The Paris System for Reporting Urinary Cytology: A Paradigm Shift

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Conflict of Interest:

- None
Why 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%
A reliable system has to be build based on:

- Consensus
- Evidence
- Inclusion
- Acceptance
- Understanding

Surgeons misunderstood pathologists’ reports 30% of the time. 

Powsner, SM. Costa J, Homer RJ. Clinicians are from Mars and pathologists are from Venus. Clinician Interpretation of Pathology Reports. Arch Pathol Lab Med 2000. 124:1040–1046
Normal Urothelium

Hyperplasia

Dysplasia

Low Grade Carcinoma

High Grade Carcinoma

Carcinoma in situ

Invasive Carcinoma

Papillary Pathway
80-90%

Non-Papillary Pathway
10-20%

9p-, 9q-, p16

FGFR3 (~85%)

Genetically Stable

p53 (~60%)

Genetically Unstable

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 (> T2)
  - >60% overall survival

Question…. “Carcinoma”? 
Classifications

WHO 1973

Papilloma
- Grade I
- Grade II
- Grade III

Papilloma
- PUNLMP
- Low Grade
- High Grade

WHO/ISUP 2004

URINE CYTOLOGY SENSITIVITY

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

• Urine cytology is all about detecting High Grade Urothelial Carcinoma (HGUC)

• “Negative for High Grade Urothelial Carcinoma”

• AUC Quality and Quantity SHGUC Quantity HGUC

• LGUN – Low Grade Urothelial Neoplasm
What really matters?

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

- 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 that is based on consensus, wide participation and evidences
  - Ultimate goal – detection of HGUC

- Sponsorship by the ASC and IAC
- Contract with Springer
- Numerous face-to-face meetings
"What happens in Paris, stays in Paris."
I. Adequacy of Urine Specimens (Adequacy)

Matthew T. Olson, Güliz A. Barkan, Monique Courtade-Saidi, 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.)

• **20 bladder barbotage cases** (6 neg, 3 AU, 1 susp, 10 pos) with sufficient material remaining in the liquid based media were **serially diluted**.

• Between 6 and 9 slides (dilutions) from each case, including the original slide, were de-identified and given to 1 cytotechnologist, 1 fellow and 3 cytopathologists for diagnosis.

• In total, **155 slides** were reviewed from **20 patients**.

<table>
<thead>
<tr>
<th>Cellularity</th>
<th>AU+</th>
<th>UC</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10 per 10 hpf</td>
<td>60.5%</td>
<td>37.2%</td>
</tr>
<tr>
<td>&gt;10 per 10 hpf</td>
<td>95.2%</td>
<td>76.2%</td>
</tr>
<tr>
<td>p value</td>
<td>0.0001</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cellularity</th>
<th>AU+</th>
<th>UC</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20 per 10 hpf</td>
<td>68.3%</td>
<td>43.3%</td>
</tr>
<tr>
<td>&gt;20 per 10 hpf</td>
<td>100.0%</td>
<td>88.0%</td>
</tr>
<tr>
<td>p value</td>
<td>0.001</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

**Conclusion:**

• In the absence of atypical or malignant cells, obscuring inflammation/lubricant an adequate bladder barbotage specimen should have a minimum of **2644 (20 per 10 hpfs)** well-visualized, well-preserved urothelial cells to increase positive predictive value of this test.
Guidelines for estimating cellularity in urinary tract specimens

<table>
<thead>
<tr>
<th>Prep Diam (mm)</th>
<th>Area (mm²)</th>
<th>FN20 eyepiece 10X objective</th>
<th>FN20 eyepiece 40X objective</th>
<th>FN22 eyepiece 10X objective</th>
<th>FN22 eyepiece 40X objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>132.7</td>
<td>42.3</td>
<td>62.5</td>
<td>3.9</td>
<td>34.9</td>
</tr>
<tr>
<td>20</td>
<td>314.2</td>
<td>100</td>
<td>26.4</td>
<td>1.7</td>
<td>82.6</td>
</tr>
</tbody>
</table>

Adapted from the Bethesda System from Reporting Cervical Cytology, Editors Diane Solomon and Ritu Nayar, 2nd Ed, 2004, Chapter 1, pg 8

Acta Cytol. 2016;60(3):185-97
Should urine volume be a factor in specimen adequacy? *(VandenBussche et al.)*

- 15,731 voided urine specimens, SurePath, >10 years
- Inadequate cellularity during this period was purely subjective

Yes, especially if the volume is <20mL and no malignant cells are seen.
Adequacy in Voided Urine Cytology Specimens: The Role of Volume and a Repeat Void Upon Predictive Values for High-Grade Urothelial Carcinoma

Christopher J. VandenBussche, MD, PhD; Dorothy L. Rosenthal, MD; and Matthew T. Olson, MD

Enough Is Enough: Adequacy of Voided Urine Cytology

Güliz A. Barkan, MD
II. 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:

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; polyomavirus (BK virus—decoy cells)
– Post-therapy effect, including epithelial cells from urinary diversions
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!
“Negative, NOT atypia”

Wojcik EM: What should not be reported as atypia in urine cytology: JASC 2015;4;3;30-36
What is the NPV of UTC?

<table>
<thead>
<tr>
<th></th>
<th>History of UC</th>
<th>Hematuria</th>
<th>Other indications</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>VU POS</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Neg</td>
<td>25</td>
<td>339</td>
<td>92</td>
<td>456</td>
</tr>
<tr>
<td>total</td>
<td>26</td>
<td>341</td>
<td>95</td>
<td>462</td>
</tr>
<tr>
<td>%</td>
<td>3.85%</td>
<td>0.59%</td>
<td>3.16%</td>
<td>1.30%</td>
</tr>
<tr>
<td>NPV</td>
<td>96.15%</td>
<td>99.41%</td>
<td>96.84%</td>
<td>98.70%</td>
</tr>
<tr>
<td>BB/BW Pos</td>
<td>67</td>
<td>5</td>
<td>6</td>
<td>78</td>
</tr>
<tr>
<td>Neg</td>
<td>592</td>
<td>1096</td>
<td>290</td>
<td>1978</td>
</tr>
<tr>
<td>total</td>
<td>659</td>
<td>1101</td>
<td>296</td>
<td>2056</td>
</tr>
<tr>
<td>%</td>
<td>10.17%</td>
<td>0.45%</td>
<td>2.03%</td>
<td>3.79%</td>
</tr>
<tr>
<td>NPV</td>
<td>89.83%</td>
<td>99.55%</td>
<td>97.97%</td>
<td>96.21%</td>
</tr>
<tr>
<td>Other Pos</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Neg</td>
<td>29</td>
<td>64</td>
<td>0</td>
<td>93</td>
</tr>
<tr>
<td>total</td>
<td>32</td>
<td>64</td>
<td>0</td>
<td>96</td>
</tr>
<tr>
<td>%</td>
<td>9.38%</td>
<td>0.00%</td>
<td></td>
<td>3.13%</td>
</tr>
<tr>
<td>NPV</td>
<td>90.63%</td>
<td>100.00%</td>
<td></td>
<td>96.88%</td>
</tr>
<tr>
<td>TOTAL POS</td>
<td>71</td>
<td>7</td>
<td>9</td>
<td>87</td>
</tr>
<tr>
<td>Neg</td>
<td>646</td>
<td>1499</td>
<td>382</td>
<td>2527</td>
</tr>
<tr>
<td>total</td>
<td>717</td>
<td>1506</td>
<td>391</td>
<td>2614</td>
</tr>
<tr>
<td>%</td>
<td>9.90%</td>
<td>0.46%</td>
<td>2.30%</td>
<td>3.33%</td>
</tr>
<tr>
<td>NPV</td>
<td>90.10%</td>
<td>99.54%</td>
<td>97.70%</td>
<td>96.67%</td>
</tr>
</tbody>
</table>

- UTCy has a high (96.7%) NPV
- NPV was highest in the hematuria patient group
- NPV of UTCy in patients with history of UC was only 90%, suggesting that UTCy should be used in conjunction with cystoscopy results to rule out recurrences of UC in this group of patients.

What is Atypia?
Atypia - Pubmed Search

“atypia” /“atypical” through a PubMed title search

Cytopathology journals 2.28% (337/14775) articles

Anatomic/surgical pathology journals 1.26% (469/37371) articles

General medical journals 0.1% (161/154,358) of articles

Pambuccian SE: What is Atypia? Use, misuse and overuse of the term "atypia" in diagnostic cytopathology JASC 2015;4;1;44-52
Setting the criteria – The evidence

Diagnostic terminology for urinary cytology reports including the new subcategories ‘atypical urothelial cells of undetermined significance’ (AUC-US) and ‘cannot exclude high grade’ (AUC-H)

E. Piaton*†, M. Decaussin-Petrucci†, F. Mege-Lechevallier†, A.-S. Advenier*, M. Devonec† and A. Ruffion*†

(1) an increased N/C ratio, exceeding 0.7 (55%)
(2) nuclear hyperchromasia with dense chromatin (69%)
(3) a irregularly outlined nuclear shape (88%)

1. Individual abnormal cells  74%
2. Hyperchromatic nuclei 71%
3. Irregular nuclear borders  65%
4. Increased nuclear-to-cytoplasm ratio 56%
5. Anisonucleosis 55%

Sensitivity of both high nuclear cytoplasmic ratio and hyperchromasia 86%

The Value of the “Suspicious for Urothelial Carcinoma” Cytology Category
A Correlative Study of 4 Years Including 337 Patients
Tuyet Nhung Ton Nu, MD1; Wassim Kassouf, MD2; Babak Ahmad-Kalij, MD3; Michele Charbonneau, CT4; Manon Auger, MD5; and Fadi Brimo, MD1
Cancer Cytopathology 2014

Sub-classifying Atypia in Urine Cytology: What are the Helpful Features?
Zulfia McCroskey, Burak Bahar, Zhinong Hu, Eva M. Wojcik, Güliz A. Barkan JASC 2014
Publication stage: In Press Accepted Manuscript

Reproducibility of the Johns Hopkins Hospital template for urologic cytology samples
Matthew T. Olson, MD5, Anna Novak, CT(ASCP)6, Thiraphon Boonyaarun Nate, MD5,b, Jessi Trotter, CT(ASCP)6, Sharon Sachs, CT(ASCP) (IAC)6, Deidra Kelly, CT(ASCP)6, Sterling Ford, CT(ASCP)5, Toby C. Cornish, MD5, Adam Toll, MD5, Armanda D. Tatsas, MD5, Zahra Maleki, MD5, Yener S. Erozan, MD5, Dorothy L. Rosenthal, MD5c
JASC 2014

-N/C ratio >0.5
-irregular nuclear membranes,
-nuclear hyperchromasia, and/or clumped chromatin.

-N/C ratio >70%
-Coarse chromatin pattern

-hyperchromasia
->2 high-grade features has a significantly higher malignancy
Summary: Findings in literature

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

Atypia → Suspicious → Positive
N:C ratio problem

![Image of N:C ratios and example images from a quiz.](image)

N:C ratios and exclusively examine “real” cells. Furthermore, algorithmic processes for determining malignant potential, if they specify a decimal N:C ratio as a cutoff, typically refer to ratios of ≥0.65. Therefore, the practice of specifying discrete decimal N:C ratios for atypical cells appears to be valid.

So, when do I call atypia?
III. 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
AUC

N/C -0.5
HYPERCHROMASIA
CLUMPY CHROMATIN

N/C > 0.5
NO HYPERCHROMASIA,
IRREGULAR MEMBRANES
IV. 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 Suspicious

• Non-superficial and non-degenerated urothelial cells with a 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 contours
Suspicious HGUC

↑N/C
HYPERCHROMASIA
IRREGULAR MEMBRANES

↑N/C
HYPERCHROMASIA
CLUMPY CHROMATIN
IRREGULAR MEMBRANES
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.”

Does the Number of Atypical Urothelial Cells Matter for distinguishing the “high-grade urothelial carcinoma (HGUCA)” from the “suspicious for HGUCA” cytological categories?
Approach to Diagnosis in Urinary Tract

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

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

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

2. **Check endoscopy, radiology, and clinical impression**

3. **Reason for mild atypia? (treatment etc.)**
   - Yes
   - No

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

5. **Approach to Diagnosis in Urinary Tract**

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

   - **2.** N:C > 0.7 (required)
     - Plus at least one of:
       1. Hyperchromasia (required)
       2. Coarse chromatin
       3. Irregular chromatinic rim

- **Negative**
- **LGUN**
- **Atypical**
- **Suspicious HGUC**
- **Positive HGUC**
IX. Clinical Management

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

- **Negative**
  - Follow up as Normal/ as needed

- **Atypical**
  - Individualized
  - Role of FISH?

- **Suspicious HGUC**
  - Close follow up (within 1-3 months)
  - Biopsy, Stage

- **Positive HGUC**

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2/15/2017
### Table 4.1 Published reporting rates and the follow-up of atypical urothelial cells

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Rate of AUC (%)</th>
<th>Follow-up HGUC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barasch et al. [6]</td>
<td>2013</td>
<td>5.7</td>
<td>14.3</td>
</tr>
<tr>
<td>Rosenthal et al. [7]</td>
<td>2013</td>
<td>31.0</td>
<td>18.0</td>
</tr>
<tr>
<td>Piaton et al. [8]</td>
<td>2014</td>
<td>&lt;2</td>
<td>8.3</td>
</tr>
<tr>
<td>Muus et al. [9]</td>
<td>2012</td>
<td>8.1</td>
<td>21.0</td>
</tr>
<tr>
<td>Mokhtar et al. [10]</td>
<td>2010</td>
<td>2.1</td>
<td>37.5</td>
</tr>
<tr>
<td>Streeter et al. [12]</td>
<td>2008</td>
<td>N/A</td>
<td>30.9</td>
</tr>
<tr>
<td>Kapur et al. [13]</td>
<td>2008</td>
<td>6.9</td>
<td>33.0</td>
</tr>
<tr>
<td>Bhatia et al. [14]</td>
<td>2006</td>
<td>1.9</td>
<td>20.0</td>
</tr>
<tr>
<td>Deshpande et al. [15]</td>
<td>2005</td>
<td>N/A</td>
<td>13.0</td>
</tr>
</tbody>
</table>

*AUC* Atypical urothelial cells, *HGUC* high-grade urothelial carcinoma, *N/A* not applicable

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The Paris System: Eds Rosenthal D, Wojcik EM, Kurtycz DFI, Springer 2015, Chapter 4
## Follow up on SHGUC and HGUC

<table>
<thead>
<tr>
<th>Study</th>
<th>Specimen Type</th>
<th>Clinical Indications</th>
<th>Cases</th>
<th>PPV</th>
<th>Cases</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joudi et al. 2016</td>
<td>Inst: 86%</td>
<td>New Symptoms: 10% Surveillance: 90%</td>
<td>150</td>
<td>55.3%</td>
<td>459</td>
<td>79.2%</td>
</tr>
<tr>
<td>Ton nu et al 2014</td>
<td>Ins: 29%</td>
<td>New symptoms: 29% Surveillance: 71%</td>
<td>191</td>
<td>79%</td>
<td>256</td>
<td>86%</td>
</tr>
<tr>
<td>VandenBussche et al.2013</td>
<td>N/A</td>
<td>N/A</td>
<td>82</td>
<td>71%</td>
<td>143</td>
<td>77%</td>
</tr>
<tr>
<td>Piaton et al. 2013</td>
<td>Ins: 96%</td>
<td>New Symptoms: 21% Surveillance: 79%</td>
<td>185</td>
<td>37.8%</td>
<td>162</td>
<td>59.9%</td>
</tr>
</tbody>
</table>

V. High Grade Urothelial Carcinoma

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

HGUC Definition and Criteria

• Urine cytology cannot distinguish invasive HGUC from non-invasive HGUC or CIS.

• The background in CIS: clean without blood, abundant inflammation and cell debris

• HGUC: N/C ratio that is 0.7 or greater, nuclear hyperchromasia, irregular nuclear membranes and coarse chromatin
HGUC Definition and Criteria

• A minimum of **5-10 viable malignant cells** will qualify as HGUC.

• Depends on the specimen type and comfort level of the pathologist

• Upper urinary tract specimens will require at least 10 abnormal cells, whereas voided urine specimens may require a lesser number of cells to establish a definitive diagnosis of HGUC.
Squamous differentiation

Glandular differentiation
Upper Tract Problem

Morphologic Criteria For Atypia in Upper Urinary Tract Cytology: Should It Be Different than The Lower Urinary Tract Criteria of The Paris System of Reporting Urinary Tract Cytology (PSRUC)?

Fidan-Özbilgin Ö. et al. Modern Pathology 2016;29(Sup 2):98A

<table>
<thead>
<tr>
<th>CYTOMORPHOLOGIC FEATURE</th>
<th>OR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuclear cytoplasmic (NC) ratio</td>
<td>46.750</td>
<td>0.000</td>
</tr>
<tr>
<td>Irregular nuclear contours</td>
<td>13.000</td>
<td>0.002</td>
</tr>
<tr>
<td>Coarse chromatin</td>
<td>20.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Nucleus pushed out of cytoplasm</td>
<td>9.100</td>
<td>0.009</td>
</tr>
<tr>
<td>Nuclear “cannibalism” (cell in the cell)</td>
<td>5.820</td>
<td>0.036</td>
</tr>
<tr>
<td>Nuclear eccentricity</td>
<td>2.760</td>
<td>0.136</td>
</tr>
<tr>
<td>Pleomorphism</td>
<td>5.550</td>
<td>0.095</td>
</tr>
<tr>
<td>Nuclear hyperchromasia</td>
<td>2.000</td>
<td>0.293</td>
</tr>
<tr>
<td>Prominent nucleoli</td>
<td>2.860</td>
<td>0.216</td>
</tr>
<tr>
<td>Pseudopapillary structures</td>
<td>0.955</td>
<td>0.942</td>
</tr>
<tr>
<td>Background</td>
<td>1.040</td>
<td>0.933</td>
</tr>
<tr>
<td>Anisonucleosis</td>
<td>3.850</td>
<td>0.216</td>
</tr>
<tr>
<td>Mitosis</td>
<td>2.760</td>
<td>0.136</td>
</tr>
<tr>
<td>Polyomavirus changes</td>
<td>1.818</td>
<td>0.283</td>
</tr>
<tr>
<td>Degenerative changes</td>
<td>0.666</td>
<td>0.549</td>
</tr>
</tbody>
</table>
Upper Tract Problem

The Performance of the Paris System for Reporting Urine Cytology (PSRUC) in Lower and Upper Tract Specimens: A Comparative Study of 358 Cases.

*Brimo and Barkan et al. Modern Pathology 2016;29(Sup 2):92-93A*

<table>
<thead>
<tr>
<th>Cytological Diagnosis, Lower tract (n=250)</th>
<th>Benign (n=131)</th>
<th>AUC (n=47)</th>
<th>SHGUC (n=23)</th>
<th>PHGUC (n=45)</th>
<th>Unsatisfactory (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>88</td>
<td>19</td>
<td>3</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>LGN</td>
<td>29</td>
<td>7</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>HGUC</td>
<td>14</td>
<td>21</td>
<td>18</td>
<td>39</td>
<td>1</td>
</tr>
<tr>
<td>Predictive Value for HGUC</td>
<td>11%</td>
<td>45%</td>
<td>78%</td>
<td>87%</td>
<td>25%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cytological Diagnosis, Upper tract (n=108)</th>
<th>Benign (n=46)</th>
<th>AUC (n=22)</th>
<th>SHGUC (n=9)</th>
<th>PHGUC (n=28)</th>
<th>Unsatisfactory (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>28</td>
<td>7</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>LGN</td>
<td>12</td>
<td>6</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>HGUC</td>
<td>6</td>
<td>9</td>
<td>8</td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td>Predictive Value for HGUC</td>
<td>13%</td>
<td>41%</td>
<td>89%</td>
<td>86%</td>
<td>33%</td>
</tr>
</tbody>
</table>
VI. 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
– LGPUC
– flat, low grade intraurothelial neoplasia
Is a consistent cytologic diagnosis of low-grade urothelial carcinoma in instrumented urinary tract cytologic specimens possible? A comparison between cytomorphologic features of low-grade urothelial carcinoma and non-neoplastic changes shows extensive overlap, making a reliable diagnosis impossible.

• The majority of the features described previously as diagnostic for LGPUC were observed almost equally in patients with or without biopsy-proven LGPUC, regardless of whether the specimens were from the upper or the lower urinary tract
• Mild nuclear membrane irregularity was present in 48% of LGPUC and 47.2% of negative controls (p=0.93); mild nuclear enlargement was observed in 42.9% of LGPUC patients and 49.1% negative controls (p=0.26)

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
VII. Other Malignancies Primary and Metastatic and Miscellaneous Lesions

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

Epithelial Malignancies
• Squamous cell carcinoma
• Adenocarcinoma
• Neuroendocrine Tumors
• Melanoma

Non-epithelial malignancies
• Sarcoma
• Hematologic Malignancies
Squamous Cell Carcinoma
Small cell carcinoma

Diffuse Large B cell Lymphoma

Leiomyosarcoma

Melanoma
VIII. 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, and Philippe Vielh

• Ancillary Tests: UroVysion FISH (Abbott Molecular Inc, Des Plaines, IL), ImmunoCyt (Scimedx, Denville, NJ), BTA stat (Polymedco, Cortlandt Manor, NY), and NMP 22 (Allere, Waltham, MA).

• When NOT to use the Ancillary studies: NHGUC, HGUC

• When ancillary studies may be of use: AUC (Selected conditions)
**UroVysion FISH in AUC**

U-FISH in the setting of AUC: detection of HGUC

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
<th>False Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>48.39%</td>
<td>78.77%</td>
<td>28.3%</td>
<td>89.81%</td>
<td>74.29%</td>
<td>52.83%</td>
</tr>
</tbody>
</table>

“A positive U-FISH result may heighten this degree of suspicion, but a negative U-FISH test cannot be used to limit the need for routine cystoscopic surveillance.”

The Value Of The UroVysion® FISH Assay In The Risk-Stratification Of Patients With “Atypical Urothelial Cells” In Urinary Cytology Specimens

Virk et al. Diagnostic Cytopathology 2017
X. Cytopreparatory Techniques
Gary W. Gill, William N. Crabtree, and Deidra P. Kelly

_Collection, Processing, Preparation methods_

Surepath  
Cytospin  
ThinPrep®

The most commonly used preparation techniques are ThinPrep (57.4%) and Cytospin (45.5%).
Barkan et al Modern Pathology 2015;28 (Supp 2):83A
The opportunities: Future studies

• Using the new system does the rate of equivocal diagnosis (AUC, SHGUC) change?
• Does the cytology:histology correlation change?
• Should SHGUC and HGUC remain as separate categories or should they merge?
• What are individual and laboratory ratios or equivocal:definitive diagnosis (akin to ASC-US:LSIL ratio) Can it be used as a quality assurance tool?
• Wish list at the back of the book: Anyone looking for project ideas?
## Risk of malignancy – ongoing studies

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk of Malignancy</th>
<th>Management</th>
</tr>
</thead>
<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>0-10%</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>SHGUC</td>
<td>50-90%</td>
<td>More aggressive follow up, cystoscopy, biopsy, staging</td>
</tr>
<tr>
<td>HGUC</td>
<td>&gt;90%</td>
<td>More aggressive follow up, cystoscopy, biopsy, staging</td>
</tr>
<tr>
<td>LGUN</td>
<td>≤10%</td>
<td>Need biopsy to further evaluate grade and stage</td>
</tr>
<tr>
<td>Other malignancy</td>
<td>&gt;90%</td>
<td>More aggressive follow up, cystoscopy, biopsy, staging</td>
</tr>
</tbody>
</table>
Take Home Points

• Efforts to standardize the Urinary Tract Cytology
• Outcome data, reporting rates of categories
• Know the past medical history and clinical findings and speak the same language with your Urologist enables YOU to help your patient better
Thank you!
Thank you!