Workshop 6

*Diagnostic Approach to Urine Cytology*

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There are no disclosures necessary.
Diagnostic Value of Urine Cytology

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Conflict of Interest

The speakers have no financial or commercial relationships that create a conflict of interest with any material presented in this talk.

What are the Problems Encountered in Urinary Cytology?

Apparent lack of consistent correlation with biopsies particularly in low grade lesions.
Some cystoscopic findings don’t appear to correlate with cytology and biopsies e.g.
- negative cytology in the presence of a papillary lesion,
- positive cytology in the absence of a visible lesion.
Agenda

Introduction, Historical Overview and Collection Techniques
Cytological Features of Urothelial Carcinoma
Reactive Conditions and Mimickers of Urothelial Carcinoma
Beyond Morphology (Ancillary Studies)
Clinical Cytological Correlation
Take Home Message

Objectives

At the conclusion of this presentation, participants should be able to:

• Approach the cytologic diagnosis of urothelial carcinoma using the ISUP/WHO classification.
• Recognize the limitations and the potential pitfalls in the diagnosis of urothelial carcinoma.
• Be aware of the role of new technology in diagnosing urothelial carcinoma.
• Understand the importance of clinical, cytologic and histologic correlation.

Koss: from his textbook on urinary cytology

Urine cytology is one of the most important diagnostic methods in urologic oncology provided that:
Urologists use it under well defined circumstances and for well defined reasons

Urine cytology is not a screening test for urothelial carcinoma
Urine cytology is one of the most important diagnostic methods in urologic oncology provided that:

- It is performed in a laboratory competent in processing and interpreting such specimens.
- Expertise in preparation and interpretation is necessary.

Both the urologist and the cytologist understand the limitations of the method and are familiar with various sources of errors.

Familiarity with the limitations and sources of errors in urine cytology are very important.

More than 6000 years ago
Misuse of Urine Examination

Middle Ages

Examination of Urine is a Medical Art

1627
First Description of Malignant Cells in Urine by Lamle

Early 1900’s

Vermont in the Fall

Normal Urothelium

- Urothelial/Transitional cells
- Friedrich Henle (1800s) coined term “transitional” for urinary epithelium (transitional between squamous and glandular)
- Can differentiate along squamous or glandular lines
- Cells are columnar when bladder is empty, flattened to cuboidal when bladder is full
The Urinary Tract

Histologic appearance of urothelium

Umbrella and Basal Cells
Variations in shape of urothelial cells

**Glandular cells**

- Cystitis glandularis
- Littre's glands (periurethral mucus crypts)
- Lacunae of Morgagni
- Contamination from gynecologic or male genitourinary tracts
- Endometriosis
- Renal tubular cells
Glandular Cells in Urine

Squamous Cells

- Urethra of both men and women
- The trigone in 50% of women and 10% of men is lined by squamous epithelium
- Intermediate and superficial squamous cells
<table>
<thead>
<tr>
<th>Method</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voided</td>
<td>Non-invasive</td>
<td>Contamination, Sparsely Cellular</td>
</tr>
<tr>
<td>Catheterized</td>
<td>Exclude contamination</td>
<td>Invasive</td>
</tr>
<tr>
<td>Bladder Irrigation</td>
<td>Large number of well preserved cells</td>
<td>Invasive</td>
</tr>
<tr>
<td></td>
<td>Best for ancillary studies</td>
<td></td>
</tr>
<tr>
<td>Upper Tract Irrigation</td>
<td>Localization of tumor cells when bladder irrigation is negative</td>
<td>Invasive</td>
</tr>
<tr>
<td>Brush Cytology</td>
<td>Sample a localized lesion</td>
<td>Invasive, Many artifacts</td>
</tr>
<tr>
<td>Ileal Conduit Urine</td>
<td>Non-invasive</td>
<td>Degeneration</td>
</tr>
</tbody>
</table>
Bladder Cancer

The 6th most common cancer in US
More than 70,000 new cases of bladder carcinoma occur annually (US)
Over 14,500 death of disease every year in US.
Male to Female ratio 3:1
Mean age is 50 years
Histologic types
- Urothelial 90%
- Squamous 5%
- Adenocarcinoma 2%

GU Malignancies in Males

Bladder Carcinoma Compared to Leading Cancers

<table>
<thead>
<tr>
<th>Organ</th>
<th>New cases</th>
<th>Death rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>69,250</td>
<td>14,990</td>
</tr>
<tr>
<td>Breast</td>
<td>232,000</td>
<td>40,000</td>
</tr>
<tr>
<td>Prostate</td>
<td>240,890</td>
<td>33,720</td>
</tr>
<tr>
<td>Lung</td>
<td>221,130</td>
<td>156,940</td>
</tr>
</tbody>
</table>
**Known Causes of Bladder Cancer**

- **Aromatic amines**: Nitrosamine and 2-Naphthyl amine
- **Drugs**: Cyclophosphamide and Phenacetine
- **Parasites**: Schistosoma hematobium
- **Physical factors**: Prolonged irritation
- **Congenital malformation**: Bladder extrophy
- **Smoking**

**Characteristics of Urothelial Carcinoma**

- Multifocality
- High rate of recurrence
- Two types (biologically):
  - Superficial, low tendency for invasion
    - (Low grade papillary carcinoma)
  - Invasive
    - High grade papillary carcinoma
    - Flat carcinoma

**Urothelial Carcinoma**

- Papillary 80%
- Flat 20%

- Low Tendency for Invasion
- High Tendency for Invasion
Papillary Tumor
Cystoscopic Image

Multiple Papillary Tumors
Gross

Massive Papillary Neoplasm

Opened Bladder “Cystectomy Specimen”
WHO 2004 Classification, Low Grade Lesions

- Papillary Lesions
  - Papilloma
  - Papillary Urothelial Neoplasm of Low Malignant Potential
  - Low Grade Urothelial Carcinoma
  - High Grade Urothelial Carcinoma

- Flat Lesions
  - Hyperplasia
  - Reactive Atypia of Undetermined Significance
  - Dysplasia
  - Carcinoma in-situ

### Papilloma

- Rare Lesion
  - Can’t be detected by cytology
  - Due to lack of significant cytologic atypia

### Papillary Urothelial Neoplasm of Low Malignant Potential

- Orderly Proliferation of urothelial cells
- Papillae lined by more than 7 layers
- Occasional atypia
- Predilection for ureteral orifice
- Risk for recurrence 20%
- Risk of progression 8%
**Low Grade, Papillary Carcinoma**

- Comprises 80% of Urothelial Carcinoma
- 75% recurs
- 30% progress to muscle invasion

**Low Grade Urothelial Carcinoma**

- Cellular specimen
- Increased N/C ratio
- Slightly irregular nuclear contour
- Homogeneous cytoplasm (lack of vacuoles)
- Eccentric nuclei
Summary

- Papilloma, PUNLMP and Low Grade Urothelial Carcinoma are Difficult Cytologic Diagnoses.
- Low Grade Urothelial Carcinoma may be diagnosed on instrumented urines with papillary structures and fibrovascular cores.
Differential Diagnosis
Low Grade Papillary Tumors

• Instrumentation
• Hyperplasia
• Calculi
• Papilloma
• PUNLMP

WHO 2004 Classification, High Grade Lesions

• Papillary Lesions
  • Papilloma
  • Papillary Urothelial Neoplasm of Low Malignant Potential
  • Low Grade Urothelial Carcinoma
    • High Grade Urothelial Carcinoma
• Flat Lesions
  • Hyperplasia
  • Reactive Atypia of Undetermined Significance
  • Dysplasia
    • Carcinoma in-situ

High Grade Urothelial Neoplasm
Flat Carcinoma In-situ
High Grade Urothelial Carcinoma

- High n/c ratio
- Cellular pleomorphism
- Marked nuclear hyperchromasia
- Coarsely granular chromatin
- Irregular nuclear contour
- Large nucleoli (occasional)
Squamous Differentiation
Flat Urothelial Carcinoma

Cystoscopic Appearance

- The most important high grade neoplastic lesion
- Found often in association with papillary lesions
Flat Urothelial Carcinoma

• Most common in men above 50 years
• Symptoms include frequency, dysuria and hematuria (microscopic or gross)
• Not always recognized cystoscopically
• Cytology:
  • Fewer cells with minimal variation in size
  • High n/c ratio
  • Coarse chromatin
  • Irregular nuclear contour
  • Scant cytoplasm
Case Presentation

65 year-old male
Voided Urine
Follow-up

- Cystoscopy: No lesion noted
- Bladder Biopsies: Negative
- Right Renal Pelvis washing: Positive
- Left Renal Pelvis washing: Negative
Right Kidney Pelvis Washing
Right Nephrectomy was Performed

Histologic Section of Right Ureter
NATURAL HISTORY AND CLINICAL BEHAVIOR OF
IN SITU CARCINOMA OF THE HUMAN
URINARY BLADDER

MYRON R. MELEMER, M.D., NEDA G. VOITIS, M.D.,* AND HARRY GANETALD, M.D.
Flat Urothelial Carcinoma

Summary

• Cystoscopically not always identified as a tumor
• May be asymptomatic or produce non-specific symptoms
• 60% of untreated patients may progress to invasive carcinoma

Characteristics of Urothelial Carcinoma

<table>
<thead>
<tr>
<th>Feature</th>
<th>Low Grade</th>
<th>High Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasiveness</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Cytology</td>
<td>Low sensitivity</td>
<td>High sensitivity</td>
</tr>
<tr>
<td>Morphology</td>
<td>Majority Papillary Low Grade</td>
<td>Majority Flat CIS Papillary High Grade</td>
</tr>
</tbody>
</table>

Squamous Carcinoma

• 5% of all bladder carcinoma
• Most cases arise in squamous metaplasia due to:
  • Chronic cystitis
  • Lithiasis
  • Prior Cyclophosphamide therapy
  • Schistosomiasis
Pathologic Staging of Bladder Carcinoma

- T1a: affects superficial muscle
- T1b: affects deep muscle
- T1c: affects perivesical fat or pericystic tissues

- T2a: affects adjacent organs
- T2b: affects lymph nodes
- T3: affects contiguous organs

- T4: affects distant metastases

Treatment of Urothelial Carcinoma

Superficial Urothelial Carcinoma:
- Excision, fulguration, BCG
- Monitor with cystoscopy and cytology

Invasive Urothelial Carcinoma:
- Cystectomy
- Nephroureterectomy
- Monitor with cytology
Sensitivity of Urine Cytology

- Low Grade Urothelial Carcinoma < 25%
- High Grade Urothelial Carcinoma 80%
**Reactive/Benign/Pitfalls**

- Inflammation/Reactive Changes
- Infectious Agents
- Instrumentation and Urolithiasis
- Therapeutic Changes
- Contaminants

**Inflammatory/Reactive Changes**

- Inflammatory background
- Check clinical history
- Look for an infectious agent
- Smooth nuclear contours
- “Lack” of nuclear hyperchromasia
  - Degeneration
- N/C “usually” not high
- Small nucleoli
- Bi-nucleation and multinucleation
- Vacuolated cytoplasm

**Infectious Agents**

- Bacterial
  - Common
  - Enteric bacteria (gram-negative)
  - E. coli, Entrobacter, Proteus
  - Polys
  - Tuberculosis
    - Usually secondary to renal
    - Lymphocytes
    - Renal transplant
    - AIDS patients
- Fungal
  - Not common
  - Candida albicans
  - Diabetes, antibiotic usage
  - Impaired immunity
  - Contaminant
Infectious Agents

- Herpes Simplex
  - Infects urothelial cells
  - Multinucleation, molding, margination
  - Intracellular inclusions

- Cytomegalovirus
  - Primarily infects kidney tubule cells, endothelial cells
  - Large intranuclear inclusion and cytoplasmic inclusions

- Immunocompromised
  - Hemorrhagic cystitis

Human polyoma virus

- BK virus, DNA virus
- Urothelial cells and renal tubular cells
- “Decoy cells”
  - Andrew Ricci
  - Infection acquired in childhood
  - Reactivated by immunosuppression
  - Transplant patients, AIDS
    - Interstitial nephritis
    - Eosinophils

- Single cells
- “Enlarged” nuclei
- Homogeneous, basophilic nuclear inclusion (classic)
- Smudgy chromatin
- Lack of nuclear membrane irregularities
- Occasional bi-nucleated forms
Infectious Agents

- Human polyoma virus
  - Inclusion stage with basophilic inclusions and pale inclusions
  - Post-Inclusion stage with a network of chromatin filaments and chromocenters
    - Fish Net Chromatin

Infectious Agents

Polyoma virus  High grade urothelial carcinoma

Infectious Agents

Centurynovelty.com
• Confirmation by
  — Simian Virus 40 (SV40) immunocytochemistry
• Transplant patients monitored
  — PCR
    • BK DNA
    • Urine and serum

Infectious agents

• Human Papilloma Virus (HPV)
  — Contamination
  — Bladder
    • Squamous metaplasia
    • More common in women
    • HPV 6, 11
    • Immunosuppression

Non-Viral Inclusions

— Cytoplasmic red inclusions
— Metarubric(os)is cells
— Common in infections/inflammation and ileal conduit urines
  • Condensed cytoplasmic filaments
  • Giant lysosomes
— Single and multiple
— Various sizes
— Nuclear changes
  • karyopyknosis
  • karyolysis
  • karyorrhexis
Non-Viral Inclusions

- **Lead Poisoning**
  - Intranuclear inclusions
  - Renal tubule cells
  - Acid fast
  - Industrial workers, children
  - Heavy minerals
    - Lead
    - Mercury
    - Bismuth

Non-Viral Inclusions

- **Malakoplakia**
  - Soft, tan yellow plaques
  - Uncommon granulomatous disease
    - Usually in women, HIV and renal transplant patients
  - Defect in the ability of histiocytes to phagocytise bacteria
    - Michaelis-Gutmann bodies
    - 5-10 u, concentric laminations
    - Mineralized lysosomes
Non-Viral Inclusions

- Michaelis-Gutman bodies
  - Von Kossa Stain
  - PAS positive

Infectious Agents

- Parasites
  - Trichomonas vaginalis
    - Rare
    - Secondary to vaginal disease
  - Schistosoma hematobium
    - "Endemic" in parts of Africa and Middle East
    - Immigrants/Refugees

Infectious Agents

Schistosomiasis

www.nhm.ac.uk/.../behaviour/index.htm
www.stanford.edu/.../schisto/website.html
Infectious Agents

- **Schistosoma hematobium**
  - Eggs are oval, 100-150 u
  - Terminal spine
  - Viable, degenerated and/or calcified eggs
  - Squamous metaplasia
    - May have nuclear atypia and keratinization
  - Risk factor for squamous cell carcinoma

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Infectious Agents

Ureteral biopsy

Primary adenocarcinoma of the bladder
Urate Crystals
- Relatively common
- Caused by a change in the pH of the urine after collection

Instrumentation and Urolithiasis
- Instrumentation
  - Increased cellularity
  - Mixture of urothelial cells
  - Pseudopapillary clusters, pitfall for low grade UCC
  - Smooth even borders
  - Cytoplasmic collar
  - Cytoplasm tends to be vacuolated
  - Good polarity, less nuclear overlapping and crowding
  - Fine chromatin, occasional nucleoli
  - Lack of isolated atypical cells

Cytoplasmic "collar"
Urolithiasis

- Most frequent in the bladder and renal pelvis
- More common in men
- Composed of mineral salts
  - Calcium oxalate
- Chronic abrasion
  - Groups of urothelial cells
- Clinical correlation is important

Urolithiasis

- Smooth, round borders
- "Relatively" normal n/c
- Vacuolated cytoplasm
- Uniform nuclear contours
- Fine chromatin
- Nucleoli
- Nuclear hyperchromasia possible
- Inflammation, blood and necrosis can mimic a tumor diathesis
- "Note lack of single abnormal cells"
Therapeutic Changes

- **Systemic Chemotherapy**
  - Alkylating agents such as Cyclophosphamide and Busulfan
  - Used for non-urothelial tumors and non-neoplastic diseases
    - Rheumatoid arthritis
  - Active metabolite concentrate in urine
  - Toxic injurious effect
  - Degenerative nuclear changes

- **Clinical correlation**
  - May be a risk factor for urothelial carcinoma
Therapeutic Changes

- Systemic Chemotherapy
  - Cyclophosphamide
  - Protocols include massive hydration
  - Hemorrhagic cystitis

Therapeutic Changes

- Intravesical chemotherapy for non-invasive Urothelial Carcinoma
  - Mitomycin, Thiotepa, Doxorubicin
  - Nuclear enlargement
  - Nucleoli
  - Hyperchromasia
    - Smudgy chromatin
    - Vacuolated cytoplasm

Therapeutic Changes

- Intravesical Immunotherapy
  - Bacillus Calmette-Guerin (BCG)
    - Preferred treatment for non-invasive UC
  - Attenuated mycobacterium
  - Prompts an intense granulomatous inflammatory response which may or may not be evident in urinary specimens
    - Epitheloid histiocytes
    - Giant cell histiocytes
    - Urothelial sloughing
**Therapeutic Changes**

- Bacillus Calmette-Guerin (BCG)
  - Reactive and degenerating urothelial cells due to inflammatory process
    - Normal n/c
    - Smooth nuclear contours
    - Nucleoli

- Radiation
  - Primary invasive UC and other pelvic malignancies
  - Large urothelial cells but maintain n/c
  - Hyperchromatic nuclei
    - Look for signs of degeneration and smudgy chromatin
  - Vacuolated cytoplasm and polychromasia
  - Inflammatory background possible
  - Clinical correlation
    - Changes may persist

- 72 yr. old male with a history of prostatic cancer and urothelial cancer
  - Diagnosis:
    - Features consistent with radiation changes
Therapeutic Changes

- Laser/Cautery/Thermal Effect
  - Non-invasive urothelial ca
  - Injured cells
  - Spindle cell artifact
  - Elongated nuclei
  - Dense chromatin
  - Distorted appearance
  - Differential
    - UC with spindle cells
    - Stromal tumor

Therapeutic Changes

Case A
Bile duct brushing

Case B
Courtesy of Jill Caudill
Gyn ThinPrep, post leep

Contaminants

- Seminal vesicle cells
  - Large
  - Hyperchromatic nuclei
  - Nucleoli possible
  - Lipofuscin pigment
  - Look for sperm
Contaminants

Seminal vesicle biopsy

Ask Yourself...

- How was the specimen collected?
- Is there an inflammatory background?
- Did I look for an organism?
- Are there degenerative changes in the cytoplasm?
- Could the nuclear changes be caused by degeneration?
- Is the patient immunocompromised?
- Did I consider human polyoma virus?
- Is there a history of urolithiasis?
- Has this patient received any treatment?
- Could this be contamination?
- Is this a case that warrants ancillary studies?

Beyond Morphology
Ancillary Studies
Available Techniques

- Variety of non-morphologic techniques
- Rely on differences between benign and malignant cells
- Advantages:
  - Non-invasive

Ancillary Studies

<table>
<thead>
<tr>
<th>Test</th>
<th>No. Patients</th>
<th>Sensitivity % (Range)</th>
<th>Specificity % (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology</td>
<td>1143</td>
<td>54 (35-88)</td>
<td>95 (83-100)</td>
</tr>
<tr>
<td>DNA-Cytometry</td>
<td>1573</td>
<td>62 (45-86)</td>
<td>69 (79-100)</td>
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<tr>
<td>QF23-Immunocyt</td>
<td>478</td>
<td>51 (87-94)</td>
<td>78 (67-97)</td>
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<tr>
<td>Immunocyt</td>
<td>1143</td>
<td>76 (50-100)</td>
<td>76 (69-84)</td>
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<td>Quantocyt</td>
<td>341</td>
<td>52 (45-59)</td>
<td>82 (71-93)</td>
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<td>3096</td>
<td>61 (34-100)</td>
<td>74 (40-96)</td>
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<tr>
<td>FDP</td>
<td>774</td>
<td>68 (33-83)</td>
<td>78 (66-87)</td>
</tr>
<tr>
<td>Molecular Testing</td>
<td>272</td>
<td>83 (73-85)</td>
<td>97 (92-100)</td>
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<tr>
<td>NMP-22</td>
<td>1964</td>
<td>69 (47-100)</td>
<td>75 (50-85)</td>
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<tr>
<td>Telomarase</td>
<td>222</td>
<td>74 (82-81)</td>
<td>79 (50-96)</td>
</tr>
</tbody>
</table>

Fluorescence In Situ Hybridization

Utilizes fluorescently-labeled DNA probes to detect various types of chromosomal alterations.

FISH probes are two types:
- Chromosome enumeration probes CEP
  - To study aneusomy
- Locus specific indicator LSI
  - To detect deletions or amplification of a specific gene
**Fluorescence In Situ Hybridization (FISH)**

- Uses molecular probes to detect genetic abnormalities
- Fluorescent signal attached to probes
- These abnormalities are NOT thought to be present in benign cells

**Molecular Testing**

- Look at the genetic makeup of exfoliated cells
- Low grade lesions:
  - Trisomy of chromosomes 7
  - Loss of the 9p21 locus
- High grade lesions:
  - Aneuploidy for chromosomes 3, 17
  - Increased # of alterations is associated with a worse prognosis

**UroVysion™ System**

- Vysis®
- Only system FDA approved for use
- Surveillance screening in patients treated for bladder cancer
- Symptomatic patients suspected of having bladder carcinoma
Atypical Cells on Cytology

Reflex testing option

Isolated cells lysed on a glass slide - allows chromosomes to attach to slide surface

Heat Denature hybridization

4 Probe Mixture:
- Centromeric probes:
  - 3
  - 7
  - 17
- Locus-specific probe:
  - 9p21 (p16)
Reporting

• Negative: No evidence of numeric chromosomal aberrations associated with urothelial carcinoma identified.

• Positive: Numeric chromosomal aberrations associated with urothelial carcinoma identified.

Limitations

• Results are intended for use, in conjunction with and not in lieu of current standard diagnostic procedures, as an aid for initial diagnosis of bladder carcinoma in patients with hematuria and subsequent monitoring for tumor recurrence in patients previously diagnosed with bladder cancer.
FISH Studies

- Following patients with known carcinoma
  - High sensitivity and specificity
- Screening patients with hematuria
  - Decreased sensitivity and specificity
- ** FISH positive patients without disease
- ? False positives with Polyoma virus

Additional Limitations

- Results impaired by:
  - Low cellularity
  - Cell deterioration or necrosis
- Other malignancies may also be detected
  - RCC
  - Metastases to urinary tract
- Expensive $$
- Turn-around time: 2 - 5 working days

Summary

- Ancillary tests, especially FISH, add value
- Used in conjunction with cytology and/or cystoscopy
- Sensitivity and specificity vary
- Uncertain how to deal with FISH + patients with a negative work-up
Cystoscopy

61 year old male with a history of urothelial carcinoma
Cytology Negative

Biopsy Papilloma

Cystoscopy Papillary Tumor

Cytology Negative

Biopsy Papilloma

Clinical Correlation

Cystoscopy

45 year old female with a history of urinary frequency and dysuria

Cystoscopy
Clinical Correlation

Cystoscopy

72 year old male with a history of chronic hematuria
**Clinical Correlation**

Cystoscopy
Not definitive

Cytology
Positive

Biopsy
Flat carcinoma in-situ

**Clinical and Cytologic Correlation**

<table>
<thead>
<tr>
<th>Clinical Finding</th>
<th>Cytology</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visible Papillary Tumor</td>
<td>Negative</td>
<td>a) Papilloma b) Low grade lesion</td>
</tr>
<tr>
<td></td>
<td>Positive/</td>
<td>a) High Grade papillary Lesion</td>
</tr>
<tr>
<td></td>
<td>Suspicious</td>
<td></td>
</tr>
<tr>
<td>No Visible Tumor</td>
<td>Positive/</td>
<td>a) Flat CIS/Ca – bladder b) High grade lesion – upper tract</td>
</tr>
<tr>
<td></td>
<td>Suspicious</td>
<td></td>
</tr>
</tbody>
</table>
WHO Classification
Cytologic Correlation - Papillary Lesions

<table>
<thead>
<tr>
<th>Histologic Diagnosis</th>
<th>Cytologic Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papilloma</td>
<td>Negative</td>
</tr>
<tr>
<td>Papillary neoplasm of low malignant potential</td>
<td>Negative/Atypical*</td>
</tr>
<tr>
<td>Low Grade Papillary Ca</td>
<td>Atypical*</td>
</tr>
<tr>
<td>High Grade Papillary Ca</td>
<td>Positive</td>
</tr>
</tbody>
</table>

* Specific comments will vary

WHO Classification
Cytologic Correlation - Flat Lesions

<table>
<thead>
<tr>
<th>Histologic Diagnosis</th>
<th>Cytologic Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypia of undetermined significance</td>
<td>Negative/Atypical*</td>
</tr>
<tr>
<td>Dysplasia</td>
<td>Atypical*</td>
</tr>
<tr>
<td>Flat carcinoma in-situ</td>
<td>Positive</td>
</tr>
</tbody>
</table>

Invasive carcinoma

* Specific comments will vary

Utility of Urine Cytology

High Grade lesions
- Flat carcinoma in-situ/Invasive carcinoma
- High Grade papillary carcinoma

Follow-up
- Patients with urothelial carcinoma for detection of recurrent disease
  - First year - every 3-6 months urine cytology and cystoscopy
  - Reduced intervals subsequent years

Screening
High risk patients for high grade lesions
Take Home Message…

• Variability is the norm for urothelial cells
• Collection techniques impact morphology
• Not all inclusions are viral in nature
• Clinical correlation is critical
• Biological differences between low grade and high grade lesions
• Importance of detecting flat urothelial carcinoma
• Urinary cytology is an important diagnostic method in the right setting