# 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


## 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)
  - 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
- Catheterized urine and bladder wash, invasive, but higher cellularity, shed in sheets and clusters, decreased contamination
  - Instrumentation artifact can be a problem
  - May lead to a reading of “atypical” which mandates further workup
  - Must inform pathologist if neobladder, ileal loop, or urethral wash


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

- Retrospective review of 1672 pts in 3 practice settings

- 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 appears1

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

How does cytology change my surgical planning?

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“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%; specificity 6%-100%
- To me, Cytoatypia usually = recollect or obtain ancillary tests (i.e. FISH)

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)

Novotzki et al. Cost-effective evaluation of indeterminate urinary cytology
What Adjunctive Urinary Marker Tests Can Increase Diagnostic Yield?

- **Flow cytometry**: SN 45%/SP 87%; requires high % of abnl cell (>10%)
- **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
- **p53**: alterations in 60% of TCCs, rarely in low grade, freq false +s
- **BTA Trak**: human complement factor H-related protein 72% 48% FP
- **BTA Stat**: human complement factor H-related protein 67-87% 40-70%
- **NMP22**: Lewis X Ag
- **Lewis X Ag**: expressed in neoplastic urothelium in 85-89% of TCCs independent of grade; drawback – 51% of reactive urothelia express this Ag
- **Telomerase**: not readily available
- **Hyaluronic Acid**: (does not detect Gr I)
- **ProteinChip**: 80% 90-97%

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

2. Loy et al. Mod Path 8:587-590, 1995

**FISH**

- Fluorescence 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%

**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 cytology, 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." 190 pt, 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