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

Classifications

**WHO 1973**

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

**WHO/ISUP 2004**

- ~10-20%
- ~50-60%
- ~80-90%

**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).

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<th>Answer</th>
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<td>2</td>
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<td>15%</td>
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<td>3</td>
<td>Comments/Suggestions:</td>
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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%
- Normal Urothelium
- Hyperplasia
- Genetically Stable FGFR3 (~85%)
- Low Grade Carcinoma
- Recurrence

Non-Papillary Pathway
- 20%
- Normal Urothelium
- Dysplasia
- Genetically Unstable p53 (~60%)
- High Grade Carcinoma
- Recurrence

- 9p-, 9q-
- p16
- Carcinoma in situ
- <10%
- Recurrence

Papillary Pathway
- 80%

Non-Papillary Pathway
- 20%

Genetically Stable FGFR3 (~85%)
Genetically Unstable p53 (~60%)
RAS (?)
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

“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”?
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

<table>
<thead>
<tr>
<th>Cytologic Classification</th>
<th>Histologic Classification</th>
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<tr>
<td><strong>Papanicolaou 1947</strong>&lt;sup&gt;5&lt;/sup&gt; (Papanicolaou Classification System)</td>
<td><strong>Mostofi &amp; Torlone 1973</strong>&lt;sup&gt;3&lt;/sup&gt; (WHO&lt;sup&gt;10&lt;/sup&gt;)</td>
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<td>Koss 1985&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Hopkins Template</td>
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<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Papanicolaou</th>
<th>Ooms &amp; Veldhuizen</th>
<th>Layfield et al 2004&lt;sup&gt;13&lt;/sup&gt; (Papanicolaou Society of Cytopathology)</th>
<th>Hopkins Template</th>
<th>Mostofi &amp; Torlone 1973&lt;sup&gt;3&lt;/sup&gt; (WHO&lt;sup&gt;10&lt;/sup&gt;)</th>
<th>Epstein 1998&lt;sup&gt;14&lt;/sup&gt; (WHO/ISUP)</th>
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<tbody>
<tr>
<td>I</td>
<td>Benign cells, ATY 1 cells, few clusters</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>NUAM</td>
<td>Papilloma</td>
<td>Papilloma</td>
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<tr>
<td>II</td>
<td>Clusters, nuclear elongation, few ATY 2 cells</td>
<td>Dysplastic cells</td>
<td>Atypical, significance uncertain</td>
<td>Atypical urothelial cells</td>
<td>AUC-US</td>
<td>TCC, grade 2</td>
<td>PUNLMP</td>
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<tr>
<td>III</td>
<td>Malignant tumor cells, many ATY 2 cells</td>
<td>Suspicious</td>
<td>Suspicious</td>
<td></td>
<td>AUC-H</td>
<td>TCC, grade 2</td>
<td>LGUC</td>
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<td>IV</td>
<td>Malignant cells</td>
<td>Neoplastic cells present</td>
<td>Urothelial carcinoma</td>
<td>Urothelial carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V</td>
<td></td>
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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 $\rightarrow$ SHGUC $\rightarrow$ HGUC
  - Quality and Quantity $\rightarrow$ Quantity
- LGUN – Low Grade Urothelial Neoplasms
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.)

“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

Melamed – Wolinska body
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 hyperchromasemia
3. Coarse, clumped chromatin
4. Irregular nuclear membranes
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 \( \geq 10 \) 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-Kalijji, 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)
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

- **Cytologic atypia present?**
  - No
  - Yes

- **Are there fibrovascular cores?**
  - No
  - Yes

  - Check endoscopy, radiology, and clinical impression

- **Degree of atypia?**
  - Mild
  - Severe

  - 1. N:C > 0.5 (required)
  - Plus at least one of:
    2. Hyperchromasia
    3. Coarse chromatin
    4. Irregular chromatinic rim

- **Reason for mild atypia?**
  - (treatment etc.)

  - Yes
  - No

  - Quantity of atypical cells?
    - Rare, <5-10 cells
    - Many

  - Negative
  - LGUN

- **Atypical**

  - Suspicious HGUC
  - Positive HGUC

G. Barkan, MD
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
Nuclear / cytologic atypia

Probability of high grade UC: low, moderate/high, certain

AUC/SHGUC: 8%-30%

Ancillary Testing
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

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<th>How are UT specimens processed in your laboratory? n = 739 (Multiple responses allowed)</th>
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<td>Cytospin</td>
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<td>Cell block</td>
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<td>Conventional smear</td>
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<td>2.2</td>
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<td>Other</td>
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<td>1.5</td>
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2014 Supplemental Questionnaire of the College of American Pathologists (CAP) Cytopathology Interlabatory Comparison Program (CICP), Barkan et al.
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

**Risk of malignancy – ongoing studies**

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

Non-Paris CP Post vs pre %AUC, p<0.05
Paris CP Post vs pre %AUC, p<0.05
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

Circariform 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 \textbf{N/C ratio} \textgreater{} \textbf{0.7} (required)
- \textbf{Hyperchromasia} (compared to the umbrella cells or the intermediate squamous cell nucleus) (required)

and one of the following:
- \textbf{Irregular clumpy chromatin}
- \textbf{Irregular nuclear membranes}

\textless{}10 cells
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
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
A 68-year-old man presents 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
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
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
GYN contamination

Sq metaplasia – chronic irritation (stones)

Sq differentiation in HGUC or pure SqCCa

GYN contamination - LSIL
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)
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
A 92-year-old man presents with a history of bladder cancer. Ilial 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**
- 2\(^{nd}\) 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
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!