Update on
“the Paris System for Reporting Urinary Cytology”

Rana Hoda, MD, FIAC
Professor of Pathology, Chief Papanicolaou Cytology Lab &
Director of Cytopathology Fellowship Training Program
Weill Cornell, New York
rhoda@med.cornell.edu

Atlas of Exfoliative Cytology, 1954
“In our judgement, cytology of the urinary tract is one of the most important diagnostic methods in urologic oncology.”

Koss & Hoda. Diagnostic Cytology and its Histopathologic Bases, 2012

74,690 new cases & 15,580 men & women will die of disease in the US in 2015
ASR of Bladder Cancer in Arab World

<table>
<thead>
<tr>
<th>Country</th>
<th>Males</th>
<th>Females</th>
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<tr>
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<tr>
<td>USA</td>
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<td>24.5</td>
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Dr. Elattar, NCI, Egypt

Urine Cytology

- Has a high specificity for detection of UC
- High sensitivity for high grade tumors ~80%
- Poor sensitivity for low grade tumors ~25%
The Paris System - 10 Points

1. Paris Classification
2. Collection Techniques
3. Benign entities
4. NHGUC, cannot exclude LGUN
5. Atypical
6. Suspicious
7. HGUC
8. LGUC
9. Non-urothelial Tumors
10. FISH

Bladder Cancer

- 6th most common cancer in US
- >95% of tumors are urothelial carcinoma
- Most common etiology: smoking
- Most common presentation: hematuria
- 80% of new cases >60 yrs, generally white men
- Urothelial carcinoma also occurs in ureter, renal pelvis, & urethra

American Cancer Society, 2015
2004 WHO Classification of Bladder Tumors

- Flat Lesions
- Papillary Neoplasms
  - Papilloma
  - Inverted papilloma
  - Papillary neoplasm of low malignant potential
  - Papillary carcinoma, low grade
  - Papillary carcinoma, high grade
- Invasive Neoplasms
  - Lamina propria or muscularis propria invasion

Bladder cancer – more than one disease?

- ~75% Non-muscle-invasive (Ta/Tis/T1)
  - Good prognosis
  - Recurrence (30-50%)
  - 10%-15% progression (5% LG, 30% HG)

Pan CC. AJCP 2010;133; Nielsen ME. Cancer 2014:120:86
Bladder cancer – more than one disease?

- ~25% Muscle-invasive (≥T2)
- ≤60% overall survival

Nielsen ME. Cancer 2014:120:86
# Evolution of the Classification

<table>
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<td>Grade III</td>
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<td>High Grade</td>
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**Abbreviations:** ATY, atypical cells with hyperchromasia and predominantly round or oval contours; ATY 2, cells with hyperchromasia and nuclei membrane abnormalities; AUC-US, atypical urothelial cells of uncertain significance; HGC, 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 1.

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# Classification of Bladder Tumors

**WHO 1973**

- **Papilloma**
  - Grade I
  - Grade II
  - Grade III

- **Papilloma**
  - PUNLMP
  - Low Grade
  - High Grade

**WHO/ISUP 2004**

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

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**Urine Cytology Sensitivity**

Very high probability that we are going to be wrong
Why do we need a new classification system?

An International Telecytologic Quiz on Urinary Cytology Reveals Educational Deficits and Absence of a Commonly Used Classification System

- 48.4% misdiagnosed HGUC as a reactive lesion
- 54.5% misdiagnosed decoy cells as susp/HGUC
- 79.2% misdiagnosed basal cells in BW as atypia
- 64% misdiagnosed atypia in LGUC as a benign

Am J Clin Pathol. 2006 Aug;126:294

The Paris System for Reporting Urinary Cytology

Update Paris reporting criteria
Point #1

“The Paris System for Reporting Urinary Cytology”, 2014
Goal of The Paris System -
...to do what cytology does best

Find the High Grade lesions!

The Paris System with...

- Standardized criteria, terminology & reporting
- Improve communication
Diagnostic Categories of TPS & Chairs of Sub-groups

- **Negative for HGUC**
  - Dr. Dorothy Rosenthal, Johns Hopkins
- **Atypical Urothelial Cells**
  - Dr. Guliz Barkan, Lyola Univ.
- **Suspicious for HGUC:**
  - Dr. Fadi Brimo
- **High Grade Urothelial Carcinoma**
  - Dr. Momin Siddiqui, Emory Univ.
- **Low Grade Urothelial Neoplasia**
  - Dr. Eva Wojcik, Lyola Univ.
- **Other malignancies – Primary/secondary**
  - Dr. Rana S. Hoda, Weill Cornell

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### Diagnostic Categories

#### Hope

<table>
<thead>
<tr>
<th>HGUC</th>
<th>Everything else</th>
</tr>
</thead>
</table>

#### Reality

<table>
<thead>
<tr>
<th>Positive</th>
<th>Atypical/Suspicious</th>
<th>Negative</th>
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</thead>
</table>
Case #2

57-year-old man,
previous “atypical cytology”

Bladder washing, ThinPrep
Cytological Diagnosis: Negative for HGUC

TPS - Negative Category

- Negative for High Grade Urothelial Carcinoma
- Cases where “low grade urothelial carcinoma” cannot be excluded
Urine Collection Techniques

- Voided
- Catheterized
- Washings & brushings
- Retrograde catheterization: ureter, renal pelvis
- Ileal conduit
- Reactive changes due to stones
- Clusters in instrumented urine
- Polyomavirus (Decoy cells)
- Superficial umbrella cells
- Seminal vesicle cells
- Treatment effect
- Ileal conduit

"Negative, NOT Atypia"

Umbrella cell

BUTF

stone

Seminal vesicle cell
"Negative, NOT Atypia"

Ileal conduit

Treatment effect

Granuloma

Decoy cells

Urolithiasis

LGUC
Point 2 & 3 - Collection techniques & stones

- Influence makeup of urinary sediment
- Benign changes should not be diagnosed as “atypical”

Case #4

68-year-old man with prior h/o bladder cancer
Voided urine, ThinPrep
Cellular, single cells & clusters of elongated urothelial cells

Clusters of elongated urothelial cells with pale to dark, bland, smooth elongated or oval nuclei, low N:C, dense cytoplasm

Cytological Diagnosis: NHGUC, A LGUN cannot be excluded
Histological Diagnosis: Polypoid/papillary Cystitis

Isolated papillary fronds with marked edema & inflammation lined by relatively bland urothelium of normal thickness, focal prominent umbrella cells and mitosis

Significant Cytological Criteria in LGUC vs BPUL

- Loss of polarity
- Irregular borders
- (-) columnar cells
- Hobnail features


DDX of Polypoid/Papillary Cystitis

- Papillary hyperplasia
- Polypoid cystitis
- Urothelial papilloma

LGUC
Point 4 – NHGUC cannot exclude LGUN

- Knowledge of benign papillary lesions in surgical pathology is important

Case #5

67-year-old man,
With urinary frequency
Voided urine, ThinPrep
Voided urine

Cytological diagnosis: Atypical

Urothelial dysplasia
Evolution of Urinary Cytology Classification

<table>
<thead>
<tr>
<th>Cytologic Classification</th>
<th>Histologic Classification</th>
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<tbody>
<tr>
<td>Papanicolaou 1967 (Papanicolaou Classification System)</td>
<td>Koss 1980</td>
</tr>
<tr>
<td>Layfield et al. 2004 (Papanicolaou Society of Cytopathology)</td>
<td>Hopkins Template</td>
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<tr>
<td>Mostofi &amp; Torloni 1973 (WHO)</td>
<td>Epstein 1958</td>
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</tbody>
</table>

- I: Negative
- II: Atypical, uncertain
- III: Atypical urothelial cells
- IV: Malignant tumor cells, many ATY 2 cells
- V: Malignant cells, few ATY 2 cells

Problems with Atypia in Urine Cytology

- Lack of well-defined criteria
- Rate ranges from 1.9% to 31%
- Progression to HGUC ranges from 12-47%
- What should we call “atypical”?
  - Clusters of cells in VU, worrisome for LGUC
  - Rare single cells, suggestive of HGUC
  - Degenerated cells

Owens. Cancer Cytopathology 2013;121:9

Barzelli et al. JASC 2014
**AUC – Definition**

- Mild to moderate cytological (not architectural) atypia that falls short of the “suspicious for high grade urothelial carcinoma” (SHGUC) category

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**TPS - Criteria for “Atypical Urothelial Cells”**

- Deeper well-preserved cells with high N/C ratio (>0.5)

  *and one of the following:*

- Nucleus:
  - Hyperchromatic
  - Clumped chromatin
  - Irregular membranes
AUC

- N/C - 0.5
  - Loss of polarity
  - Hyperchromasia
  - Clumpy chromatin

- N/C > 0.5
  - Irregular thick membranes

Urothelial dysplasia

- Morphologically, dysplasia is low grade papillary UC on a flat surface
  - CIS is equivalent to high grade papillary UC on a flat surface

Point 5 - “Atypical”

- The goal should be to identify patients who are at an increased risk of HGUC
Case #6

55-year-old man
with irritative voiding symptoms

Voided urine, ThinPrep

Bx: Urothelial Denudation

Cytological Diagnosis: Suspicious for HGUC
TPS - Suspicious for HGUC (SHGUC)

- Severe atypia that quantitatively falls short of a definitive diagnosis of HGUC but beyond AUC

Suspicious vs. HGUC = quality & quantity

- Hyperchromasia
- Irregular membranes
- 5-10 malignant cells
- ↑N/C
- Hyperchromasia
- Clumpy chromatin
- Irregular membranes
Urothelial denudation

• Variety of causes
  – Prior instrumentation/indwelling catheter
  – Prior intravesical therapy
  – Calculi
  – Artifact of procedure (thermal artifact)
  – Carcinoma *in situ*

• Extensive or complete denudation is worrisome
• Include in report if extensive, especially if no other cause of denudation present

Urothelial denudation

• Flat lesions with denudation
  – 31% of patients developed CIS within 24 months
    • 75% of patients with prior history of CIS
  – 54% of patients with concurrent positive urine

Urothelial denudation

• Papillary lesions with denudation
  – 79% were associated with high grade tumors

Point 6 - SHGUC

- Diagnosis of SHGUC is based on quality & quantity of abnormal cells
- “Denudation may sometimes reflect cases of CIS where the discohesive tumor cells have shed into the urine.”
- Recommend urine cytology if not performed recently!!!
Case #7

78-year-old man presents with hematuria & a prior history of NI HGUC

Voided urine, SurePath

Cytological Diagnosis: HGUC
HGUC - Histologic Definition

- Papillary structures, frequently fused, lined by disorderly, cytologically malignant cells (WHO, 2004 classification)

The EASY diagnosis: HGUC
Invasive HG Papillary UC

Non-invasive HG Papillary UC

Cytology cannot distinguish between Inv & CIS

In situ UC  Invasive UC
HGUC with Divergent Differentiation – Significance

- Frequent phenomenon (20-80% of all UC)
- Usually keratinizing squamous or glandular
- Clinical significance generally unclear
- Mostly important for pathologists when dealing with future metastasis

Fairey et al. Uro Onc 2014
Xylinas et al. Eur J Cancer 2013
Amin et al. Mod Pathology 2015
Diagnostic Pitfalls

- Polyomavirus (Decoy) cell
- Non-urothelial tumor
- Treatment effect

No wonder it’s called a DECOY!

Polyoma Virus  HGUC
The DECOY Cell: What’s a DECOY?

- Looks like a duck
- Bobs like a duck
- Doesn’t Quack!
- NOT A DUCK!!

Point 7 - HGUC

- Cytology cannot distinguish between in situ & invasive urothelial carcinoma
- BK virus may pose a potential pitfall
Case #8

51-year-old man
with a prior h/o bladder cancer
Voided urine, ThinPrep

Cytotological Diagnosis: LGUC
TPS - Low Grade Urothelial Neoplasm – LGUN

- Combined cytologic term for low grade papillary urothelial neoplasms (LGPUN) (which include urothelial papilloma, PUNLMP and LGPUC) and flat, low grade intraurothelial neoplasia

Cytological diagnosis of LGUC can only be made in the presence of a fibrovascular core
LGUN may be considered in correlation with cystoscopic or biopsy findings

- 3-D cellular clusters without fibrovascular cores
- Many monotonous single (non-umbrella) cells


Benign

LGUC

LGUC
Point 8 - LGUN

- Cytological diagnosis of LGUC can only be made in the presence of a fibrovascular core

Point 9: Non-urothelial Tumors
WHO (2004)/ISUP Classification of Bladder Tumors

- 90% - 95% are urothelial
- <5% are non-urothelial
- Epithelial
- Non-Epithelial

Diagnosis of non-urothelial tumors is restricted to pure tumors

Importance of Cytologic Recognition of Various Types of Bladder Tumors

- Different clinical outcome
- Different therapeutic approach
- Facilitate diagnosis if tumor metastasizes

Improves cyto-histologic correlation

Non-Epithelial Primary Tumors

melanoma

DeSimone RA, Hoda RS. Diagn Cytopathol. 2015;43:680
Cytology cannot distinguish:

- Primary non-urothelial ca from UC with another epithelial component
- Or primary vs metastatic non-epithelial tumor
- Clinical history may be crucial

Point #10

Fluorescence In Situ Hybridization (FISH) for Bladder Ca Detection

## Urine-Based Ancillary Tests

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<th>Specificity%</th>
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</table>

### UroVysion™

- **CEP 3 (SpectrumRed)**
- **CEP 7 (SpectrumGreen)**
- **LSI 9p21 SpectrumGold (p16 gene)**
- **CEP 17 (SpectrumAqua)**
UroVysion FISH Test

- AUC
  - Main strength of FISH
  - HGUC with AUC: 48/52 (92%) FISH +
  - High specificity (>90% in most studies)

Dimashkieh. CCP. 2013

Point 10 - FISH

- Helpful tool in difficult AUC & Suspicious cases
