Applying the Paris system for reporting Urinary Cytology

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And
Ashish Chandra
Outlines

• 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?
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
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.
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
- Hyperplasia
- Genetically Stable FGFR3 (~85%)
- Low Grade Carcinoma
- Genetically Unstable p53 (~60%)
- High Grade Carcinoma
- Carcinoma in situ

Non-Papillary Pathway
- Dysplasia
- Genetically Unstable p53 (~60%)
- Invasive Carcinoma

9p-, 9q-, p16

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

"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>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Papanicolaou 1947</strong>&lt;sup&gt;5&lt;/sup&gt; (Papanicolaou Classification System)</td>
<td><strong>Layfield et al 2004</strong>&lt;sup&gt;13&lt;/sup&gt; (Papanicolaou Society of Cytopathology)</td>
</tr>
<tr>
<td>Koss 1985&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Hopkins Template&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>I</td>
<td>Negative</td>
</tr>
<tr>
<td>II</td>
<td>Benign cells, ATY 1 cells, few clusters</td>
</tr>
<tr>
<td>III</td>
<td>Clusters, nuclear elongation, few ATY 2 cells</td>
</tr>
<tr>
<td>IV</td>
<td>Malignant tumor cells, many ATY 2 cells</td>
</tr>
<tr>
<td>V</td>
<td>Malignant cells</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Papilloma</td>
<td>Papilloma PUNLMP LGUC</td>
</tr>
<tr>
<td>TCC, grade 1</td>
<td>TCC, grade 2</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>TCC, grade 3</td>
<td></td>
</tr>
</tbody>
</table>

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 → SHGUC → HGUC

  Quality and Quantity → Quantity

• 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.)

“Negative, NOT atypia”

Wojcik EM: What should not be reported as atypia in urine cytology: JASC 2015;4;3;30-36
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
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 $\rightarrow$ Suspicious $\rightarrow$ 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
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
"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\textsuperscript{a,*}, Bin Xu, MD\textsuperscript{a}, Wassim Kassouf, MD\textsuperscript{b}, Babak Ahmadi-Kaliji, MD\textsuperscript{a}, Michele Charbonneau, CT\textsuperscript{a}, Ayoub Nahal, MD\textsuperscript{a}, Yonca Kanber, MD\textsuperscript{a}, Derin Caglar, MD\textsuperscript{a}, Manon Auger, MD\textsuperscript{a}

JASC 2015;4(4)232–238

5 – 10 cells – gray zone, based on experience, history, individual threshold, etc
What happened to LGUC??

- Cytologically normal nuclei
- Much more common than HGUC
- BUT, not life threatening
- Is it truly a carcinoma?
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
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
Other Malignancies Primary and Metastatic and Miscellaneous Lesions

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

ADC

Lymphoma

Clear cell adc bladder

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
Nuclear/cytologic atypia

NFHG

AUC/SHGUC
8%-30%

Ancillary Testing

HGUC

Probability of high grade UC

low

moderate/high
certain
No generally accepted best materials and methods of collecting and processing urine to detect urothelial malignancies

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

<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>0-2%</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>
</tr>
</tbody>
</table>
Final take home message

- HGUC – this is the one that matters – Negative for HGUC
- Not everything is atypical
- 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