Applying the Paris system for reporting Urinary Cytology

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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
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%
- 9p-, 9q-, p16
- Dysplasia
- Genetically Unstable p53 (~60%)
- Carcinoma in situ
- Invasive Carcinoma
- <10%

RAS (?)

High Grade Carcinoma
- 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

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

GU

GI
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><strong>I</strong></td>
<td><strong>Mostofi &amp; Torloni 1973</strong>&lt;sup&gt;9&lt;/sup&gt; (WHO&lt;sup&gt;6&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Benign cells, ATY 1 cells, few clusters</td>
<td>Papilloma TCC, grade 1</td>
</tr>
<tr>
<td>II</td>
<td>Papilloma PUNLMP LGUC</td>
</tr>
<tr>
<td>Clusters, nuclear elongation, few ATY 2 cells</td>
<td>Papilloma TCC, grade 2</td>
</tr>
<tr>
<td>Dysplastic cells</td>
<td>TCC, grade 2</td>
</tr>
<tr>
<td>Atypical, significance uncertain</td>
<td>AUC-US</td>
</tr>
<tr>
<td>Atypical urothelial cells</td>
<td>AUC-H</td>
</tr>
<tr>
<td>III</td>
<td>TCC, grade 3</td>
</tr>
<tr>
<td>Suspicious</td>
<td>HGUC</td>
</tr>
<tr>
<td>Suspicious</td>
<td>Urothelial carcinoma</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>Neoplastic cells present</td>
<td>Urothelial carcinoma</td>
</tr>
<tr>
<td>Urothelial carcinoma</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 — Quality and Quantity → SHGUC — Quantity → HGUC

• LGUN — Low Grade Urothelial Neoplasm
Adequacy of Urine Specimens (Adequacy)

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

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

“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
Benign Superficial (Umbrella) Urothelial Cells
“Atypical” Umbrella Cells
Glandular Cells

- Sources: endometrium, prostate, kidneys, urachal remnants, metaplasia
Cystitis cystica/glandularis
Renal Tubular Epithelial Cells
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
Survey: What do YOU call atypia in urine specimens?

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

Negative for High Grade Urothelial Carcinoma
Findings in literature

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

Atypia → Suspicious → Positive
Criteria for AUC

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

- Hyperchromasemia (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 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 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.”
Approach to Diagnosis in Urinary Tract

- **Cytologic atypia present?**
  - Yes
  - **Degree of atypia?**
    - **Mild**
      - 1. N:C > 0.5 (required)
      - Plus at least one of:
        2. Hyperchromasia
        3. Coarse chromatin
        4. Irregular chromatinic rim
    - **Severe**
      - 1. N:C > 0.7 (required)
      - Plus at least one of:
        2. Coarse chromatin
        3. Irregular chromatinic rim

- **Are there fibrovascular cores?**
  - No
  - **Check endoscopy, radiology, and clinical impression**
  - **Yes**
  - **Reason for mild atypia?** (treatment etc.)
    - **Yes**
    - **Quantity of atypical cells?**
      - Rare, <5-10 cells
      - Many
      - **Negative**
      - **LGUN**
      - **Atypical**
      - **Suspicious HGUC**
      - **Positive HGUC**
Other Malignancies Primary and Metastatic and Miscellaneous Lesions
Rana S. Hoda, Stefan E. Pambuccian, Jae Y. Ro, and Sun Hee Sung
Melanoma
Lymphoma
ADC
Clear cell adc bladder
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%)
- HGUC

Probability of high grade UC
- Low
- Moderate/high
- Certain

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

<table>
<thead>
<tr>
<th>How are UT specimens processed in your laboratory? (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>
</tr>
<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.
<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>
The opportunities: Future studies

• Using the new system does the atypia rate change?
• Does the cytology:histology correlation change?
• What is the outcome of ancillary tests in the atypical category (especially UroVysion FISH testing)?
• What are individual and laboratory AUC:HGUC ratios? Can it be used as a quality assurance tool?
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
JOIN US for the ASC 64th Annual Scientific Meeting!
November 4-7, 2016
Hyatt Regency
New Orleans, Louisiana