Outline

- Urine cytology – general considerations
- Cytologic features of neoplasms involving the urinary tract
- Review of the urine cytology reporting systems
- Ancillary techniques with special emphasis on Urovysion FISH
Clinical Indications of Urine Cytology

- Hematuria
- Follow-up of patients treated for Urothelial carcinoma
- High-risk of bladder cancer
Processing

- **Fixation**
  - 1-12hr, no fixation needed
  - 12-24hr, refrigeration
  - 24hr or more, fixation with equal volume of 50-70% alcohol or carbowax

- **Slide Preparation**
  - Sedimentation and smearing
  - Membrane Filtration
  - Cytocentrifugation
  - Cell Blocks
Accuracy

- **Sensitivity, Moderate**
  - Positive rate 25%-72%
    - Increases if “suspicious” included
    - Multiple urine samples increases sensitivity
    - Grade of urinary bladder tumor

- **Specificity, High**
  - 95%-100%
  - False positive seen in bladder stones, polyoma virus, chemotherapy
Types of Urinary Specimens

- Voided Urine
- Catheterized Urine
- Bladder Washings
- Upper Tract Washings and Brushings
- Ileal Conduit Samples
Voided Urine

- Collected 3-4hrs after the last void (100-300ml)
- Sparse cellularity, superficial and intermediate cells
- Degenerative changes
- Contamination: Squamous cells from trigone or vulva
- Non-cellular constituents such as crystals, casts, corpora amylacea
- Non-invasive technique and no instrumentation effect
Catheterized Urine

- Moderate to highly cellular
- Superficial, intermediate and basal cells
- Typically pooled specimen with degenerative changes - poor preservation
- Urethra not sampled
- Instrumentation artifacts: Urothelial clusters can mimic low-grade urothelial carcinoma
- Risk of infection
Catheterized Urine

Basal Urothelial Cells in Catheterized Urine Specimen
Obtained through a catheter by irrigating the bladder with 5-10 pulses of 50 ml sterile saline

Better cellularity and preservation

Less contamination by background debris

Increase sensitivity

Only bladder epithelium represented – upper tract not sampled

Quality of sample dependent on the skill of urologist
Bladder Washings
Upper Tract Washings / Brushings

- Comparable sensitivity to other type of urinary specimens
- Technically and morphologically challenging
- Prone to false positive results – marked cellularity
- Comparison of bilateral specimens (normal vs lesional) helpful in making diagnosis
- Cytological diagnosis with conservative approach
  - Ureterectomy or nephrectomy
Urethral Brushings
Ileal Conduit

- Surveillance of ureters and renal pelves post cystectomy
- Cellular specimen with large amount of degenerated intestinal epithelial cells and background debris
- Malignant cells may be obscured
Normal Urinary Elements

- Urothelial cells
  - Intermediate and superficial (umbrella) cells (voided urine)
  - Intermediate, superficial and basal cells (catheterized urine, washing)
- Squamous cells
- Miscellaneous findings
  - Prostate and seminal vesicle epithelial cells
  - Renal tubular cells and casts
  - Corpora amylacea
  - Crystals
  - Inflammatory cells
- Degenerated intestinal epithelial cells (ileal conduit)
Normal Urinary Elements

Melamed-Wolinska Bodies
Casts

- **Renal Diseases:**
  - RBC casts: Glomerular diseases
  - WBC casts: Tubulointerstitial diseases and transplant rejection
  - Renal tubular casts: Renal parenchymal diseases
  - Fatty casts: Nephrotic syndrome

- **Physiologic:**
  - Hyaline and granular casts: Secondary to dehydration, fever, exercise etc
Normal Urinary Elements

RBC Cast

Renal Tubular Cast

Corpora Amylacea
Crystals

- Common finding, no clinical significance in most cases
- Crystals analysis part of routine urinalysis rather than urine cytology
- Uric acid: most common, variable shape
- Triple-phosphate: prism shaped and resemble coffin lids
- Ammonium biurate: “Thorn apples”
- Pathologic crystals: much less common, bilirubin (brown granules and needles), cholesterol, cysteine (hexagonal plates), leucine (spheres with radiating striations) and tyrosine (slender needles)
Non-Urinary Elements

Seminal Vesicle Cells  
Endometrial Cells
Infections

- Bacterial
  - Dense concentration of WBC’s (predominantly neutrophils)
  - Bacterial organisms
  - Bacterial organisms without inflammation = contamination
  - Malakoplakia: Histiocytes with abundant granular cytoplasm filled with bacteria and bacterial fragments
Infections

Malakoplakia with Michealis Gutmann Bodies
Infections

- Fungal
  - Candida - most common organism
  - Mixed inflammatory response
  - Reactive changes of urothelial cells
  - Candida with abundant squamous cells - likely due to contamination
Infections - Fungal
Infections - Viral

- Polyomavirus
  - Infects both healthy and immunocompromised individuals
  - 4% of urine specimens
  - No clinical significance in immunocompetent

- Herpes: Uncommon, immunocompromised patients

- CMV: Most commonly effects renal tubular cells

- HPV: Vaginal contamination
Infections - Viral

Polyomavirus Cytopathic Changes
Infections - Viral

CMV

HSV

HPV
NEOPLASMS

UROTHELIAL AND NONUROTHELIAL
Neoplasms Involving the Urinary Tract

- **Primary Urinary Tract Tumors**
  - Urothelial Neoplasms
    - Papilloma
    - PUNLMP
    - Low-grade UC (urothelial carcinoma)
    - High-grade UC (urothelial carcinoma)
  - Squamous Cell Carcinoma
  - Adenocarcinoma
  - Small Cell

- **Secondary Tumors**
  - Renal Cell Carcinoma
  - Prostate Carcinoma
  - Mullerian Tumors
  - Mullerian Tumors
  - Colorectal
  - Testicular
  - Melanoma
Low-grade UC

- Low accuracy (sensitivity ~30%; specificity 80%)

- Architectural Features:
  - Papillary fragments with fibrovascular cores
  - Cell clusters without cores
  - Irregular cell clusters

- Cytologic Features:
  - Cytoplasmic homogeneity
  - High N/C ratio
  - Irregular nuclear membranes
Low-grade UC
Low-grade UC
High-grade UC

- High accuracy (specificity ~95%; sensitivity ~80%)
- Cytologic Features
  - Single dispersed abnormal cells
  - Hyperchromasia
  - Irregular nuclear borders
  - Increased N/C ratio
  - Anisonucleosis
  - Elongated nuclei
  - Cell clusters
High-grade UC
High-grade UC

Bladder Washing

Squamous differentiation
High-grade UC - Differential Diagnosis

- Polyomavirus
- Stone atypia
- Normal upper tract washing or brushings
- Treatment effect
- Non specific reactive changes
Polyomavirus
Stone Atypia
Urethral Brushings
Intravesical Chemotherapy Changes

- Predominantly effect the superficial cells
- Marked cytomegaly with abundant vacuolated cytoplasm with one or more nuclei
- Nuclear chromatin chunky, clumped, deeply staining or structureless and smudgy with smooth borders
- Prominent nucleoli
- Frayed borders
- No significant effect on neoplastic cells
Systemic Chemotherapy Changes

- Degenerative changes with frayed cell borders
- Enlarged hyperchromatic but smudgy nuclei
- Vacuolated cytoplasm
- Irregular dark nucleoli
- Multinucleation
Chemotherapy Changes

Thiotepa

Mitomycin

High-grade UC
Radiation Changes

- Cytomegaly with binucleation or multinucleation
- Enlarged nuclei without significant increase in N/C ratio
- Smudgy chromatin
- Nucleoli
- Cytoplasmic polychromasia and vacuolation
Squamous Cell Carcinoma

- 5% of bladder cancers
- Pure squamous cell carcinoma rare – associated with caliculi, diverticuli, parasites
- Squamous differentiation in UC
- Cytoplasmic keratinization
- Hyperchromatic angulated nuclei
Primary Adenocarcinoma

- Rare, <2% of bladder cancer
- Colonic type
- Signet ring type
- Clear cell adenocarcinoma
Secondary Tumors

- **Prostatic Adenocarcinoma**
  - Seen in high-grade prostatic carcinoma
  - Prominent nucleoli with relatively abundant cytoplasm
  - Dark nuclei resembling UC
  - History helpful!
Secondary Tumors

Colonic Adenocarcinoma

Endometrial Adenocarcinoma
<table>
<thead>
<tr>
<th>Class</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Absence of abnormal or atypical cells</td>
</tr>
<tr>
<td>2</td>
<td>Atypical cells present but without abnormal features</td>
</tr>
<tr>
<td>3</td>
<td>Cells with abnormal features but not sufficiently pathognomonic</td>
</tr>
<tr>
<td>4</td>
<td>Fair number of pathognomonic cells and cell clusters</td>
</tr>
<tr>
<td>5</td>
<td>Large number of conclusive cells and cell clusters</td>
</tr>
</tbody>
</table>
### Comparison of Classification Schemes for Urine Cytology and Histologic Classification of Papillary Urothelial Tumors

<table>
<thead>
<tr>
<th>Cytologic Classification</th>
<th>Histologic Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papanicolaou 1947 (Papanicolaou Classification System)</td>
<td>Nuorti 1973 (WHO)</td>
</tr>
<tr>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>Benign cells, ATY 1 cells, few clusters</td>
<td>Negative</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>NUAM</td>
<td>AUC-US</td>
</tr>
<tr>
<td>Papilloma</td>
<td>Papilloma</td>
</tr>
<tr>
<td>PUNLMP</td>
<td>LGUC</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.*
The Paris System for Reporting Urinary Cytology
Proposed Categories

I. Nondiagnostic or Unsatisfactory
II. Negative for malignancy
III. Atypical Urothelial Cells of Uncertain Significance
IV. Atypical Urothelial Cells Suspicious for HGUC
V. Low Grade Urothelial Carcinoma (LGUC)
VI. High Grade Urothelial Carcinoma (HGUC)
VII. Other Malignancies, Primary vs. Metastatic
Diagnostic Categories of the Johns Hopkins Template for Urinary Tract Cytologic Samples

- No urothelial atypia or malignancy identified (NUAM)
- Urothelial carcinoma, specify
  - High grade (HGUC)
  - Low grade (LGUC)
- Urothelial cells of uncertain significance (AUC-US)
- Atypical urothelial cells, cannot exclude HGUC (AUC-H)
- Other (squamous carcinoma, adenocarcinoma, etc)
- Inadequate
## Results of Urinary Tract Cytologic Specimens for Fiscal Years 2007 to 2009 With Biopsy Data

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Cases</th>
<th>Biopsied</th>
<th>Cancer on Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>NUAM</td>
<td>2894 (60)</td>
<td>180 (6)</td>
<td>58 (32)</td>
</tr>
<tr>
<td>AUC-US</td>
<td>1246 (26)</td>
<td>183 (14)</td>
<td>82 (45)</td>
</tr>
<tr>
<td>AUC-H</td>
<td>237 (5)</td>
<td>82 (34)</td>
<td>58 (71)</td>
</tr>
<tr>
<td>LGUC/HGUC</td>
<td>283 (6)</td>
<td>143 (50)</td>
<td>110 (77)</td>
</tr>
<tr>
<td>Inadequate</td>
<td>193 (4)</td>
<td>13 (6)</td>
<td>2 (15)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>4853 (100)</td>
<td>601 (12)</td>
<td>310 (52)</td>
</tr>
</tbody>
</table>

Abbreviations: AUC-H, atypical urothelial cells, cannot exclude high-grade urothelial carcinoma; AUC-US, atypical urothelial cells of uncertain significance; HGUC, high-grade urothelial carcinoma; LGUC, low-grade urothelial carcinoma; NUAM, no urothelial atypia or malignancy.
### Distribution of Patients With Atypical Urothelial Cells, Cannot Exclude High-Grade Urothelial Carcinoma According to Clinical Indication, Sex, and Outcome

<table>
<thead>
<tr>
<th>Clinical Indication</th>
<th>HGUC</th>
<th>Non-HGUC</th>
<th>Sex: M:F Ratio</th>
<th>Total No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surveillance</td>
<td>47 (96)</td>
<td>2 (4)</td>
<td>3.9</td>
<td>49</td>
</tr>
<tr>
<td>Hematuria</td>
<td>8 (89)</td>
<td>1 (11)</td>
<td>2.0</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>55 (95)</td>
<td>3 (5)</td>
<td>3.5</td>
<td>58</td>
</tr>
</tbody>
</table>

### Distribution of Patients With Atypical Urothelial Cells of Undetermined Significance According to Clinical Indication, Sex, and Outcome

<table>
<thead>
<tr>
<th>Clinical Indication</th>
<th>HGUC</th>
<th>Non-HGUC</th>
<th>Sex: M:F Ratio</th>
<th>Total No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surveillance</td>
<td>23 (22)</td>
<td>81 (78)</td>
<td>3.3</td>
<td>104</td>
</tr>
<tr>
<td>Hematuria</td>
<td>13 (13)</td>
<td>88 (87)</td>
<td>2.5</td>
<td>101</td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0)</td>
<td>12 (100)</td>
<td>2.0</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>36 (18)</td>
<td>181 (82)</td>
<td>2.8</td>
<td>217</td>
</tr>
</tbody>
</table>

1. Abbreviations: HGUC, high-grade urothelial carcinoma; M:F, male:female.
## Johns Hopkins Template for Urologic Cytologic Samples

Cytologic Features Recorded for Each Sample Diagnosed With Atypical Urothelial Cells, Cannot Exclude High-Grade Urothelial Carcinoma According to Frequency Observed

<table>
<thead>
<tr>
<th>Cytologic Feature</th>
<th>Frequency Observed: No. of Samples (%)</th>
<th>n = 62</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual abnormal cells</td>
<td>46 (74)</td>
<td></td>
</tr>
<tr>
<td>Hyperchromatic nuclei</td>
<td>44 (71)</td>
<td></td>
</tr>
<tr>
<td>Irregular nuclear borders</td>
<td>41 (66)</td>
<td></td>
</tr>
<tr>
<td>Increased nuclear-to-cytoplasm ratio</td>
<td>35 (56)</td>
<td></td>
</tr>
<tr>
<td>Anisonucleosis</td>
<td>34 (55)</td>
<td></td>
</tr>
<tr>
<td>Elongated nuclei</td>
<td>24 (39)</td>
<td></td>
</tr>
<tr>
<td>Cell clusters</td>
<td>23 (37)</td>
<td></td>
</tr>
<tr>
<td>BK polyomavirus change</td>
<td>11 (18)</td>
<td></td>
</tr>
</tbody>
</table>
Ancilliary Urine Based Techniques

- DNA ploidy
- Bladder Tumor Antigen (Bard BTA stat®)
- Nuclear Matrix Proteins (NMP22™)
- FISH (UroVysion)
- ImmunoCyt/uCyt™
- Telomerase
- Hyaluronic Acid Hyaluronidase
- Fibrin-Fibrinogen Degradation Product
Ancillary Urine Based Techniques

- **Bladder Tumor Antigen (Bard BTA stat®)**
  - Soluble urine marker test, detects basal membrane antigen in urine using latex agglutination test
  - Variable sensitivity (34%–100%) modest for low-grade UC
  - Specificity (40–96%)

- **Nuclear Matrix Proteins (NMP22™)**
  - Soluble urine marker test, immunoassay based
  - High sensitivity (60–86%) for the detection of urothelial neoplasia
  - Specificity (48–81%), many false positive tests

- **ImmunoCyt/uCyt™**
  - Immunofluorescence based test using three monoclonal antibodies M344, LDQ10 and CEA
  - Sensitivity 53–100% (mean 90%) including low-grade UC
  - Specificity was 64–95% (74%)
Chromosomal abnormalities in UC first described in 1990s

Initial studies tested single chromosome probes

Suklova et al published first study with multiple probes (10 probes tested)

Highest sensitivity achieved with combination of 4 probes

- Chromosome 3 (CEP)
- Chromosome 7 (CEP)
- Chromosome 17 (CEP)
- Chromosome 9p21 (LSI probe)

Sensitivity: 84% Specificity: 92%

Cutoff: 5 abnormal cells
FISH UroVysion

- Multicolor multitarget FISH UroVysion test approved by FDA in 2001

- Approved Indications:
  - Surveillance of patients with bladder cancer
  - Detection of bladder cancer in persons with hematuria suspected of having bladder cancer

- Meta-analysis of several studies by Hajdinijak
  - Sensitivity (72%) ; Specificity (83%)

- Targeted-UroVysion (CK7 immunophenotyping followed by UroVysion) improves diagnostic efficiency
UroVysion - Interpretation

Positive

- Four or more cells with gains of 2 or more chromosomes
- Ten or more cells with a gain of a single chromosome or 10 or more cells with tetrasomic signal patterns (i.e., 4 copies for each of the 4 probes)
- Homozygous deletion of the 9p21 locus in 12 or more cells or ≥20% of the cells analyzed

Negative

- Fewer than 4 cells with gains of 2 or more chromosomes
- Fewer than 10 cells with gain of a single chromosome or tetrasomy
- Less than 20% of cells with homozygous 9p21 deletion
Urovysion - Interpretation

Normal Pattern

Polysomy and deletion of 9p21

Polysomy
The Effectiveness of UroVysion and Cytology for Bladder Cancer Detection

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UroVysion</strong></td>
<td>61.9%</td>
<td>89.7%</td>
<td>46.1%</td>
<td>92.4%</td>
</tr>
<tr>
<td><strong>Cytology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With AUC as −</td>
<td>29.1%**</td>
<td>96.9%**</td>
<td>64.4%*</td>
<td>87.5%***</td>
</tr>
<tr>
<td>With AUC as +</td>
<td>60.9%</td>
<td>83.8%**</td>
<td>42.2%**</td>
<td>91.7%</td>
</tr>
</tbody>
</table>

AUC: Atypical Urothelial Cells; PPV: Positive Predict Value; NPV: Negative Predict Value

*p<0.01 when compared to the same diagnostic test characteristic for UroVysion; **p<0.0001

Cytopathol. 2013 Oct;121(10):591-7
The Effectiveness of UroVysion and Cytology for Bladder Cancer Detection in Patients with Hematuria and History of Urothelial Cell Carcinoma

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematuria</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UroVysion</td>
<td>60.0%</td>
<td>88.1%</td>
<td>35.5%</td>
<td>97.5%</td>
</tr>
<tr>
<td>Cytology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With AUC as−</td>
<td>33.3%**</td>
<td>98.5%†</td>
<td>57.7%*</td>
<td>96.1%**</td>
</tr>
<tr>
<td>With AUC as+</td>
<td>57.8%</td>
<td>88.6%***</td>
<td>23.4%**</td>
<td>97.2%</td>
</tr>
<tr>
<td><strong>UCC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UroVysion</td>
<td>62.2%</td>
<td>86.2%</td>
<td>59.2%</td>
<td>87.7%</td>
</tr>
<tr>
<td>Cytology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With AUC as−</td>
<td>28.3%</td>
<td>95.3%†</td>
<td>66.1%</td>
<td>80.56%†</td>
</tr>
<tr>
<td>With AUC as+</td>
<td>61.4%</td>
<td>79.3%†</td>
<td>48.8%***</td>
<td>86.5%</td>
</tr>
</tbody>
</table>

UCC: Urothelial Cell Carcinoma; AUC: Atypical Urothelial Cells; PPV: Positive Predict Value; NPV: Negative Predict Value

*p<0.05 when compared to the same diagnostic test characteristic for UroVysion; **p<0.01; *** p<0.001; †p<0.0001
The Effectiveness of UroVysion and Cytology for Bladder Cancer Detection in Patients with History of Low Grade and High Grade Urothelial Cell Carcinoma

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low Grade UCC (n=468)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UroVysion</td>
<td>40.8%</td>
<td>87.8%</td>
<td>42.1%</td>
<td>84.9%</td>
</tr>
<tr>
<td>Cytology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With AUC as -</td>
<td>14.3%†</td>
<td>96.8%†</td>
<td>53.8%</td>
<td>81.0%***</td>
</tr>
<tr>
<td>With AUC as +</td>
<td>45.9%</td>
<td>80.2%**</td>
<td>38.1%*</td>
<td>84.9%</td>
</tr>
<tr>
<td><strong>High Grade UCC (n=576)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UroVysion</td>
<td>75.65%</td>
<td>84.8%</td>
<td>64.86%</td>
<td>90.4%</td>
</tr>
<tr>
<td>Cytology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With AUC as -</td>
<td>37.2%†</td>
<td>94.1%†</td>
<td>70.5%</td>
<td>80.2%†</td>
</tr>
<tr>
<td>With AUC as +</td>
<td>71.2%</td>
<td>78.3%**</td>
<td>55.7%**</td>
<td>88.0%</td>
</tr>
</tbody>
</table>

UCC: Urothelial Cell Carcinoma; AUC: Atypical Urothelial Cells; PPV: Positive Predict Value; NPV: Negative Predict Value

*p<0.05 when compared to the same diagnostic test characteristic for UroVysion; **p<0.01; ***p<0.001; †p<0.0001
UroVysion - Pitfalls

- Cytological appearance not taken into account
- Viral cytopathic changes and abundance of umbrella cells may result in a false positive UroVysion test
- Non-standardized interpretation criteria
Variable results in literature

Recent study by Reynolds et al. showed increased false positive rates of upper tract Urovysion

- Patients with history bladder UC
- Tetrasomic FISH pattern
Performance of Cytology and FISH in Patients With and Without Concomitant Bladder UC

<table>
<thead>
<tr>
<th></th>
<th>True-Positive</th>
<th>True-Negative</th>
<th>False-Positive</th>
<th>False-Negative</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology</td>
<td>8</td>
<td>81</td>
<td>10</td>
<td>13</td>
<td>38</td>
<td>89</td>
<td>44</td>
<td>86</td>
</tr>
<tr>
<td>FISH HT</td>
<td>9</td>
<td>76</td>
<td>15</td>
<td>12</td>
<td>43</td>
<td>84</td>
<td>38</td>
<td>86</td>
</tr>
<tr>
<td>FISH tetrasomy and HT</td>
<td>14</td>
<td>48</td>
<td>43</td>
<td>7</td>
<td>67</td>
<td>53</td>
<td>25</td>
<td>87</td>
</tr>
<tr>
<td>Cytology and FISH HT</td>
<td>11</td>
<td>70</td>
<td>21</td>
<td>10</td>
<td>52</td>
<td>77</td>
<td>34</td>
<td>88</td>
</tr>
</tbody>
</table>

After Exclusion of Cases With Concomitant UTUC and Bladder UC (7 Cases) and Cases With No UTUC But History of Bladder UC (33 Cases)

<table>
<thead>
<tr>
<th></th>
<th>True-Positive</th>
<th>True-Negative</th>
<th>False-Positive</th>
<th>False-Negative</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology</td>
<td>7</td>
<td>53</td>
<td>3</td>
<td>7</td>
<td>50</td>
<td>95</td>
<td>70</td>
<td>88</td>
</tr>
<tr>
<td>FISH HT</td>
<td>7</td>
<td>50</td>
<td>6</td>
<td>7</td>
<td>50</td>
<td>89</td>
<td>54</td>
<td>88</td>
</tr>
<tr>
<td>FISH tetrasomy and HT</td>
<td>11</td>
<td>29</td>
<td>27</td>
<td>3</td>
<td>79</td>
<td>52</td>
<td>29</td>
<td>91</td>
</tr>
<tr>
<td>Cytology and FISH HT</td>
<td>9</td>
<td>47</td>
<td>9</td>
<td>5</td>
<td>64</td>
<td>84</td>
<td>50</td>
<td>90</td>
</tr>
</tbody>
</table>

1. Abbreviations: FISH, fluorescence in situ hybridization; HT, hypertetrasomy (>4 signals per probe); NPV, negative predictive value; PPV, positive predictive value; UC, urothelial carcinoma; UTUC, upper urothelial tract urothelial carcinoma.

2. *Tetrasomy indicates 4 signals per probe.
Summary

- Most urine specimens are negative
- Diagnosis of low-grade UC remains challenging due to overlapping features with reactive atypia
- Urine cytology has high accuracy for high-grade lesions
- FISH (UroVysion) more sensitive than cytology in detection of UC but produces more false positive results. Data suggest its use as a reflex test following equivocal cytologic diagnosis
- Upper tract urinary samples including FISH should be interpreted with reserve due to higher false positive rate


