The Paris system for Reporting Urinary Cytology: The quest for standardized terminology

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Outline

- What is the goal of urine cytology?
- Why to standardize, why Paris?
- What is the guiding principle of TPS?
- What are diagnostic TPS categories?
- What are the criteria?
- What adjuvant studies?
- What are ROMs for TPS categories?

The main purpose of urine cytology

To detect bladder cancer
Bladder cancer - current status

- ~ 80,470 new cases in 2019 in the USA
- ~ 17,670 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

<table>
<thead>
<tr>
<th>Papilloma</th>
<th>Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
</tr>
</thead>
</table>

WHO/ISUP 2004

<table>
<thead>
<tr>
<th>Papilloma</th>
<th>PUNLMP</th>
<th>Low Grade</th>
<th>High Grade</th>
</tr>
</thead>
</table>

Why to standardize reporting of urinary cytology?

- Reproducibility
- Improvement of communication
- Atypical cells
  - Wide intraobserver variability
- Nationally rates of atypical vary among institutions (before TPS)
  - 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 Cytology
  - 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.

The goal of urine cytology is to detect clinically significant high grade lesions (HGUC).

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
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”?  

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

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 → HGUC
- LGUN – Low Grade Urothelial Neoplasm

The Process

- **INCLUSION**
  - International Working Group consisted of 49 members, 28 from 12 US states, and 21 from 9 countries
  - Open forum hosted by ASC and IAC seeking an international input

- **EVIDENCE**
  - Review of existing literature
  - Design and publish studies that address the issue

- **CONSENSUS**
  - Numerous face-to-face meetings
  - Regular conference calls
  - Daily (almost) emails
  - Final approval of the manuscript by the group

Adequacy of Urine Specimens (Adequacy)

Matthew T. Olson, Güliz A. Barkan, Monique Courtrade-Saini, Z. Laura Tabatabai, Koji Takada, Tepasiri Tsuuki, and Christopher J. VandenBussche

- Presence of atypical or malignant cells
- Specimen type
  - Instrumented (Cellularity, 2000 cells, 2 urothelial cells/10HPF) (***)
  - Voided (must be more likely "adequate" [**] (SurePath)
- Obscuring elements (blood, lubricant, etc.)


The sensitivity of voided cases with a volume of at least 30 mL was higher than that of cases with a volume <30 mL, but this was not statistically significant (31% vs 17%; P = .07)
### Reactive Umbrella Cells

**Cells**
- Large, often bi- or multinucleated
- Cytokinesis often difficult and rarely demonstrated

**Nuclei**
- Centrally located, nuclear membrane is smooth and chromatin is fine
- Occasional chromocenters

**PITFALL**
- May contain abnormal DNA

**Dx.** Negative for High Grade Urothelial Carcinoma

### Squamous and Glandular Cells

**Squamous cells**
- GYN tract, trigone, metaplasia, dysplasia

**Glandular epithelium**
- Cystitis glandularis, metaplasia, prostatic glandular cells, seminal vesicle cells

**Renal tubular cells**

**Dx.** Negative for High Grade Urothelial Carcinoma
Benign Urothelial Tissue Fragments – BUTF and Low Grade Urothelial Neoplasia - LGUN

- Instrumentation, stones
- Can be present in voided urines after DRE
- LGUN – Fibrovascular cores
- Second line diagnosis after the NHGUC

Treatment/Procedure Effects

- Positive
- Suspicious
- Atypical
- Negative

- Atypical Dx. Negative for High Grade Urothelial Carcinoma

Polyoma Virus

- Positive
- Suspicious
- Atypical
- Negative

- Atypical Dx. Negative for High Grade Urothelial Carcinoma
What is Atypia?

Positive Suspicious Atypical Negative

Definition of Negative for High-Grade Urothelial Carcinoma

A sample of urine, either voided or instrumental, 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 for High-Grade Urothelial Carcinoma
(Negative)

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

Atypical

What should not be reported as atypia in urine cytology:

JASC 2015;4;3;30-36

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

Negative, NOT atypia
Findings in literature
1. High nuclear cytoplasmic ratio (>0.7)
2. Nuclear hyperchromasia
3. Coarse, clumped chromatin
4. Irregular nuclear membranes

Atypical Urothelial Cells

<table>
<thead>
<tr>
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<th>Suspicious</th>
<th>Negative</th>
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<tbody>
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<td>Dx. Atypical Urothelial Cells</td>
<td></td>
<td></td>
</tr>
</tbody>
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- Non-superficial and non-degenerated urothelial cells with an high N/C ratio > 0.5 (required)
- Hyperchromasia (compared to the umbrella cells or the intermediate squamous cell nucleus)
- Irregular clumpy chromatin
- Irregular nuclear contours

Suspicious for High Grade Urothelial Carcinoma

<table>
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<tr>
<th>Positive</th>
<th>Suspicious</th>
<th>Atypical</th>
<th>Negative</th>
</tr>
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<tbody>
<tr>
<td>Dx. Suspicious for High Grade Urothelial Carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
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- 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)
- Irregular clumpy chromatin
- Irregular nuclear membranes
Positive vs. Suspicious for High Grade Urothelial Carcinoma

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.

<table>
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<th>Suspicious</th>
<th>Atypical</th>
<th>Negative</th>
</tr>
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<tbody>
<tr>
<td>Dx. High Grade Urothelial Carcinoma</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

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
Suspicious HGUC

This could be a HGUC

I think, this is a HGUC

I know, this is a HGUC

TPS – didn’t eliminate the GRAY ZONE – it DEFINED it!
What happened to LGUC??

• **Almost** Practically 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 Shiraishi

• LGUN - combined cytologic term for low grade papillary urothelial neoplasms (LGPUT) (which include urothelial papilloma, PUNLMP and LGPUT) 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

How about these – Negative for HGUC
Comment – Suggestive of LGUN
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 Rubendorf, Nancy P. Caraway, Andrew H. Fischer, Ruth L. Katz, Matthew T. Olson, Fernando Schmitt, Margarita Stojan Fiežar, Theodorus H. Van Der Kwast, Philippe Vielh
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?</th>
<th>n = 739</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>ThinPrep</td>
<td>424</td>
<td>57.4</td>
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<tr>
<td>Cytospin</td>
<td>336</td>
<td>45.5</td>
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<tr>
<td>Cell Block</td>
<td>207</td>
<td>27.7</td>
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<tr>
<td>Conventional smear</td>
<td>60</td>
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<tr>
<td>SurePath</td>
<td>40</td>
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<tr>
<td>Filter preparation</td>
<td>16</td>
<td>2.2</td>
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<tr>
<td>Other</td>
<td>11</td>
<td>1.5</td>
</tr>
</tbody>
</table>

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

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>&gt;5%</td>
<td>Repeat cytology, cystoscopy in 3 months if increased clinical suspicion</td>
</tr>
<tr>
<td>Negative for HGUC</td>
<td>0-5%</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>

Time to ......

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