The Surgeon's Dilemma: reconciling the cytopathology with other diagnostic findings

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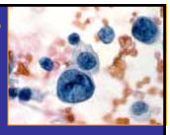
What's the trouble with cytology?

- Urinary cytopathology has never been completely satisfactory – median sensitivity 35-48%, specificity 94%
- Lack of consensus of histological classification and terminology
- Lack of surgeon confidence in cytopathologists
  - Varying degrees of training and expertise, operator dependent, experience with cervical cytology ≠ expertise in urinary cytology
  - Perceived adversity associated with an incorrect interpretation - i.e. better to over-interpret

1. Murphy W. What's the trouble with cytology? J Urol 176: 2343-2346, 2006.
2. Van Rhijn. Urine markers for bladder cancer surveillance. Eur Urol 2005; 47:736-48

When do I obtain a cytology?



SCREENING
- Initial workup of gross or microscopic **hematuria**
- Persistent **irritative symptoms**

SURVEILLANCE
- Patients with a **history of TCC**
  -Bladder, ureteral, upper tract (incidence of upper tract 2.4-17% after neobladder[1])
  -After cystectomy (e.g. neobladder or urethral washings)
- **After intravesical therapy** for CIS, T1G3 (e.g. BCG, mitomycin)

• ***Low Risk***: *routine cytology unnecessary if initial cytology is neg*

• ***Intermediate and High-Risk***: *cytology with each cystoscopy*

1. Eur Urol 41:124, 2002

Localizing The Source of Positive Cytology

- Bladder (most common)
- Upper tracts (selective cytologies to lateralize)
- Ureteroscopy
- Prostatic urethra (biopsy/TUR)
- GYN source in women if workup is negative (up to 15%)
- If full workup negative 80% likelihood coming from the bladder
- BCG treatment usually appropriate once localized

How does the type of specimen come into play?

- The sensitivity of urinary cytology is affected by the collection method
- Voided urine, noninvasive, but often hypocellular, transitional cells shed singly, may be contaminated
  - 3 samples on separate days increases sensitivity [1]

• Catheterized urine and bladder wash, invasive, but higher cellularity, shed in sheets and clusters, decreased contamination

- Instrumentation artifact can be a problem [2]
- May lead to a reading of "atypical" which mandates further workup
- Must inform pathologist if neobladder, ileal loop, or urethral wash

1. *Badalament RA et al. The sensitivity of bladder wash flow cytometrey, bladder wash cytology, and voided cytology in the detection of bladder carcinoma. Cancer 60: 1423-1427, 1987.*
2. *Kannan, Bose. Low grade TCC and instrument artifact: A challenge in urinary cytology. Acta Cytol 37: 899-902, 1993.*

Mitigating factors with invasive collection

- Large amounts of lidocaine jelly obscure cellular elements of sample
- Many allow residual urine to escape upon placement of cystoscope
- Cystoscopic flow may distort cellular architecture

- Ideal: obtain residual urine + immediate lavage before endoscopic manipulation with minimal jelly

The Accuracy of Urinary Cytology in Daily Practice

Differences in diagnostic yield exist between academic, community, and cancer referral medical centers

• Retrospective review of 1672 pts in 3 practice settings

Diagnostic Yield of Urinary Cytology

	Overall	UPMC	SIH	COHNMC
Sensitivity	64%	47%	85%	66%
Specificity	95%	98%	74%	98%
PPV	75%	81%	56%	88%
NPV	92%	91%	93%	94%
Diagnostic accuracy	89%	90%	77%	96%
% TCCa-1	29%	44%	33%	11%
Non-determinant	45%	11%	82%	4%

UPMC: University of Pittsburgh Medical Center; SIH: St. Joseph's Hospital; COHNMC: City of Hope National Medical Center; UFCM: University of Florida College of Medicine; TCCa-1: transitional cell carcinoma, Grade 1.

How does cytology change my surgical planning?

• If **cytology is positive** yet bladder tumor appears papillary and non-invasive, random bladder biopsies are performed

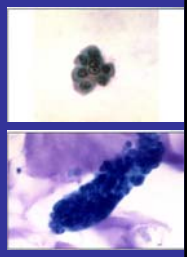
• If **cytology is positive** and there are no visible bladder lesions, upper tract studies are warranted AND random bladder biopsies are performed because malignant cells may appear in the urine long before any cystoscopically detectable lesion appears[1]

• Positive cytology from urethral washings after cystectomy warrant topical BCG treatment or urethrectomy

Murphy WM, Soloway MS et al. Urinary cytology and bladder cancer: the cellular features of transitional cell neoplasms. Cancer 53:1555-1565, 1984.

"Atypical urothelial cells present; cannot rule out a low-grade lesion" and "Cytoatypia"

- The diagnosis of low grade TCC is very difficult to make on urine cytology
- Low grade features subjective
- Collection method is a factor
- Sensitivity ranges from 0%-100%[1], specificity 6%-100%
- To me, Cytoatypia usually = recollect or obtain ancillary tests (i.e. FISH)



Renshaw et al: Cytology of grade 1 papillary TCC: A comparison of cytologic architectural and morphometric criteria in cystoscopically obtained urine. Acta Cytol 40: 676-682, 1996.

50yo male with "PUNLMP"

- Outside slides read at UCLA → T1G3
- Cytology "atypical"
- Repeat cystoscopy
- TUR → T1G3

77yo male w/ T1G3

- Initial resection T1G3
- Underwent BCG x 6
- Repeat cystoscopy
- Cytology "atypical"
- TUR → T1G3, cis

The Fate of indeterminant cytology

- 9,763 cytologies
- 675 were indeterminate, 389 with complete eval
- 15% were found to have malignancy

- Multivariate analysis:
  - -History of bladder cancer (**OR 5.57**,p=0.001)
  - -Hematuria (OR **3.21**, p = 0.001)
  - -Smoking (OR **1.85**, p =0.072)
  - -All 3 (**OR 9.8**)

Novicki et al. Cost-effective evaluation of indeterminate urinary cytology J Urol 160, 734-736, 1998.

What Adjunctive Urinary Marker Tests Can Increase Diagnostic Yield?

-**Flow cytometry**: SN 45%m SP 87%; requires high % of abnl cell (>10%)[1]
-**Image analysis/morphometrics**: poor SN for normal vs Gr 1
-**Lewis X Ag**: expressed in neoplastic urothelium in 85-89% of TCCs independent of grade; drawback – 51% of reactive urothelia express this Ag[2]
-**p53**: alterations in 60% of TCCs, rarely in low grade, freq false +s

	SN	SP
BTA Trak: human complement factor H-related protein	72%	48% FP
BTA Stat: human complement factor H-related protein	67-87%	40-70%
NMP22	66%	
AuraTek (fibrinogen, fibrin etc)	48-68%	
Telomerase (not readily available)	70%	99%
Hyaluronic Acid (does not detect Gr I)	92%	92%
ProteinChip	80%	90-97%

False positives with gross hematuria, BCG, UTI, stones, instrumentation

1. *Sidranksy et al. Science 252:706-709, 1991*
2. *Loy et al. Mod Path 8:587-590, 1995*

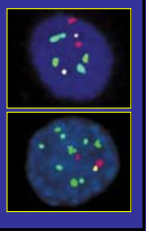
FISH

• Fluoroescence in situ hybridization – detects chromosomal anomalies in exfoliated bladder cells

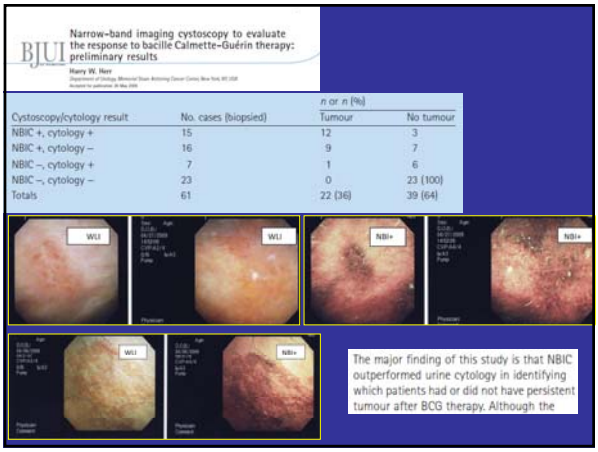
UroVysion:
-Aneuploidy of chromosomes 3, 7, 17; loss of 9p21 (CDKN2) locus

•Sensitivity varies 69%-87%, specificity 89-96%

• Low grade: 36-57%
• High grade: 83-97%
• CIS: close to 100%



Vrooman O. Molecular markers for detection, surveillance, and prognostication of bladder cancer. Int J Urol, 16:234-243, 2009.



Recent trends at the AUA

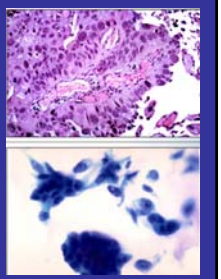
#940: Hovius et al, Netherlands. "Urine cytology is of no added value in the primary evaluation of patients with hematuria." 1841 pt with microscopic or gross hematuria, 204 (11%) had abnormal cytol, 134 (7.3%) found to have cancer. All pts had cancers diagnosed on endoscopy or imaging. *Conclusion: cytology is of no added value.*

#941: Falebita et al, Ireland."Urine cytology in the evaluation of urological malignancy revisited-is it still necessary?" 2568 pt with cytology, 25 positive. 210,421 Euros spent for a positive cytology yield of 0.96%. Conclusion: *routine cytology not cost effective*.

#942: Feifer et al, Canada. "Utility of urine cytology in the workup of asymptomatic microscopic hematuria." 190pt, 0% had positive cytol, 11% atypical, 89% normal. 4.2% found to have TCC. Cost for 190 pt =$59,875. *Conclusion: no diagnostic benefit added in pt with asymptomatic microhematuria.*

Conclusions

- The primary mission of urinary cytology is to detect high grade urothelial neoplasms
- Cytology performs well in this setting
- And it is cheap
- I do not routinely utilize any adjunctive tests other than FISH at this time



High grade TCC