Implementation of the Paris System (TPS) for Reporting Urine Cytology into a Daily Practice

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Maywood, IL

Objectives
- Appreciate the significance of separation between low and high grade urothelial carcinomas
- Understand morphologic criteria for various diagnostic categories
- Recognize challenges associated with the implementation of TPS

What led to Paris?
• Rate of atypia – range from 2% to >50%
• Wide interobserver variability
• No reproducibility
• Dwindling credibility
• Simultaneous publications on atypia
• Better understanding of the bladder cancer
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

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.

1. Pathogenesis of Urothelial Carcinoma
2. Adequacy
3. Negative for High Grade Urothelial Carcinoma
4. Atypical Urothelial Cells
5. Suspicious for High Grade Urothelial Carcinoma
6. High Grade Urothelial Carcinoma
7. Low Grade Urothelial Neoplasm
8. Other malignancies, both primary and secondary
9. Ancillary Studies
10. Clinical management
11. Preparatory techniques relative to Urinary Tract samples

System has to be built 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

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**Diagnostic Categories**

**Hope**

HGUC  
Everything else

**Reality**

Positive  
Atypical/Suspicious  
Negative

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**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 Quantity HGUC
- LGUN – Low Grade Urothelial Neoplasm

Definition of Negative for High-Grade Urothelial Carcinoma (Negative)

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

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

Cells from basal layer
What is 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 (AUC)
Güliz A. Barkan, Tarik M. Elshelikh, 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, Hai Guan, Mitsuru Kinjo, Eric Piaton, Dorothy L. Rosenthal, Tatsuro Shimokama, and Rosemary H. Tambouris

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

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
Low-Grade Urothelial Neoplasia (LGUN)

Eva M. Wojcik, Tatjana Antic, Ashish Chandra, Michael B. Cohen, Zulfia McCroskey, Jee Y. Ro, and Taizo Shiraishi

- 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

LGUN may be considered in correlation with cystoscopic or biopsy findings

First Line Diagnosis - NHGUC

- Three-dimensional cellular clusters without fibrovascular cores
- Increased numbers of monotonous single (non-umbrella) cells
Clinical Management
Marcus L. Quek, Trinity J. Bivalacqua, Ashish M. Kamat, and Mark P. Schoenberg

Risk of malignancy (HGUC) – ongoing studies

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk of Malignancy</th>
<th>Management</th>
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<tbody>
<tr>
<td>Un satisfactory/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>

Implementation

Approach to Diagnosis in Urinary Tract

G. Barkun, MD
Visual aids for diagnostic criteria in the lab:

- In the sign out/fellows room
- In the cytotech screening room

Standardized categories - statistical benefits:

<table>
<thead>
<tr>
<th>Cytology Cases by Interp % Department Summary</th>
<th>Date/Time Printed</th>
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<tr>
<td>Standardized categories - statistical benefits:</td>
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<tr>
<td>%AUC (blue) and %SUSP (red) at LUMC 2008-2016</td>
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</table>
Rate of Atypia at Loyola per pathologist

%AUC and %SUSP before and After TPS Implementation at LUMC

Were We Able To Reduce The Atypia Rate?

- 5 institutions; pre-TPS - 15,589, post-TPS - 15,311

<table>
<thead>
<tr>
<th>Category</th>
<th>Mean Pre-Paris</th>
<th>Mean Post-Paris</th>
<th>P value</th>
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<tbody>
<tr>
<td>UNSAT</td>
<td>0.47%</td>
<td>0.59%</td>
<td>0.16</td>
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<td>NEG/NHGUC</td>
<td>82.20%</td>
<td>85.59%</td>
<td>&lt;0.0001</td>
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<tr>
<td>ATYPICAL/AUC</td>
<td>13.49%</td>
<td>9.40%</td>
<td>&lt;0.0001</td>
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<tr>
<td>SUSPICIOUS/SHGUC</td>
<td>2.53%</td>
<td>2.04%</td>
<td>0.05</td>
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<tr>
<td>POSITIVE/HGUC</td>
<td>2.26%</td>
<td>2.34%</td>
<td>0.68</td>
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<tr>
<td>LGUIN</td>
<td>0.00%</td>
<td>0.01%</td>
<td>n/a</td>
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<tr>
<td>OTHER MAUXINANCIES</td>
<td>0.05%</td>
<td>0.02%</td>
<td>n/a</td>
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Post-Paris publications

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Year</th>
<th>No Cases</th>
<th>Pre-Paris</th>
<th>Post-Paris</th>
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<tr>
<td>Long T. et al.</td>
<td>Cytojournal</td>
<td>2017</td>
<td>357</td>
<td>N/A</td>
<td>22%</td>
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<td>Granados K. et al.</td>
<td>Acta Cytol</td>
<td>2017</td>
<td>149</td>
<td>6.60%</td>
<td>15.80%</td>
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<tr>
<td>Suh J. et al.</td>
<td>Cytopathology</td>
<td>2017</td>
<td>142</td>
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<td>Malheya K. et al.</td>
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<td>5.30%</td>
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<tr>
<td>Torus VF et al.</td>
<td>ASC</td>
<td>2017</td>
<td>2295</td>
<td>29.50%</td>
<td>20.10%</td>
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<tr>
<td>Roy M. et al.</td>
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<td>2017</td>
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<td>11.30%</td>
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<td>Wang Y. et al.</td>
<td>Cancer Cytol</td>
<td>2017</td>
<td>4764</td>
<td>18.60%</td>
<td>14.40%</td>
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<tr>
<td>Hassan et al.</td>
<td>AJCP</td>
<td>2016</td>
<td>124</td>
<td>39%</td>
<td>26%</td>
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</tbody>
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Challenges – N/C ratio


Basal cells

Challenges – N/C ratio – Many faces of HGUC
Challenges – Fibrovascular cores

HGUC have fibrovascular cores too!

79 years old man with hx of LGUC
What are possible methods to reduce the "Atypia" rate?

At the cytopathology community level:

- Raise awareness of the cytopathology community of why it is important to keep the atypia rates under control and how to achieve that goal
- Enable education of the cytopathology community in face to face meetings, webinars, publications, and internet based learning
- Recommend use of reference image banks - training website for The Paris System, hosted under the University of Wisconsin [https://paris.soc.wisc.edu/](https://paris.soc.wisc.edu/) maintained by Dr. Daniel F. I. Kurtycz

Barkan, Wojcik, Pambuccian. Cancer Cytopathol in press

What are possible methods to reduce the "Atypia" rate?

At the cytopathology laboratory level:

- Review the laboratory and individual atypia rates, and identify outliers and problems
- Clarify and communicate to the cytotechnologists, trainees and pathologists the purpose behind the desired outcome of low atypia rates
- Institute consensus meetings; and recommend showing "atypical" cases to another pathologist
- Run quality assurance metrics (such as AUC rate, ALIC:HGUC ratio, workload etc.) every 6 months and give regular confidential feedback to all diagnosticians

Barkan, Wojcik, Pambuccian. Cancer Cytopathol in press
What are possible methods to reduce the "Atypia" rate?

At the pathologist level:

• Comply with the criteria proposed for the "atypical" category
• Have a conscious attempt to reduce atypia

Barkan, Wojcik, Pambuccian. Cancer Cytopathol in press

AUC-ENTIRE LABORATORY (2018 ONLY 1RST TRIMESTER; OTHER YEARS IN SEMESTERS)

AUC rates per pathologist
Inter-Pathologist Variation in the Use of Urinary Tract Cytology Diagnostic Categories After Implementation of The Paris System

More stats (2nd semester of 2015 until 1st trimester 2018):

- 4,832 cases
- AUC - 6.87%
- SHGUC - 2%
- HGUC - 4.7%
- AUC/HGUC - 1.46
- AUC+SHGUC/HGUC - 1.9
Take home message

- HGUC – this is the one that matters – Negative for HGUC
- Atypia rate has been decreasing since the introduction of TPS but it is a slow and challenging process
- LGUN – new diagnostic category, based on presence of fibrovascular cores; HGUC also have f/v cores

In less then a year....