytoplasm
- Prominent nucleoli
- Mitoses
- Necrotic debris
- Inflammation







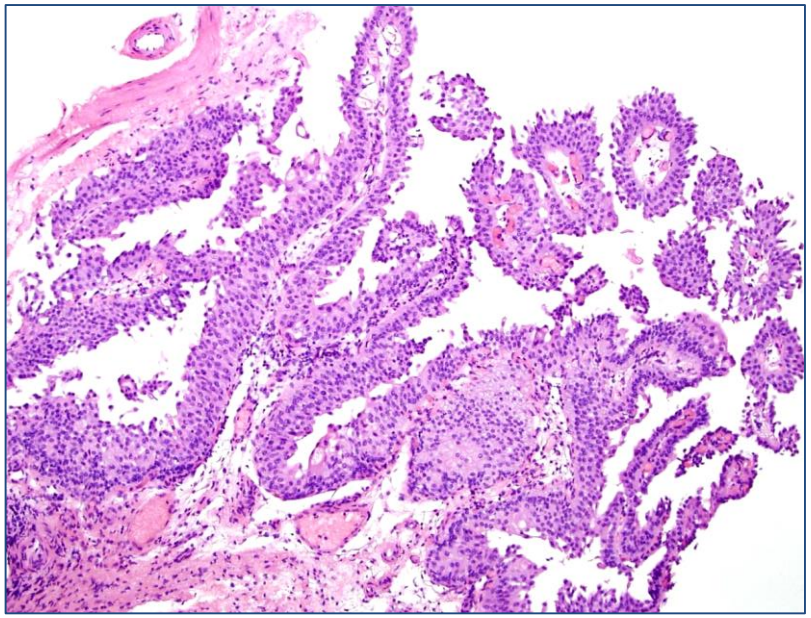




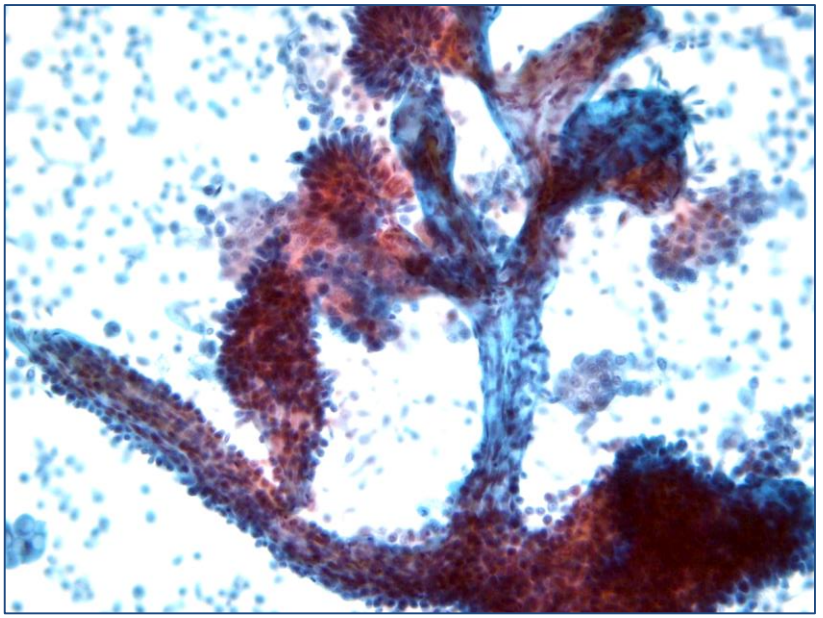
Low-Grade Urothelial Neoplasia (LGUN)

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



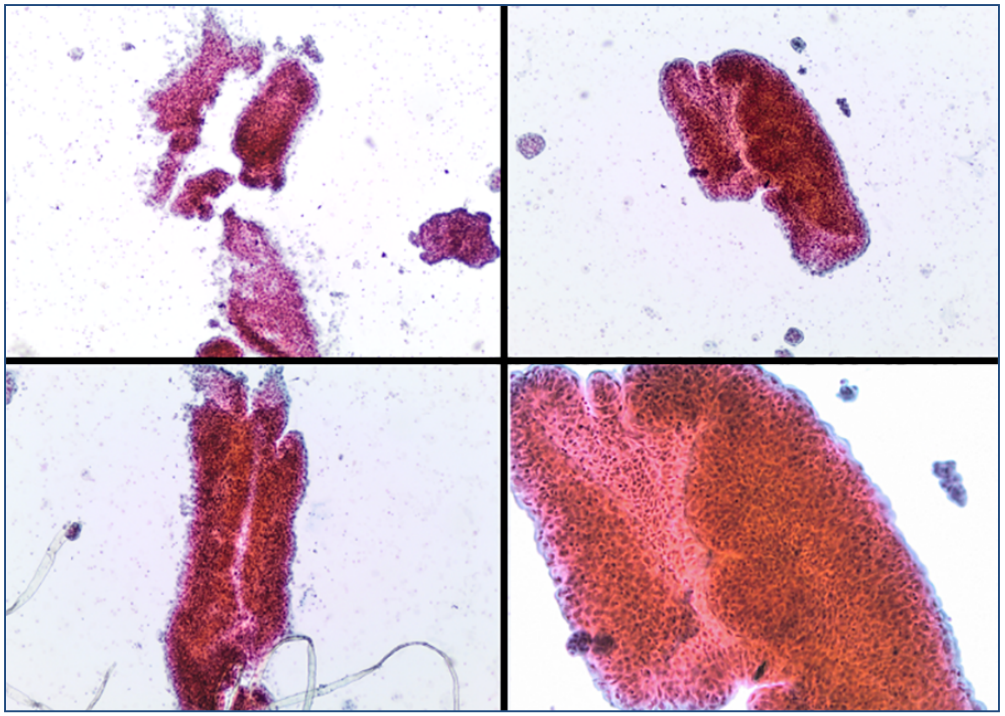
LGUC

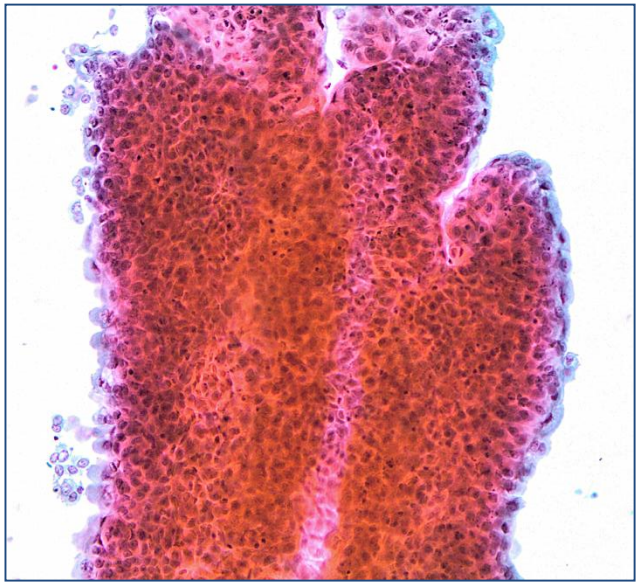


LGUN

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

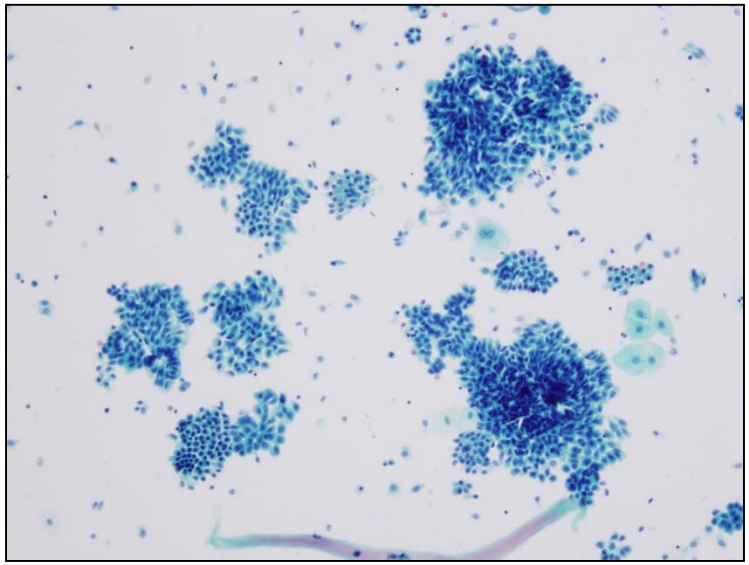
- Three-dimensional cellular papillary clusters (defined as clusters of cells with nuclear overlapping, forming "papillae") with fibrovascular cores with capillaries

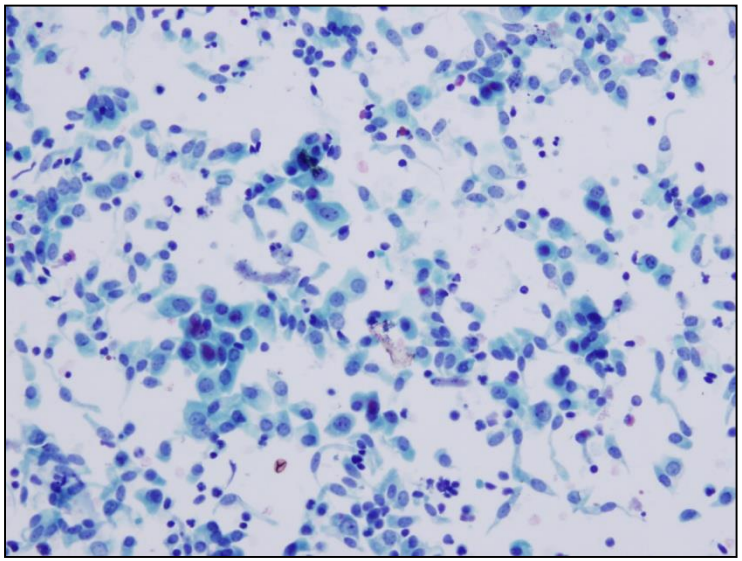




LGUN may be considered in correlation with cystoscopic or biopsy findings
Diagnosis - NHGUC

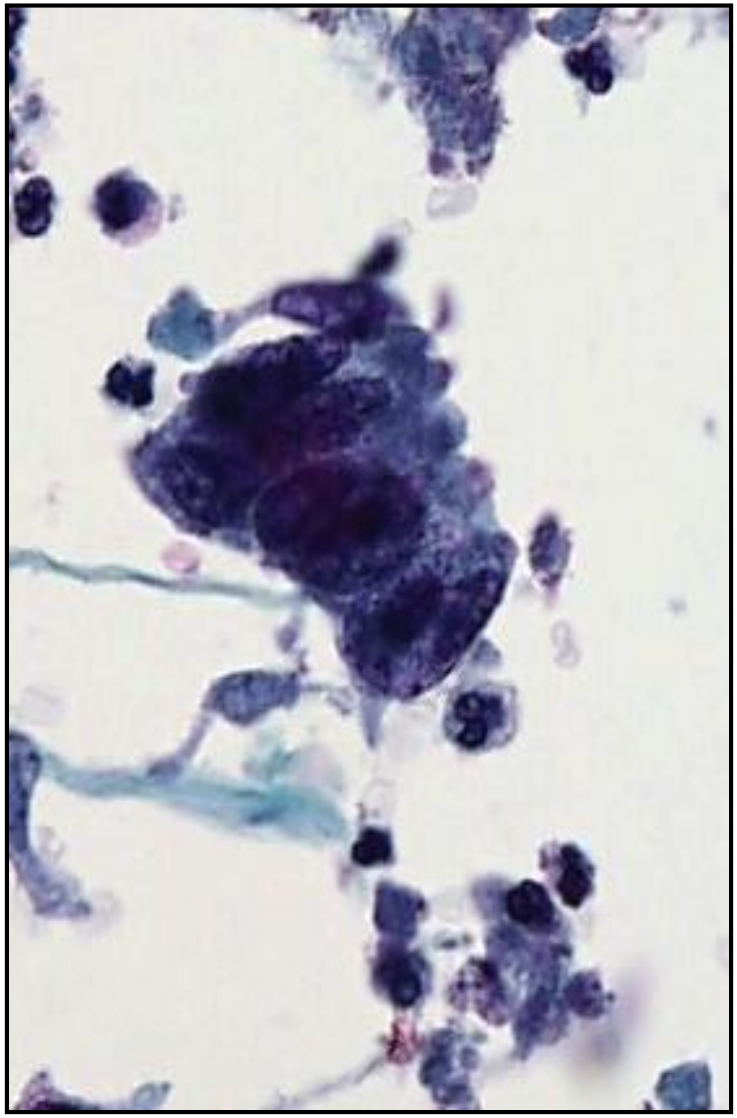
- Three-dimensional cellular clusters without fibrovascular cores
- Increased numbers of monotonous single (non-umbrella) cells

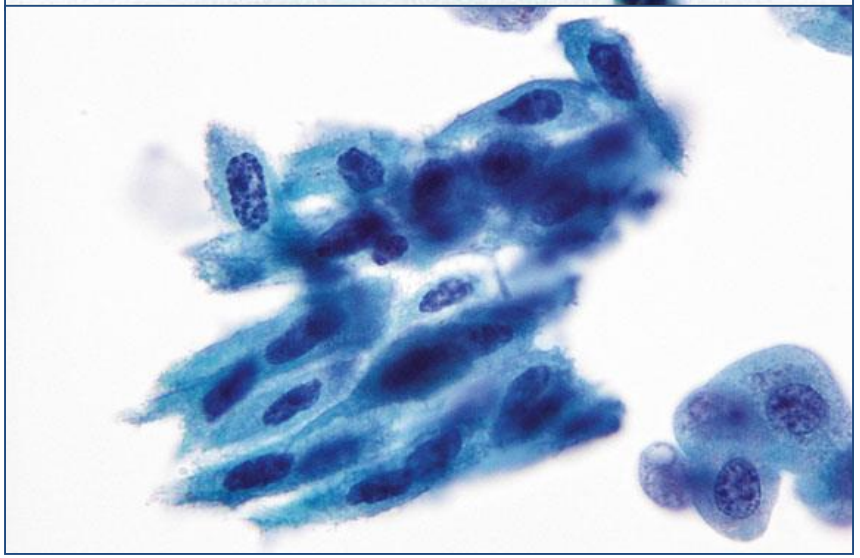




Other Malignancies Primary and Metastatic and Miscellaneous Lesions

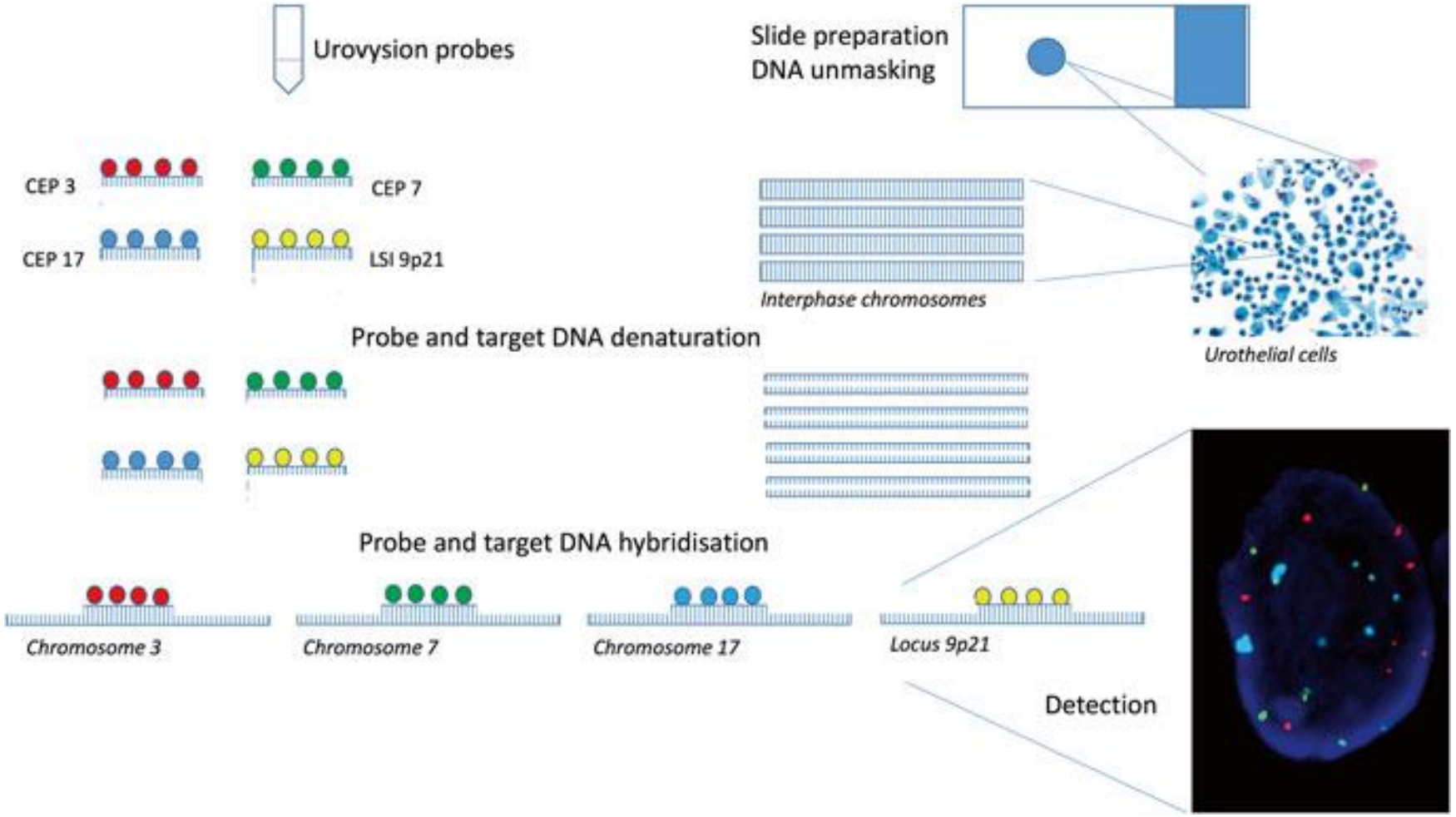
Rana S. Hoda, Stefan E. Pambuccian, Jae Y. Ro, and Sun Hee Sung

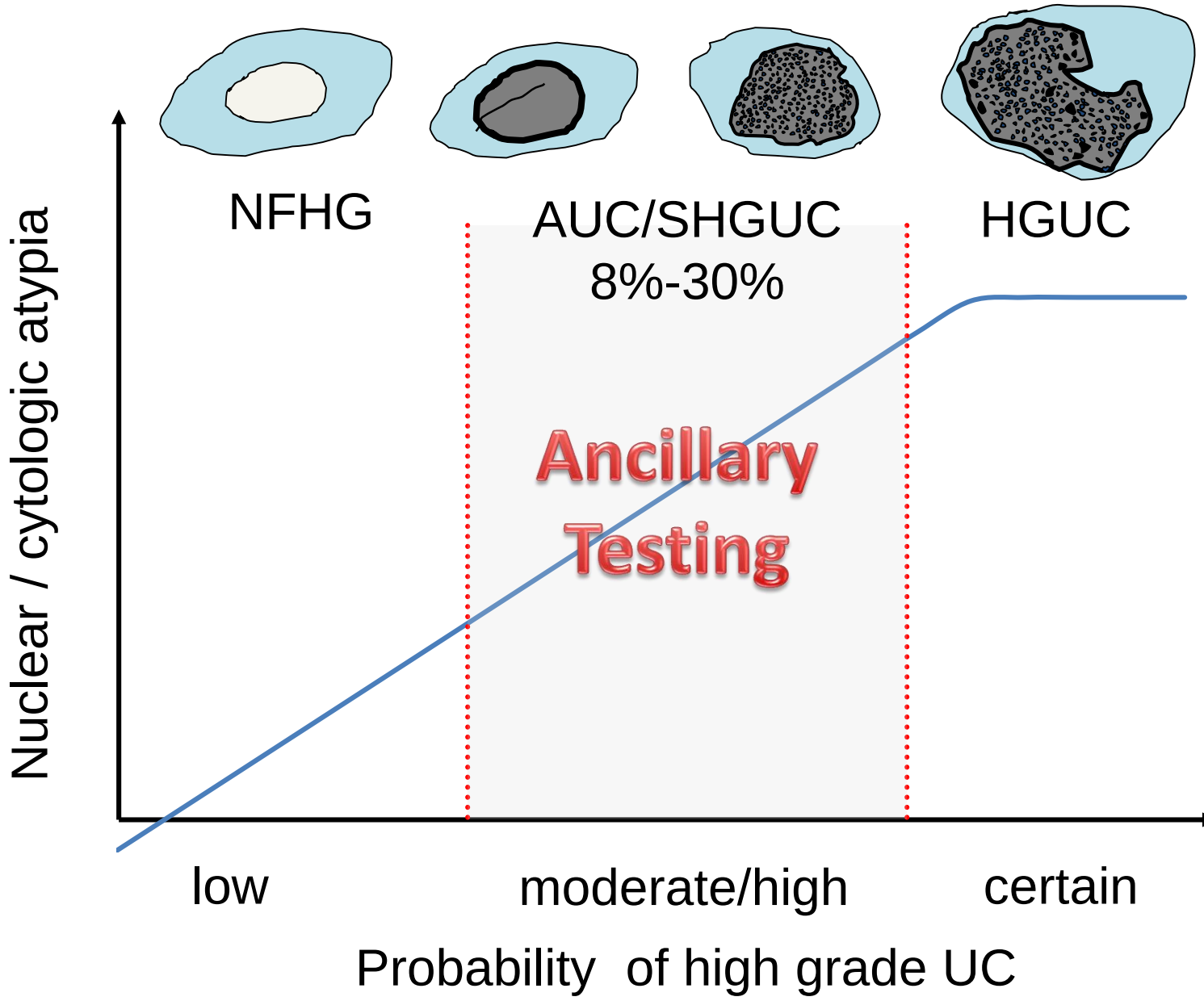




Ancillary Studies in Urinary Cytology

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




NFHG
AUC/SHGUC
8%-30%
HGUC
Ancillary Testing
Nuclear / cytologic atypia
low
moderate/high
certain
Probability of high grade UC

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

2014 Supplemental Questionnaire of the College of American Pathologists (CAP) Cytopathology Interlaboratory Comparison Program (CICP), Barkan et al.

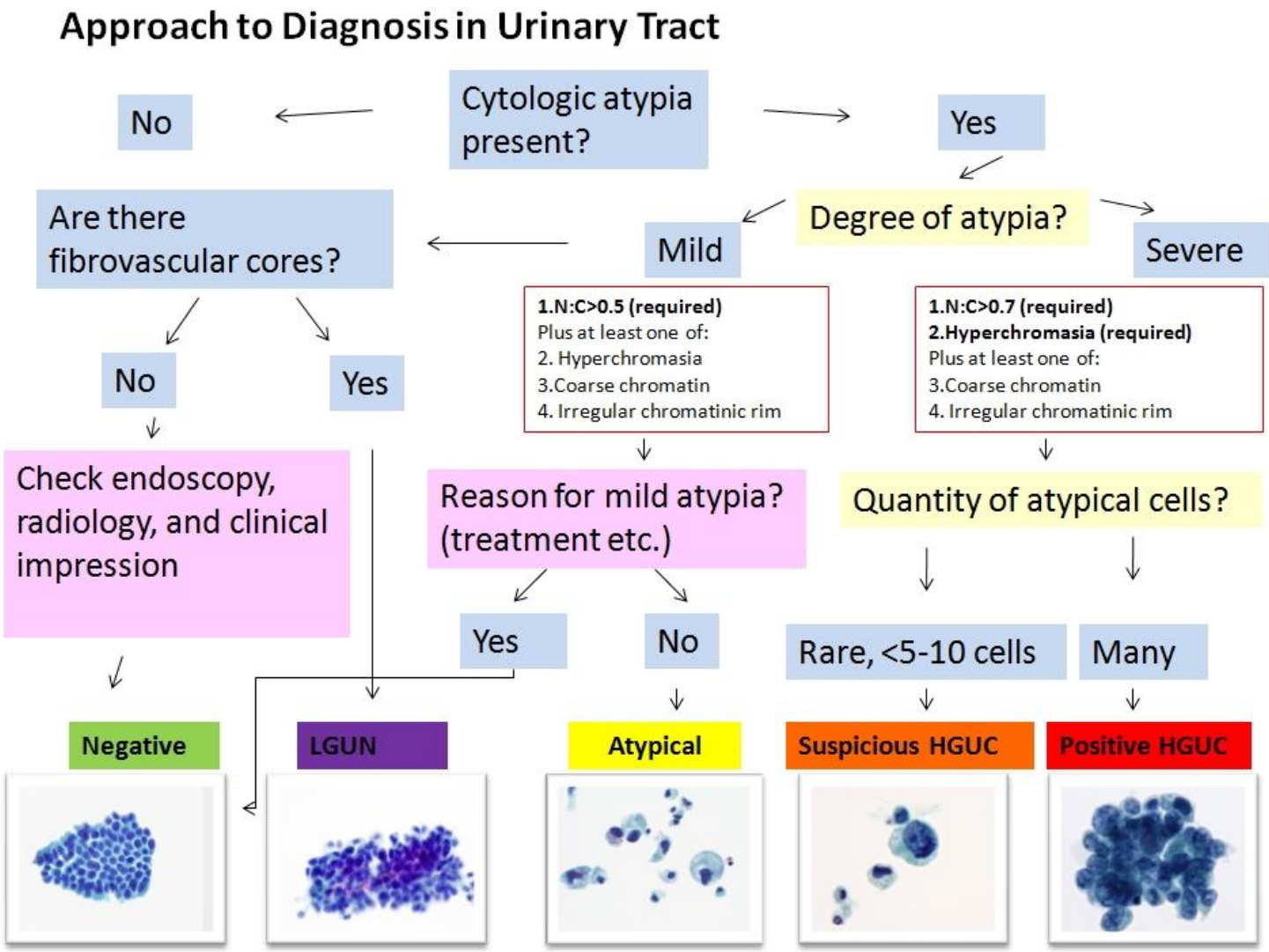
Clinical Management

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

Risk of malignancy (HGUC) – ongoing studies

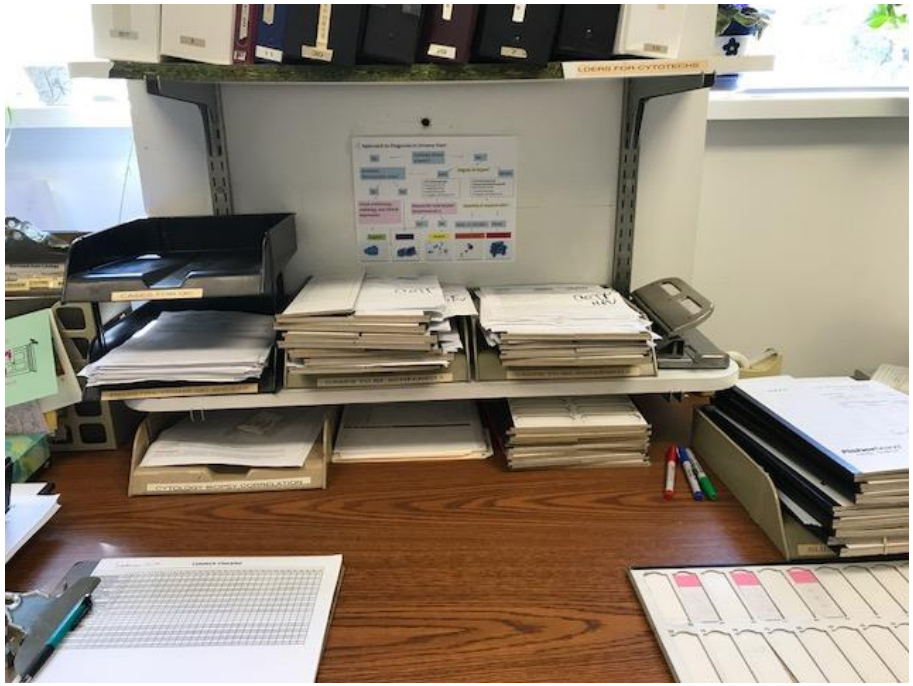
Category	Risk of Malignancy	Management
Unsatisfactory/Nondiagnostic	<5%	Repeat cytology, cystoscopy in 3 months if increased clinical suspicion
Negative for HGUC	0-2%	Clinical follow up as needed
Atypical Urothelial Cells (AUC)	8-35%	Clinical follow up as needed. Use of ancillary testing.
Suspicious 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

Implementation



G. Barkan, MD

Visual aids for diagnostic criteria in the lab:



- In the sign out/fellows room

•In the cytotech screening room

Standardized categories at LUMC for urinary tract specimens (CoPath)

- PUNSAT
  - Unsatisfactory for evaluation. Specimen processed and examined, but unsatisfactory for evaluation due to insufficient urothelial cell cellularity
- PNHGUC
  - Negative for high grade urothelial carcinoma
- PAUC
  - Atypical urothelial cells present
- PSHGUC
  - Suspicious for high grade urothelial carcinoma
- PHGUC
  - High grade urothelial carcinoma
- PLGUN
  - Low grade urothelial neoplasm

Cytology Cases by Interp % Department Summary

Date/Time Printed: 9/1/2017 12:21

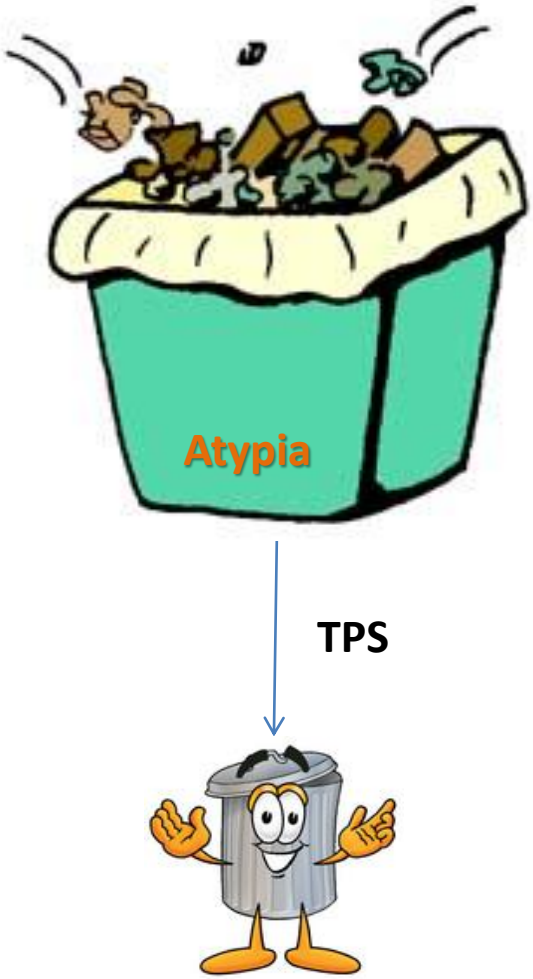
Selection Criteria: Accession Date: 1/1/2017 00:00 To 9/1/2017 12:16
Specimen Class: (1) NG (Non-GYN)
Interpretation: (7) Urine, atypical urothelial cells present ; Urine, high grade urothelial carcinoma. ; Urine, low g

Qty	Interpretation	Assigned/Part	Specimens Reviewed
159	Urine, atypical urothelial cells present	6.7%	128
112	Urine, high grade urothelial carcinoma	4.7%	64
10	Urine, low grade urothelial neoplasm	0.4%	10
1949	Urine, negative for high grade urothelial carcinoma	81.5%	1043
52	Urine, suspicious for high grade urothelial carcinoma	2.2%	40
108	Urine, unsatisfactory for urines	4.5%	67

Total Interpretations: 2390
Total Specimens: 1209

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
- Future studies are needed for validation of TPS



In less then a year….