220 Urinary Cytopathology - Its Role in Diagnostic Uropathology and Relationship to Ancillary Tests like FISH

William Murphy MD

2011 Annual Meeting – Las Vegas, NV

AMERICAN SOCIETY FOR CLINICAL PATHOLOGY
33 W. Monroe, Ste. 1600
Chicago, IL 60603
Urinary cytopathology is a staple of the systematic evaluation of patients for urothelial neoplasms in nearly all practices and yet it remains problematical to pathologists and clinicians alike. This session will cover specimen handling, diagnostic terminology, histo-cytologic correlations, treatment effects, the cytology of urinary diversions, and ancillary testing, especially FISH. It will be presented in lecture format with ample opportunities for audience participation. Histologic schemes that classify benign lesions as carcinomas, the expectation that all lesions called carcinoma should be recognized in urinary specimens if only the cytopathologists or the methodology were better, and the tendency of pathologists to use temporizing diagnostic terms such as "atypical" and "suspicious" have all contributed to the ongoing frustration with urinary cytopathology and added to the appeal of ancillary tests such as FISH. This presentation is aimed at increasing the confidence of practitioners by identifying the misconceptions and discussing exactly what can be accomplished using urinary cytopathology. For example, the often-emphasized failure of urinary cytopathology to recognize low-grade urothelial neoplasms is an advantage in clinical practice, since these lesions are not life-threatening, can be easily seen endoscopically, and do not require expensive evaluation aimed at early detection and treatment. In contrast, urinary cytopathology is the only method that can separate high-grade, life-threatening urothelial cancers from the low-grade lesions previously mentioned.

- Appreciate the historical roots of histologic classifications of urothelial neoplasms and understand that the definition of malignancy itself has never depended on the characteristics of the component cells.
- Adopt a system, including specific criteria, for the interpretation of urinary specimens that includes specimen handling, diagnostic terminology, and an approach to specimen evaluation and reporting that addresses the concerns of clinicians.
- Understand the role of ancillary testing, especially FISH, in the recognition of neoplastic urothelial cells.

FACULTY:

William Murphy MD

Practicing Pathologists
Cytopathology
Cytopathology (Non-Gynecologic)
2.0 CME/CMLE Credits

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Urinary Cytopathology

WILLIAM M. MURPHY, MD, FASCP

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WILLIAM M. MURPHY, MD, FASCP

URINARY CYTOPATHOLOGY HAS BEEN USED CLINICALLY TO ASSESS

- NEOPLASMS
- CRYSTALS
- BK POLYOMAVIRUS
- EOSINOPHILS
- MICROORGANISMS
- PARASITES
- HORMONE STATUS
- TRANSPLANT REJECTION
- HEAVY METALS
PROBLEMS WITH URINARY CYTOPATHOLOGY IN “BLADDER CANCER”

- LOW DIAGNOSTIC YIELD, esp. FOR VOIDED URINE
- LOW DIAGNOSTIC YIELD FOR LOW-GRADE TUMORS
- LOW COMFORT LEVEL AMONG PATHOLOGISTS
- RELATIVELY HIGH INTEROBSERVER VARIABILITY
- THE INSISTENCE OF UROLOGISTS ON LABELING ALL UROTHELIAL NEOPLASMS “CANCER”

THE TROUBLE WITH URINARY CYTOPATHOLOGY

- INACCURATE HISTOLOGIC CLASSIFICATION
- INAPPROPRIATE CLINICAL APPROACH
- LACK OF PATHOLOGIST CONFIDENCE

INACCURATE HISTOLOGIC CLASSIFICATION
HISTORICAL PATHOLOGY
THE DEFINITION OF MALIGNANCY

THE "INVASION" SCHOOL
PAPILLARY AND NODULAR LESIONS
PAPILLOMA
CARCINOMA
FLAT LESIONS
DYSPLASIA - LOW, HIGH GRADE
ATYPIA - MODERATE, SEVERE
DENUDING CYSTITIS

THE "RECURRENCE" SCHOOL
PAPILLARY AND NODULAR LESIONS
CARCINOMA - GRADES 0-4
FLAT LESIONS
CARCINOMA IN SITU
DYSPLASIA, ATYPIA, ???

THE DEFINITION OF MALIGNANCY HAS NEVER DEPENDED ON THE DEGREE OF
ANAPLASIA OF THE TUMOR CELLS BUT RATHER THE GROWTH PATTERN OF
THE TUMOR - FOR PAPILLARY UROTHELIAL NEOPLASMS, WE HAVE
BEEN TAUGHT TO DIAGNOSE THE STALK, NOT ITS CELLS
MODERN PATHOLOGY
CLASSIFICATION BY CONSENSUS

SCIENCE IS IMPORTANT BUT THE FACTS ARE IN DISPUTE SO LET’S USE PATHOLOGY ORGANIZATIONS FOR CONSENSUS AND COMPROMISE TO ACHIEVE CURRENT BEST PRACTICE

THE 1973 WHO CLASSIFICATION OF UROTHELIAL TUMOURS

PAPILLOMA
CARCINOMA - PAPILLARY, NODULAR
GRADE 1
GRADE 2
GRADE 3
CARCINOMA IN SITU/DENUDING CYSTITIS
THE CELLS IN URINARY SPECIMENS HAVE BEEN TELLING US ABOUT THE NATURE OF UROTHELIAL NEOPLASMS FOR 40 YEARS BUT WE WERE NOT PREPARED TO LISTEN

EVIDENCE THAT TCC-1 (1973 WHO) IS NOT A MALIGNANCY

- DNA ploidy normal - 95%
- Chromosome structure normal
- Almost no abnormalities in genes
- Blood group antigens retained - 85%
- Cytology normal 40 - 70%
- Long-term survival 95% (even with ’recurrence’)
- Experimental lesions reversible
- Neither invasion nor metastasis

TUMOR-SPECIFIC SURVIVAL (YRS)
380 CASES WITH AT LEAST A 10 YEAR F/U
THE CURRENT CLASSIFICATION OF UROTHELIAL NEOPLASMS
- Papilloma
- PUNLMP
- Carcinoma
  - Low grade
  - High grade
- CIS
- Dysplasia
- Atypia

INAPPROPRIATE CLINICAL APPROACH
(MOST) CLINICIANS REALLY KNOW BETTER

TWO PATIENTS WITH UROTHELIAL TUMORS
UROLOGISTS TELL BOTH THAT THEY HAVE BLADDER CANCER
URINARY SPECIMENS FROM BOTH PATIENTS

BASICALLY, THERE ARE ONLY TWO GRADES OF UROTHELIAL NEOPLASMS

LOW-GRADE - NOT AGGRESSIVE
   NOT EASILY DIAGNOSED CYTOLOGICALLY

HIGH-GRADE - AGGRESSIVE
   EASILY DETECTED WHEN CELLS PRESENT

THE PRIMARY CLINICAL VALUE OF URINARY CYTOPATHOLOGY IS THE IDENTIFICATION OF HIGH-GRADE CARCINOMA CELLS - UROTHELIAL, GLANDULAR, SQUAMOUS, SMALL CELL
SPECIMEN COLLECTION

RANDOM VOIED
BLADDER WASHING
CATHETERIZED
24 HOUR
EARLY MORNING

VOIDED URINE AND BLADDER WASHING – SAME PATIENT

SPECIMEN PRESERVATION

REFRIGERATION
ALCOHOL (25%)
CARBOWAX
RECONSTITUTION IN SALINE
SPECIMEN PROCESSING

CYTOCENTRIFUGATION
THIN PREP/NU VIEW
MEMBRANE FILTERS
DIRECT SMEARS

CLINICAL INFORMATION HELPFUL FOR CYTOPATHOLOGIC CONSULTATION

Hx “BLADDER CANCER” (AND GRADE)
HEMATURIA
SPECIMEN SOURCE
BLADDER
INTESTINAL CONDUIT
NEOBLADDER
BLIND URETHRA
URETER, RENAL PELVIS
DIAGNOSTIC TERMINOLOGY FOR URINARY SPECIMENS

POSITIVE, HIGH GRADE NEOPLASM

SUSPICIOUS - R/O HIGH-GRADE NEOPLASM

DYSPLASTIC CELLS, R/O LOW-GRADE NEOPLASM

NEGATIVE FOR MALIGNANCY (INCLUDES REACTIVE)
NUMEROUS CELLS (ITSELF ABNORMAL)
SCANT CELLS

INSUFFICIENT CELLS FOR ANALYSIS

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WORKING DEFINITION OF ADEQUACY FOR URINARY SPECIMENS

VOIDED URINE OR BLADDER WASHING, NO HISTORY OF “BLADDER CANCER”
AT LEAST 5 NON-SUPERFICIAL CELLS

VOIDED URINE, HISTORY OF “BLADDER CANCER”
AT LEAST 5 NON-SUPERFICIAL CELLS

BLADDER WASHING, HISTORY OF “BLADDER CANCER”
AT LEAST 15 NON-SUPERFICIAL CELLS
CELLULAR FEATURES OF HIGH GRADE UROTHELIAL NEOPLASMS

- INCREASED N:C RATIOS (>1:2)
- INCREASED NUCLEAR SIZE
- NUCLEAR ECCENTRICITY
- NUCLEAR PLEOMORPHISM
- IRREGULAR, COARSE CHROMATIN
COMMON CONFOUNDING FACTORS FOR HIGH-GRADE NEOPLASMS

SCANT CELLS IN VOIED URINES
TUMOR CELLS THAT LOOK BENIGN
REACTIVE CELLS THAT LOOK MALIGNANT

SCANT MALIGNANT CELLS IN URINARY SPECIMEN
POLYOMAVIRUSES IN URINE ARE (ALMOST) ALWAYS BK.

BK IS UBQUITOUS IN HUMANS BUT ONLY PATHOGENIC IN PEOPLE WHO ARE IMMUNOCOMPROMIZED.

NUCLEAR INCLUSIONS ARE COMMON AND ARE ESSENTIALLY CONFINED TO SUPERFICIAL CELLS.

BK NUCLEI TEND TO HAVE EVEN CONTOURS AND SMUDGED CHROMATIN; THEY ARE OFTEN DEGENERATED.

WHEN BK CAUSES DISEASE, THE DISEASE IS ALMOST ALWAYS IN THE KIDNEY, NOT THE BLADDER.

IMMUNOCYTOCHEMISTRY IS AVAILABLE BUT NOT NECESSARY IN MOST CASES; IT IS OFTEN EQUIVOCAL IN PRACTICE

I REPORT BK IN “HEMATURIA” CASES ONLY WHEN THE PATIENT IS IMMUNOCOMPROMIZED OR THERE ARE RED CELL CASTS.

CELLULAR FEATURES OF LOW GRADE UROTHELIAL NEOPLASMS AND DYSPLASIA

- INCREASED N:C (>1:2)
- INCREASED NUCLEAR SIZE
- EXTREME ECCENTRICITY
- NUCLEAR BORDER IRREGULARITIES
- EVENLY DISPERSED, FINE CHROMATIN
- HOMOGENEOUS CYTOPLASM

NB: ALL FEATURES RARELY PRESENT IN EVERY CELL
### Cyto-Histologic Correlations

**Urothelial Neoplasms**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
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<tr>
<td>Negative</td>
<td>Papilloma</td>
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<tr>
<td>Dysplastic</td>
<td>PUNLMP</td>
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<td>Grade Suspicious</td>
<td>Ca, LOW</td>
</tr>
<tr>
<td>Grade</td>
<td>Ca, HIGH</td>
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<tr>
<td>Positive</td>
<td>CIS</td>
</tr>
<tr>
<td>Grade</td>
<td>OTHER</td>
</tr>
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</table>

### Common Confounding Factors for Low-Grade Neoplasms

- Papillary Aggregates
- Cautery Artifact
- Neoplastic Cells That Look Normal

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**Case Studies**

- **57 y/o F**: Pelvic pain
- **24 y/o Pregnant**
- **Stone**
- **XRT Effect**

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**2011 ASCP Annual Meeting**

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AS A PRACTICAL MATTER, NEARLY ALL PATIENTS DYING OF BLADDER CANCER SUCCOMB TO A HIGH-GRADE TUMOR THAT WAS PRESENT AT INITIAL DIAGNOSIS. LESS THAN 10% OF PATIENTS WHO PRESENT WITH A PAPILLOMA OR PUNLMP SUFFER PROGRESSION AND LESS THAN 5% DIE OF BLADDER CANCER (NOBODY DIES OF A PUNLMP).

WHAT THEN IS THE BENEFIT TO PATIENTS OF EARLY DETECTION OF RECURRENT LOW-GRADE TUMORS?

THE PRIMARY CLINICAL VALUE OF URINARY CYTOPATHOLOGY IS TO IDENTIFY PATIENTS WHO NEED MORE AND/OR MORE AGGRESSIVE EVALUATION, USUALLY CYSTOSCOPY WITH OR WITHOUT BIOPSY. VIRTUALLY NO ONE IS TREATED BASED SOLELY ON A CYTOPATHOLOGIC ASSESSMENT OF A URINARY SPECIMEN.

CLINICAL RESPONSE TO CYTOPATHOLOGICAL DIAGNOSIS

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<tr>
<td>Dysplastic cells</td>
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</tr>
<tr>
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<td>Cystoscopy w/wo biopsy</td>
</tr>
<tr>
<td>Positive</td>
<td>Cystoscopy w biopsy</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

*scant or numerous cells - check patient status
CYTOPATHOLOGY CANNOT
RELIABLY DISTINGUISH ADENO
FROM UROTHELIAL CARCINOMA
DIFFERENTIATE IN SITU FROM
INVASIVE CARCINOMA
LOCALIZE THE LESIONS
SMALL CELL CARCINOMA

PCa IN URINE

URINARY CYTOPATHOLOGY IN DAILY PRACTICE

EVEN BELIEVERS HAVE PROBLEMS WITH URINARY CYTOPATHOLOGY
THE AUA DEFINITION OF "HIGH-RISK" FOR "BLADDER CANCER"

- HISTORY OF SMOKING
- OLDER THAN 40 YEARS
- OCCUPATIONAL EXPOSURE
- GROSS HEMATURIA
- HISTORY OF IRRITATIVE VOIDING
- HISTORY OF UTIs
- ANALGESIC ABUSE
- HISTORY OF PELVIC XRT
- HISTORY OF UROLOGIC DISORDER

USING THIS DEFINITION, NEARLY EVERYONE WITH HEMATURIA QUALIFIES FOR ANCILLARY TESTING

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DIAGNOSTIC YIELD OF URINARY CYTOLOGY SPECIMENS (%)

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<th>Spec</th>
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<td>60</td>
<td>87</td>
<td>95</td>
<td>32</td>
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A = Academe,   B = PP ,  C = Cancer Center

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DIAGNOSTIC YIELD OF UC-MULTIGROUP COLLABORATION (%)

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<td>98</td>
<td>81</td>
<td>91</td>
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<tr>
<td>Group B</td>
<td>85</td>
<td>74</td>
<td>56</td>
<td>93</td>
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<tr>
<td>Group C</td>
<td>66</td>
<td>98</td>
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<td>94</td>
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<tr>
<td>Overall</td>
<td>64</td>
<td>95</td>
<td>75</td>
<td>92</td>
</tr>
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A = Academe,   B = PP ,  C = Cancer Center
URINARY CYTOPATHOLOGY MUST BE CONSIDERED IN TWO MODES – PATIENTS MONITORED FOR “BLADDER CANCER” ARE IN A DIAGNOSTIC MODE; PATIENTS WITH HEMATURIA ARE IN A SCREENING MODE.

THE PPV IS VERY DIFFERENT
TREATMENT EFFECTS IN URINARY SPECIMENS

- ALKYLATING AGENTS – MMC/TTP
- MALIGNANT-LOOKING SUPERFICIAL CELLS
- X-RAYS
  - NONE
- BCG
  - NONE

COURTESY MS SOLOWAY, MD

2011 ASCP Annual Meeting

NECROSIS DUE TO MMC

COURTESY MS SOLOWAY, MD

NORMAL-LOOKING CYSTOSCOPY AFTER MMC

COURTESY MS SOLOWAY, MD
CYSTOSCOPY AFTER BCG

HIGH-GRADE NEOPLASM

DENUDATION OF UROTHELIUM, L.P. INVASION
URINARY CYTOPATHOLOGY AFTER CYSTECTOMY

ILEAL CONDUITS
URETHRAL WASHINGS
WHAT ABOUT CELLS FROM THE UPPER COLLECTING SYSTEM?

- LOW-GRADE NEOPLASMS DON'T LEND THEMSELVES TO CYTOPATHOLOGIC DIAGNOSIS
- IT IS NOT UNCOMMON TO SEE HIGH-GRADE CELLS IN SPECIMENS FROM BOTH SIDES EVEN THOUGH THE TUMOR SEEMS TO BE ON ONLY ONE SIDE
- RENAL CELL CARCINOMAS ARE RARE IN UPPER SYSTEM SPECIMENS
- ALL TYPES OF EVALUATION MUST CORRELATE BEFORE RESECTION
NORMAL CELLS IN RENAL PELVIS WASHING

NORMAL CELLS, LEFT MALIGNANT CELLS, RIGHT

URETERAL WASHING

UIROTHELIAL CARCINOMA, HIGH-GRADE
ESTABLISHED METHODS TO DETECT UROTHELIAL NEOPLASMS

HEMATURIA (w/ or w/o IRRITATIVE VOIDING Sx)

CYSTOSCOPY (w/ or w/o BIOPSY)

URINARY CYTOPATHOLOGY

TYPICAL CASE – NBCCG-A

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<tr>
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<th>CYSTO</th>
<th>CYTO</th>
<th>HISTO</th>
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<td></td>
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<td>POS</td>
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<tr>
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OK, SO WE NOW KNOW THE LIMITATIONS AND CLINICAL USES OF URINARY CYTOPATHOLOGY.

CAN’T WE DO BETTER WITH ANCILLARY METHODS?
ANCILLARY TESTS FOR BLADDER NEOPLASMS

- Tissue products - BTA, NMP22, DD23
- Blood group antigens - ABH, LEWIS X
- Cytokeratins - CK20, CYFRA 21-1, TPA, UBC
- Proteins/mucins - IMMUNOCYT, URO II
- Enzymes - TELOMERASE, HA/HAase
- Growth factors - EGF, TGF
- Adhesion molecules - CD44, E-cad
- DNA - QUANTICYT
- Chromosomes - UROVYSION FISH, MS
- Genes

PROBLEMS WITH THE CLINICAL APPLICATION OF MARKERS

- Very few markers specific (only PSA, URO)
  - Very few markers specific even in typical cases
- If used for detection, low PPV limits value even if high sensitivity and specificity
  - If used for detection, low PPV limits value even if high sensitivity and specificity
- If used for differential diagnosis, focal reactions often lead to high interobserver variation; imaging, history better
  - If used for differential diagnosis, focal reactions often lead to high interobserver variation; imaging, history better
- If used for prognosis, overlap between groups often too large for patient care; hypocellularity limits use
  - If used for prognosis, overlap between groups often too large for patient care; hypocellularity limits use
- With few exceptions, immunocytochemistry has been difficult to apply in most practices
  - With few exceptions, immunocytochemistry has been difficult to apply in most practices

DO YOU NEED IMMUNOS TO DIAGNOSE THIS?
WOULD YOU BELIEVE THE IMMUNOS IN THIS CASE OR WOULD YOU CALL IT SUSPICIOUS ANYWAY?

THE SEARCH FOR BETTER METHODS TO DETECT UROTHELIAL NEOPLASMS IS NOT NEW - WHAT'S NEW IS THE COMMERCIAL AVAILABILITY OF URINE-BASED MARKERS AND FDA APPROVAL (THE ABILITY TO GAIN FINANCIALLY FROM THE TESTS)

JUSTIFICATION FOR FISH
EMPIRICAL OBSERVATIONS REVEAL ABERRATIONS IN CHROMOSOMES
3 RED
7 GREEN
17 AQUA
9 YELLOW
COINCIDE WITH THE PRESENCE OF UROTHELIAL NEOPLASMS
DIAGNOSTIC YIELD IS 15-50% BETTER THAN VOIDED URINARY CYTOLOGY
510k CLINICAL DATA
UroVysion™ Bladder Cancer Recurrence Kit

SENSITIVITY (%) BY GRADE

<table>
<thead>
<tr>
<th>GRADE</th>
<th>n</th>
<th>FISH</th>
<th>BTast</th>
<th>CYTOLOGY</th>
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<td>3</td>
<td>18</td>
<td>94</td>
<td>72</td>
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DIAGNOSTIC ACCURACY OF URINARY CYTOLOGY - HIGH GRADE CARCINOMA*

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<tr>
<th>Author</th>
<th>Year</th>
<th>Patients</th>
<th>% Pos</th>
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<tr>
<td>Vickers</td>
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</tr>
<tr>
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<td>Wolfe</td>
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<td>Friedell</td>
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<tr>
<td>Murphy</td>
<td>1984</td>
<td>43</td>
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<tr>
<td>Sherry</td>
<td>1985</td>
<td>26</td>
<td>100*</td>
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*weighted average of grades II & III TCC and CIS
+ only CIS evaluated

SO YOU WANT TO FISH FOR BLADDER CANCER

EQUIPMENT ($90,000 plus)
SUPPLIES (>$125/TEST)
LOGISTICS (PREPARATION, TRANSPORT)
PERSONNEL (TECH LICENSED FOR HIGH COMPLEXITY)
SPACE (FOR DARK FIELD MICROSCOPE)
RECORD MAINTENANCE (COMPUTER, CAMERA)
ESTIMATING INCOME FROM FISH

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</thead>
<tbody>
<tr>
<td>SPECS/YR</td>
<td>2000</td>
<td>2000</td>
</tr>
<tr>
<td>% BlCa F/U</td>
<td>25</td>
<td>N/A</td>
</tr>
<tr>
<td>% HEMATURIA</td>
<td>N/A</td>
<td>100</td>
</tr>
<tr>
<td># ELIGIBLE FOR FISH</td>
<td>500</td>
<td>2000</td>
</tr>
<tr>
<td>LESS 20% (F/EW CELLS, ETC)</td>
<td>400</td>
<td>1500</td>
</tr>
<tr>
<td>LESS 10% (POS CYTO)</td>
<td>360</td>
<td>N/A</td>
</tr>
<tr>
<td>LESS 2% (POS CYTO)</td>
<td>N/A</td>
<td>100</td>
</tr>
</tbody>
</table>

INCOME (@ $200/SPEC) $72,000 $313,600

SCENARIO 1: ONLY BLCA F/U; SCENARIO 2: ALL HIGH-RISK HEMATURIA

DEFINITION OF POSITIVE FISH

AT LEAST 25 EPITHELIAL NUCLEI ON THE SLIDE

AT LEAST 4 NUCLEI WITH:
- >2 SIGNALS OF 3&7, 3&17, 7&17
- OR
- >11 NUCLEI LACKING 9

(SOME ALSO INCLUDE TRISOMY 3, 7, OR 17 IN AT LEAST 10% OF NUCLEI)

IN PRACTICE, MOST ABNORMALS ARE IN 3&7
ABNORMAL 9 IS UNUSUAL (<10%)
ALL NUCLEI MUST BE ASSESSED
PROBLEMS WITH FISH ANALYSIS

SPECIMENS WITH 1-3 ABNORMAL NUCLEI
WEAK/ABSENT YELLOW SIGNALS
NON-SPECIFIC SIGNALS, ESP. RED
WIDELY SPLIT SIGNALS
TETRAPLOID SUPERFICIAL CELLS
>2 RED/GREEN, RETENTION OF YELLOW
AUTOFLUORESCENCE
NUCLEAR CLUMPING
NEUTROPHILS
PPV BlCa 50%, PPV HEM 3% - 24%

FISH
(NOV 05 - JUNE 08)

<p>| | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>TOTAL SPECIMENS</td>
<td>1278</td>
</tr>
<tr>
<td>FISH NOT DONE</td>
<td>268 (21%)</td>
</tr>
<tr>
<td>POOR PRESERVATION</td>
<td>78 (6%)</td>
</tr>
<tr>
<td>POSITIVE CYTOLOGY</td>
<td>932</td>
</tr>
<tr>
<td>FISH PERFORMED</td>
<td>768 (82%)</td>
</tr>
<tr>
<td>UNINFORMATIVE</td>
<td>57 (6%)</td>
</tr>
<tr>
<td>NEGATIVE</td>
<td>60 (7%)</td>
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CASES WITH POSITIVE FISH
35 PATIENTS; 57 SPECIMENS

<p>| | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>TUMOR AT FOLLOWUP (1-32m)</td>
<td>11</td>
</tr>
<tr>
<td>CYTOLOGY SUSP/DYS/POS</td>
<td>5</td>
</tr>
<tr>
<td>CYTOLOGY NEGATIVE</td>
<td>3</td>
</tr>
<tr>
<td>CYTOLOGY NOT DONE</td>
<td>3</td>
</tr>
<tr>
<td>NO TUMOR AT FOLLOWUP (1-32m)</td>
<td>24</td>
</tr>
<tr>
<td>NO FOLLOWUP</td>
<td>0</td>
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</table>

DIAGNOSTIC YIELD = 31% (of 6% = 1.8%)
CASES WITH ABNORMAL FISH
46 PATIENTS; 60 SPECIMENS

<table>
<thead>
<tr>
<th>TUMOR AT FOLLOW-UP</th>
<th>13</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYTOLOGY SUSP/DYS/POS</td>
<td>5</td>
</tr>
<tr>
<td>CYTOLOGY NEGATIVE</td>
<td>6</td>
</tr>
<tr>
<td>CYTOLOGY NOT DONE</td>
<td>2</td>
</tr>
<tr>
<td>NO TUMOR AT FOLLOW-UP</td>
<td>29</td>
</tr>
<tr>
<td>NO FOLLOW-UP</td>
<td>4</td>
</tr>
</tbody>
</table>

DIAGNOSTIC YIELD = 28% (of 7% = 2%)

THE PRIMARY JUSTIFICATION FOR FISH IS ITS HIGH
SENSITIVITY; USUALLY COMPARED TO VOIDED URINARY
CYTOPATHOLOGY.

THIS SENSITIVITY IS ACQUIRED AT THE COST OF POSITIVE
PREDICTIVE VALUE (ABOUT 50% FOR PATIENTS BEING
FOLLOWED FOR "BLADDER CANCER" AND 3-25% FOR
PEOPLE WITH HEMATURIA). THE PPV CAN BE INCREASED
WITH MULTIPLE TESTS AND WHEN CYTOPATHOLOGY IS
ABNORMAL BUT SO CAN THE RESULTS OF CYTOPATHOLOGY.

FISH CANNOT DISTINGUISH AGGRESSIVE FROM INDOLENT
NEOPLASMS AND UROLOGISTS ARE VERY UNLIKELY TO
TREAT SOLELY ON THE BASIS OF FISH.

PATIENTS BENEFIT PRIMARILY FROM CHANGES IN THE
FREQUENCY AND/OR AGGRESSIVENESS OF THEIR
EVALUATIONS.

SO, WHAT CHANGES IN EVALUATION OR FOLLOWUP ARE LIKELY WHEN A PATIENT HAS
A POSITIVE TEST THAT IS LIKELY TO BE CORRECT ONLY 3-25% (HEMATURIA) OR 50%
(MONITORING) OF THE TIME?

PATIENTS WITH HEMATURIA AND A POSITIVE FISH COULD BE EVALUATED
(AGGRESSIVELY) FOR A UROTHELIAL NEOPLASM. HOW OFTEN IF NO LESION IS
FOUND HAS NOT BEEN ADDRESSED?

PATIENTS WITH HEMATURIA AND A NEGATIVE FISH COULD AVOID A BLADDER TUMOR
EVALUATION.

FOR PATIENTS WITH UROTHELIAL NEOPLASMS, LESS FREQUENT FOLLOWUP MIGHT
BE JUSTIFIED IF THE INITIAL TUMOR WERE LOW-RISK (PUNLMP/LOW-GRADE,Ta)
CYSTOSCOPY AT EACH VISIT COULD DEPEND ON FISH REMAINING NEGATIVE.

MORE FREQUENT AND AGGRESSIVE FOLLOWUP SOLELY FOR A POSITIVE FISH WOULD
BE HARD TO JUSTIFY CONSIDERING THE LOW PPV AND THE INABILITY OF THE TEST
TO IDENTIFY HIGH-RISK LESIONS.

LESS FREQUENT MONITORING WOULD BE HARD TO JUSTIFY FOR ANY PATIENT WITH A
HIGH-RISK NEOPLASM.
FISH FACTORS
SAME AS UC - LONG LEAD TIME, FLUCTUATING RESULTS, DIFFICULT TO INTERPRET RESULTING IN HIGH INTEROBSERVER VARIABILITY, HIGH COMPLEXITY TECHNOLOGISTS REQUIRED
DIFFERENT FROM UC - HIGHER SENSITIVITY, SPECIFICITY BUT LESS RELIABLE RESULTS (LOWER PPV), HIGHER COSTS AND REIMBURSEMENT
• IF PATIENTS PRESCREENED WITH CYSTO, FISH SHOULD BE COMPARED WITH BW, NOT VU
• COST EFFECTIVENESS VS UC NOT ADDRESSED
• FISH BEST (cf VU) FOR LOW-GRADE, NON-INVASIVE NEOPLASMS BUT NEED FOR EARLY DETECTION QUESTIONABLE

WHO SHOULD GET A FISH?
PATIENTS WHOSE MANAGEMENT WILL BE CHANGED BY THE RESULT
• “BiCa” F/U WITH NON-POSITIVE CYTOLOGY
• ABNORMAL CYSTO, NON-POSITIVE CYTO
• SPECIAL PROTOCOLS OF THE PRACTICE

“BiCa” PATIENT - CYTOLOGY SUSP, CYSTOSCOPY NEG
WHO SHOULD NOT GET A FISH?

PATIENTS WHO WILL BE FOLLOWED AGGRESSIVELY ANYWAY i.e. THEY HAVE A HIGH-RISK INDEX TUMOR (HIGH-GRADE UCa, CIS, TI-2, NON-UCa)

PATIENTS WITH A POSITIVE CYSTOSCOPY

PATIENTS WITH A POSITIVE CYTOLOGY

PATIENTS WITH VERY LOW-GRADE INDEX LESIONS (PUNLMP, PAPILLOMA, DYSPLASIA)

URINARY CYTOPATHOLOGY IS THE ONLY CURRENTLY AVAILABLE METHOD THAT CAN DISTINGUISH AGGRESSIVE UROTHELIAL CARCINOMAS FROM NON-AGGRESSIVE UROTHELIAL NEOPLASMS.

IT REMAINS THE BEST WAY TO MONITOR PATIENTS FOR RECURRENT/PERSISTENT DISEASE.