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045IC - Microhematuria to Intractable Hemorrhagic Cystitis - A Case-Based Approach to the Comprehensive Management of Urinary Tract Bleeding

Sunday, May 17

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Microhematuria to Hemorrhagic Cystitis: A Case-Based Approach to the Comprehensive Management of Urinary Tract Bleeding

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DISCLOSURES

- Boorjian
  - Ferring, Johnson & Johnson (consultant)
- Raman
  - Pacific Edge, Steba, Urogen, Valar, CG Oncology (site investigator for all); United Medical Systems (investment)
- Barocas
  - Lantheus, Pacific Edge, Astellas/Pfizer, Lynx Dx (Advisory Boards)
- Westerman
  - CG Oncology (consultant)

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OUTLINE OF COURSE

- Introduction + background
- AUA Microhematuria Guidelines: 2020→2025
  - What has…and what has not…changed
    - Risk stratification/evaluation
    - Upper tract imaging
    - Urine markers
- **Questions**
- BPH bleeding
- Hemorrhagic cystitis

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LEARNING OBJECTIVES

- Implement AUA Guidelines for evaluation of microscopic hematuria into clinical practice
  - Recognize risk-based stratification
  - Understand role of urinary markers
- Create strategies for treating refractory hemorrhagic cystitis

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BACKGROUND TO HEMATURIA

- One of the most common urologic diagnoses
  - 27% of all urologic evaluations
- Microhematuria noted in 6.5% of healthy participants in screening studies (range 2.4-31.1%)
- **35-65% of patients with hematuria are diagnosed with a urologic or renal condition, many of which require treatment**

Mariani AJ et al, J Urol 1989;141:350
Antoniewicz A et al, ISRN Urol 2012; 2012:710734
Davis R et al, J Urol 2012;188:2473

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UNDERSTANDING THE LANDSCAPE OF HEMATURIA: A TALE OF TWO DIAGNOSES

- Microhematuria
  - LOTS of studies, inclusive of LOTS of patients → robust data, guidelines
- Gross hematuria (hemorrhagic cystitis)
  - Fewer studies, fewer patients included → limited data, no (yet) guidelines

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ETIOLOGY OF HEMATURIA

- Considerations of source include from where urine produced to where urine excreted
- Nephrologic - medical renal disease
- Urologic
  - BPH, infection, stones
  - **Malignancy**
    - Urothelial, renal, prostate

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Who Should Be Investigated for Haematuria? Results of a Contemporary Prospective Observational Study of 3556 Patients

Wei Shen Tan [a,b,], Andrew Feber [c], Rachael Sarpong [d], Pramit Khetrapal [a,b], Simon Rodney [a,c], Rumana Jalil [d], Hugh Mostafid [e], Joanne Cresswell [f], James Hicks [g], Abhay Rane [h], Alastair Henderson [i], Dawn Watson [j], Jacob Cherian [j], Norman Williams [d], Chris Brew-Graves [d], John D. Kelly [a,b], on behalf of DETECT I trial collaborators*

- Patients referred for hematuria to 40 hospitals 2016-2017
  - 65% gross hematuria, 35% microhematuria
- All had cystoscopy + upper tract imaging
- **Incidence of urinary tract cancers = 10%**
  - Bladder cancer = 8%; renal parenchymal cancer = 1%
  - Upper tract urothelial carcinoma=0.7%; prostate cancer=0.3%
  - **Malignancy in 13.8% with gross heme vs 3.1% with micro**

Eur Urol 2018

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The IDENTIFY study: the investigation and detection of urological neoplasia in patients referred with suspected urinary tract cancer – a multicentre observational study

- International multicenter prospective observational study
- 10,896 patients (~ 2/3 with gross hematuria)
- Cancer diagnosed in 26% with gross hematuria versus 6.38% with microhematuria
  - Bladder cancer diagnosed in 22.4% vs 5.23%

Khadhouri S et al, BJU Int 2021

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SO WHERE HAS SUCH DATA LANDED US IN TERMS OF HEMATURIA EVALUATION?

- Gross hematuria: recognized risk factor for malignancy
  - → CT Urogram, cystoscopy, urine cytology
- Microhematuria: overall diagnostic yield very low (low prevalence of cancer in most with hematuria)
  - So if we did the same full evaluation for all:
    - Waste resources ($$$$)
    - False (+)'s → more testing
    - Complications/discomfort from testing

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SO WHERE HAS SUCH DATA LANDED US IN TERMS OF HEMATURIA EVALUATION?

- However…if we don't evaluate patients with microhematuria who have risk factors for malignancy
  - → risk delay in diagnosis of urinary tract cancer
    - → increased mortality
- Therefore, key with microhematuria = risk assessment
- Approach = risk-based evaluation
  - Best for patients
  - Best for healthsystem

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JAMA Internal Medicine | Original Investigation

Cost-effectiveness of Common Diagnostic Approaches for Evaluation of Asymptomatic Microscopic Hematuria

Joshua A. Halpern, MD, MS; Bilal Chughtai, MD; Hassan Ghomrawi, PhD, MPH

Figure. Cancers Detected and Costs of Diagnostic Protocols for Evaluation of Asymptomatic Microscopic Hematuria

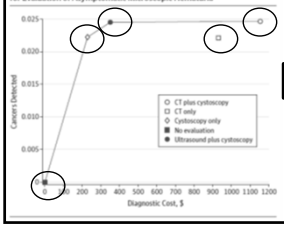

Table 3. Incremental Cost per Cancer Detected (ICCD) for Diagnostic Strategies

Strategy	Cancers Detected[a]	Cost, $[a]	Δ Cancers	Δ Cost, $	ICCD, $
No evaluation	0	0	NA	NA	NA
CT only	221	9 300 000	221	9 300 000	Dominated
Cystoscopy only	222	2 284 000	222	2 284 000	10 287
Renal ultrasound + cystoscopy	245	3 504 400	23	1 220 400	53 810
CT + cystoscopy	246	11 540 200	1	8 035 800	6 480 484

- Minimal incremental benefit for CT over US, and much higher cost

JAMA Intern Med 2017.

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GOALS OF AUA MH GUIDELINES

- Provide risk-based, patient-centered approach
  - Minimize harms and waste of over-evaluation in low-risk = *improve specificity*
  - Maintain detection in those at higher risk = *maintain sensitivity*
- Improve adherence by making a more judicious set of guidelines that remain "user friendly"
- Continued refinement with evolution of data
  - Guidelines periodically updated – most recently 2025

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KEY PRINCIPLE OF RISK BASED APPROACH TO MH:

AVOID DELAY IN OR MISSED HEMATURIA EVALUATION WHEN INDICATED…

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Delays in Diagnosis and Bladder Cancer Mortality

Brent K. Hollenbeck, MD, MS[1,2,3]; Rodney L. Dunn, MS[2]; Zaojun Ye, MS[2]; John M. Hollingsworth, MD, MS[2,4]; Ted A. Skolarus, MD[2]; Simon P. Kim, MD, MPH[2]; James E. Montie, MD[1,2]; Cheryl T. Lee, MD[1]; David P. Wood, Jr., MD[1]; and David C. Miller, MD, MPH[1,2,3]

- SEER-Medicare 1992-2002
  - Patients with hematuria within 1 year of bladder ca dx
- Delay in dx→significantly increased risk of death

Cancer 2010;116:5235-5242

Table 2. Relation Between Delays in Diagnosis and Mortality

Model	Unadjusted	HR (95%CI) Adjusted[a]	Adjusted[b]
Cancer-specific mortality			
Delay <3 mo	1.0	1.0	1.0
Delay 3 to <6 mo	1.09 (0.99-1.20)	1.00 (0.89-1.11)	1.05 (0.93-1.18)
Delay 6 to <9 mo	1.19 (1.07-1.33)	1.16 (1.03-1.31)	1.30 (1.15-1.48)
Delay 9-12 mo	1.39 (1.26-1.54)	1.34 (1.20-1.50)	1.29 (1.14-1.45)
All-cause mortality			
Delay <3 mo	1.0	1.0	1.0
Delay 3 to <6 mo	1.13 (1.07-1.19)	1.06 (1.00-1.12)	1.06 (1.00-1.13)
Delay 6 to <9 mo	1.21 (1.14-1.29)	1.15 (1.07-1.23)	1.19 (1.11-1.28)
Delay 9-12 mo	1.28 (1.21-1.36)	1.15 (1.08-1.23)	1.12 (1.04-1.20)

HR indicates hazard ratio; CI, confidence interval.
[a]Adjusted for age, sex, race, socioeconomic status, and comorbidity.
[b]Adjusted for the same variables stated above plus grade and stage.

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WHAT FACTORS MAY LEAD TO A DELAY IN HEMATURIA EVALUATION?

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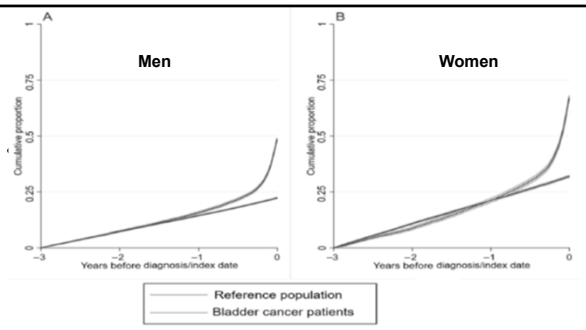

- Overlap of symptoms?

Eur Urol Oncol 2025

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Table 3 – Odds ratios for the association between exposure category and ordered bladder cancer risk categories (NMIBC to MIBC to MBC), stratified by sex

	Odds ratio (95% confidence interval) [a]			
	Men (n = 22 109)		Women (n = 7451)	
	(MBC + MIBC) [b] vs NMIBC	MBC [b] vs (NMIBC + MIBC)	(MBC + MIBC) [b] vs NMIBC	MBC [b] vs (NMIBC + MIBC)
At least one prescription of prediagnostic antibiotics indicated for UTI treatment[c]				
Never	Reference	Reference	Reference	Reference
Ever	1.28 (1.19–1.37)	1.14 (0.99–1.31)	1.42 (1.27–1.58)	1.12 (0.93–1.36)
Number of prescriptions of prediagnostic antibiotics indicated for UTI treatment[c] category				
0 prescriptions	Reference	Reference	Reference	Reference
1 prescription	1.16 (1.06–1.26)	0.99 (0.83–1.19)	1.25 (1.08–1.44)	0.95 (0.73–1.24)
2–4 prescriptions	1.33 (1.20–1.47)	1.19 (0.97–1.45)	1.41 (1.23–1.62)	1.10 (0.86–1.42)
5–9 prescriptions	1.60 (1.32–1.94)	1.64 (1.15–2.32)	1.64 (1.35–2.00)	1.31 (0.94–1.84)
>9 prescriptions	2.98 (2.21–4.00)	2.59 (1.62–4.13)	2.48 (1.85–3.32)	2.09 (1.35–3.23)

NMIBC = non-muscle-invasive bladder cancer; MIBC = muscle-invasive bladder cancer; MBC = metastatic bladder cancer.
[a] Odds ratios from generalized ordered logistic regression models, adjusted for marital status (categories), education level (categories), continent of birth (categories), Charlson comorbidity index (in four categories), drug comorbidity index (continuous), age at diagnosis (continuous), calendar year of diagnosis (two categories), and health care region (six categories; data missing for 30 men and 13 women, who were excluded from this analysis).

Liedberg F et al, Eur Urol Oncol 2025

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AND WHO IS PARTICULARLY AT RISK FOR MIS-DIAGNOSIS WITH UTI?

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Sex Disparities in Diagnosis of Bladder Cancer After Initial Presentation With Hematuria

A Nationwide Claims-Based Investigation

Joshua A. Cohn, MD[1]; Benjamin Vekhter, PhD[2]; Christopher Lyttle, MS[2]; Gary D. Steinberg, MD[1]; and Michael C. Large, MD[3]

- Days from hematuria→bladder cancer dx longer in F
- F more likely to be (mis) diagnosed with UTI
- F less likely to undergo abdominal/pelvic imaging

Cancer 2014;120:555-561

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Do differences in clinical symptoms and referral patterns contribute to the gender gap in bladder cancer?

Armin Henning, Marlies Wehrberger, Stephan Madersbacher, Armin Pycha†, Thomas Martini†, Evi Comploj†, Klaus Jeschke*, Christian Tripolt* and Michael Rauchenwald

- No significant difference in rates of gross hematuria or irritative LUTS btw men and women

HOWEVER,

- 78% of M vs 55% of F consulted a urologist ($p<0.05$)
- Sx treatment w/o further eval given to 19% of M vs 47% of F during yr before bladder cancer dx ($p<0.05$)
  - ≥ 3 tx for UTI given to 3.8% of M vs 15.8% of F ($p<0.05$)

BJU Int 2013;112:68-73

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TAKE-HOME MESSAGES

- Differential diagnosis: infection, stones, BPH, medical renal dz, **cancer**
- Risk of urinary tract cancer > for gross vs micro
- Bladder cancer = most common urinary tract cancer a/w hematuria
- **Be wary of diagnosis of UTI (esp. in women) as explanation for hematuria!**
- AUA Microhematuria Guidelines aim for risk-based, patient-centered approach

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Evaluation of Adults with Microhematuria: Emphasis on AUA/SUFU Guideline 2025 Update

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Disclosures

- Advisory boards
  - Lantheus (PSMA PET)
  - Pacific Edge (Cx bladder diagnostic test)
  - Astellas/Pfizer (enzalutamide/Xtandi)
  - Lynx Dx (MPS 2 prostate cancer diagnostic test)

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Outline

- Definition of MH
- Initial evaluation
- Risk-stratified approach
- Follow-up after evaluation

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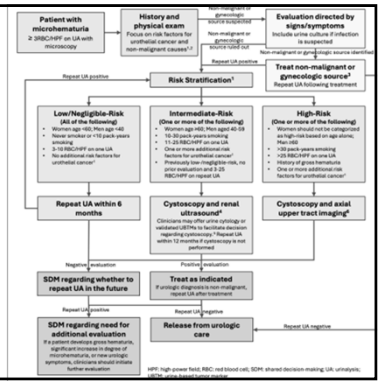
MICROHEMATURIA: 2025 AUA/SUFU GUIDELINE

*Referenced throughout the remainder of the talk



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DIAGNOSIS AND DEFINITION

MH defined as ≥ 3 RBC/HPF on microscopic evaluation of a single, properly collected specimen

Strong Recommendation; Evidence Level C

Dipstick detects peroxidase activity of hemoglobin with risk of **false positives**

- Myoglobinuria
- Dehydration
- Exercise
- Menstrual blood
- Povidone iodine

Thus, a positive dipstick test should prompt UA with microscopy.

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Diagnosis and Definition

- Cohort of 46,000 patients
- Threshold of 3-10 RBC/HPF had highest sensitivity (0.73) and lowest negative likelihood ratio (0.40) at threshold

Cut point	Sensitivity	Specificity	Classified Correctly	LR+	LR–
Index Microscopic UA					
(>=0 to 2)	1.00	0.00	0.00	1.00	
(>=3 to 10)	0.73	0.68	0.68	2.26	0.40
(>=11 to 50)	0.37	0.91	0.91	4.35	0.69
(>=51 to 100)	0.18	0.98	0.97	7.41	0.84
(>=100+)	0.14	0.99	0.98	9.87	0.87

Matulewicz RS et al, Bladder Cancer 2017; 3(1): 45-49

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INITIAL EVALUATION

- History
  - Risk factors for malignancy
  - Localizing symptoms
- Physical exam
  - Blood pressure
  - Renal function measurement
  - Directed GU exam

- Smoking!
- History of gross hematuria
- Irritative voiding symptoms
- Prior pelvic radiation therapy
- Prior cyclophosphamide/ifosfamide
- Family history of urothelial ca or Lynch syndrome
- Occupational exposures
- Chronic indwelling foreign body

- Signs of medical renal disease
- Determine imaging modality

- As clinically indicated by symptoms and signs

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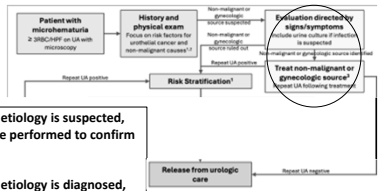
INITIAL EVALUATION



When gynecologic or non-malignant urologic etiology is suspected, appropriate physical exam and tests should be performed to confirm the suspicion.

When gynecologic or non-malignant urologic etiology is diagnosed, UA should be repeated after resolution of that problem. If MH persists, clinician should perform risk-based MH evaluation.

When MH is attributed to UTI, UA should be repeated after treatment to ensure resolution of MH.

WHY?

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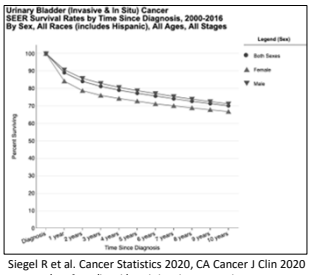
Sex Differences in Bladder Cancer Incidence and Survival

- Incidence is higher in men vs. women (3:1)
  - 62,100 vs. 19,300 cases/yr
- Inferior 5-yr DSS for women vs. men
  - 78.8% vs. 72.8%
  - Driven by delayed diagnosis → more advanced disease
  - Empiric treatment for "UTI"



Siegel R et al. Cancer Statistics 2020, CA Cancer J Clin 2020
https://seer.cancer.gov/statfacts/html/urinb.html; accessed Mar 20, 2022
Henning et al. BJU Int, 2013

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MEDICAL RENAL DISEASE

- Clinicians should refer patients with microhematuria for nephrologic evaluation if medical renal disease is suspected. However, risk-based urologic evaluation should still be performed.

Do not omit urologic evaluation just because of medical renal disease or anticoagulation

ANTICOAGULATION

- Clinicians should perform the same evaluation irrespective of whether patients are taking antiplatelet or anticoagulation therapy.

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SUMMARY

- Definition of MH
  - 3 or more RBC/HPF on UA with micro
  - Urine dip stick test insufficient
- Initial evaluation
  - History for bladder ca risk factors
  - BP and renal function
  - Directed physical exam as clinically indicated
- Risk-stratified approach
  - If benign etiology is suspected, confirm it, treat it, and repeat the UA after treatment to confirm resolution
- Follow-up after evaluation
  - Do not modify approach for patients with known or suspected medical renal disease and those on anticoagulation

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RISK-BASED MANAGEMENT

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RISK STRATIFICATION

- Following initial evaluation, clinicians should categorize patients presenting with microhematuria as low- (now low/negligible-), intermediate-, or high-risk for genitourinary malignancy based on the accompanying tables. (Strong Recommendation; Evidence Level: Grade C)

While the risk categories and risk-based evaluation recommendations have changed slightly, the concepts of risk-stratification and risk-based evaluation remain at the core of the AUA/SUFU Guideline

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EVALUATION OF 2020 RISK STRATIFICATION SYSTEM (Literature review in 2024)

1. Risk factors in 2020 system are appropriate

Risk Factors Included in AUA/SUFU Microhematuria Risk Stratification System
Age
Male sex
Smoking use
Degree of MH
Persistence of MH
History of gross hematuria

Additional Urothelial Cancer Risk Factors
Irritative lower urinary tract symptoms
Prior pelvic radiation therapy
Prior cyclophosphamide/ifosfamide chemotherapy
Family history of urothelial cancer or Lynch Syndrome
Occupational exposures to benzene chemicals or aromatic amines (e.g., rubber, petrochemicals, dyes)
Chronic indwelling foreign body in the urinary tract

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EVALUATION OF 2020 RISK STRATIFICATION SYSTEM (Literature review in 2024)

2. System stratifies patients by risk; low risk is <u>really</u> low

Risk of Malignancy	Overall Number of pts; % with cancer	Low	Intermediate	High
Sanci et al 2021	1,018 3.3%	0%	3.1%	5.7%
Woldu et al 2021	15,779 5.4%	0.4%	1.0%	6.3%
Saxon et al 2022	1,730 (women) 1.5%*	0%	0.2%	1.3%

* In the Saxon study, 50% of patients were inappropriately referred or inappropriately evaluated. The overall % with cancer is estimated from the total number of cancers divided by the number of appropriate evaluations, whereas the percentage in each risk category is computed using all evaluated patients in the denominator.

Sanci A, et al. Urology 2021
Woldu SL, et al. Urology 2022
Saxon GM, et al. Urology 2022

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EVALUATION OF 2020 RISK STRATIFICATION SYSTEM (Literature review in 2024)

3. Nuances of risk in women
   - Most cancers found in women over 60
     - So, women under 60 have low risk of malignancy
   - Most cancers found in women with lower levels of MH
     - So, evaluation of women with low degree of MH is justified if other risk factors are present

Saxon GM, et al. Urology 2022

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RISK STRATIFICATION SYSTEM 2025

Risk of malignancy*	Low/Negligible 0-0.4%[1-3]	Intermediate 0.2-3.1%[1-3]	High 1.3-6.3%[1-3]
Number of criteria patient must meet	All	One or more	One or more
Degree of hematuria on a single urinalysis	3-10 RBC/HPF	11-25 RBC/HPF	>25 RBC/HPF
Alternative criteria for degree of hematuria		Previously low-risk patient with no prior evaluation and 3-25 RBC/HPF on repeat urinalysis	History of gross hematuria
Age for women	<60 years	≥60 years	Women should not be categorized as high-risk based on age alone
Age for men	<40 years	40-59 years	≥60 years
Smoking history	Never smoker or <10 pack years	10-30 pack years	>30 pack years
Other risk factors for urothelial cancer (see Table 3)	None	One or more	One or more plus any high-risk feature

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LOW/NEGLIGIBLE-RISK (0-0.4%) 2025

Risk of malignancy*	Low/Negligible 0-0.4%[1-3]
Number of criteria patient must meet	All
Degree of hematuria on a single urinalysis	3-10 RBC/HPF
Alternative criteria for degree of hematuria	
Age for women	<60 years
Age for men	<40 years
Smoking history	Never smoker or <10 pack years
Other risk factors for urothelial cancer (see Table 3)	None

NEW

Clinicians **should obtain** repeat UA within 6 months
- ~~Release if negative~~
- Recategorize if positive
  - Intermediate (3-25 RBC/HPF)
  - High (>25 RBC/HPF)

Moderate Recommendation; Evidence Level: Grade C

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INTERMEDIATE-RISK (0.2-3.1%) 2025

Risk of malignancy*	Intermediate 0.2-3.1%[1-3]
Number of criteria patient must meet	One or more
Degree of hematuria on a single urinalysis	11-25 RBC/HPF
Alternative criteria for degree of hematuria	Previously low-risk patient with no prior evaluation and 3-25 RBC/HPF on repeat urinalysis
Age for women	≥60 years
Age for men	40-59 years
Smoking history	10-30 pack years
Other risk factors for urothelial cancer (see Table 3)	One or more

Clinicians **should recommend** cystoscopy and renal US

Strong Recommendation; Evidence Level: Grade C

Clinicians **may offer** UBTM to decide whether to do cysto or not; patients who do not undergo cysto should get still get renal/bladder US

Conditional Recommendation; Evidence Level: Grade C

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HIGH-RISK (1.3-6.3%) 2025

Risk of malignancy*	High 1.3-6.3%[1-3]
Number of criteria patient must meet	One or more
Degree of hematuria on a single urinalysis	>25 RBC/HPF
Alternative criteria for degree of hematuria	History of gross hematuria
Age for women	Women should not be categorized as high-risk based on age alone
Age for men	≥60 years
Smoking history	>30 pack years
Other risk factors for urothelial cancer (see Table 3)	One or more plus any high-risk feature

Clinicians **should perform** cystoscopy and axial imaging

CT Urogram preferred

May substitute MR Urogram or non-contrast cross-sectional imaging plus retrograde pyelograms if CKD precludes iodinated contrast.

Strong Recommendation; Evidence Level: Grade C

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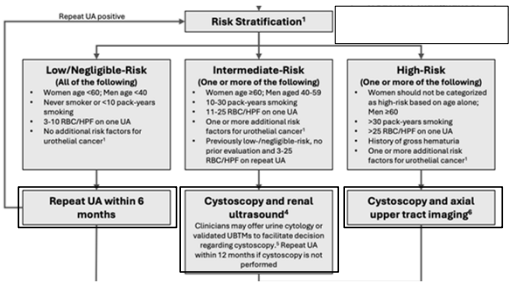
RISK-BASED EVALUATION 2025



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RISK-BASED EVALUATION 2025

- Risk stratification and risk-based management
  - Low/negligible (0-0.4%)
    - Women < 60 yrs
    - Repeat UA within 6 months (evaluate if persistent MH)
  - Intermediate (0.2-3.1%)
    - Cystoscopy + Renal U/S recommended
    - Urine-based tumor marker to triage for cystoscopy in selected cases
  - High (1.3-6.3%)
    - Cystoscopy + CT urogram

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FOLLOW-UP AFTER NEGATIVE EVALUATION

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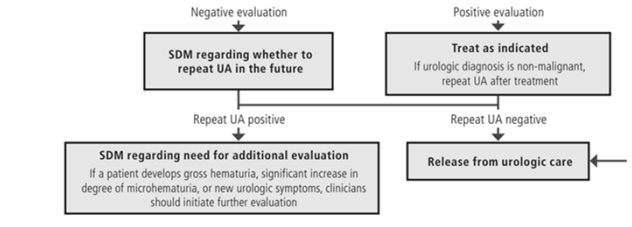
FOLLOW-UP



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CONTINUE TESTING FOR MH AFTER NEGATIVE EVALUATION?

- Studies show persistent MH is common (1/3 to 1/2), but risk of identifying malignancy on repeat evaluation is very low (1% or less)
- Benign diagnoses may cause persistent MH
  - Enlarged prostate, Randall's plaques and non-obstructing stones, pelvic organ prolapse, vaginal atrophy, interstitial cystitis

Pak et al, Uro Onc, 2021
Pichler et al, Anticancer Res, 2013

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CONTINUE TESTING FOR MH AFTER NEGATIVE EVALUATION?

- Shared decision-making to decide whether to perform follow-up UA or release from care
  - If follow-up UA is performed and negative, release from care
  - If follow-up UA is performed and positive, shared decision-making to decide whether to perform repeat evaluation
- Higher vigilance for those at higher risk (e.g., current smoker, history of pelvic XRT)

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INDICATIONS FOR REPEAT EVALUATION

- Development of gross hematuria
- Significant increase in degree of MH
- New or progressive urologic symptoms

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SUMMARY

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SUMMARY

CORE PRINCIPLES

- Definition: ≥ 3 RBC/HPF on UA with micro
- If benign etiology is suspected
  - Confirm it, treat it, and repeat the UA after treatment to confirm resolution
- Do not modify approach for
  - Suspected medical renal disease
  - Anticoagulation

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RISK STRATIFICATION SYSTEM 2025

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Number of criteria patient must meet	All	One or more	One or more
Degree of hematuria on a single urinalysis	3-10 RBC/HPF	11-25 RBC/HPF	>25 RBC/HPF
Alternative criteria for degree of hematuria		Previously low-risk patient with no prior evaluation and 3-25 RBC/HPF on repeat urinalysis	History of gross hematuria
Age for women	<60 years	≥60 years	Women should not be categorized as high-risk based on age alone
Age for men	<40 years	40-59 years	≥60 years
Smoking history	Never smoker or <10 pack years	10-30 pack years	>30 pack years
Other risk factors for urothelial cancer (see Table 3)	None	One or more	One or more plus any high-risk feature

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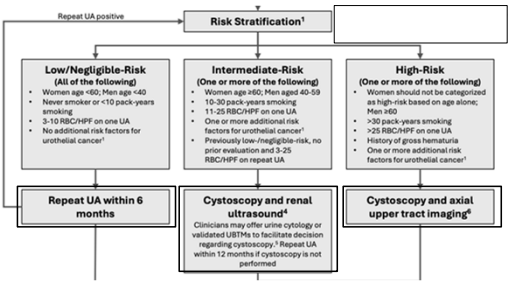
American Urological Association

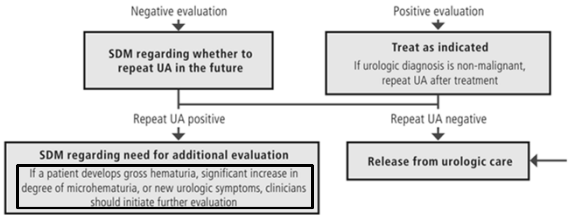
RISK-BASED EVALUATION 2025



31

American Urological Association

FOLLOW-UP



32

Thank you

dan.barocas@vumc.org
@danbarocas
https://www.auanet.org/guidelines-and-quality/guidelines

33

Imaging for Hematuria

Why? When? Who? How? Repeat?

Jay D. Raman, MD, FACS, FRCS(Glasg)
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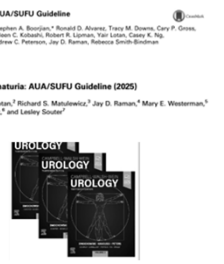
1

Disclosures

- Pacific Edge Biotechnologies
  - Study site investigator (NCT03988309)
- Urogen Pharma LTD
  - Study site investigator (NCT03558503)
  - Study site investigator (NCT06774131)
- Steba Biotech S.A.
  - Study site investigator (NCT04620239)
- CGOncology
  - Study site investigator (NCT06111235)
  - Study site investigator (NCT06567743
- Valar Labs
  - Study site investigator (NCT582950)


Microhematuria: AUA/SUFU Guideline

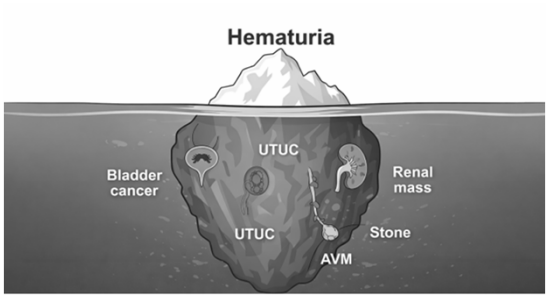
Daniel A. Barocas,*,† Stephen A. Boorjian,* Ronald D. Alvarez, Tracy M. Downs, Cary P. Gross, Blake D. Hamilton, Kathleen C. Kobashi, Robert R. Lipman, Yair Lotan, Casey K. Ng, Matthew E. Nielsen, Andrew C. Peterson, Jay D. Raman, Rebecca Smith-Bindman and Lesley H. Souter

Updates to Microhematuria: AUA/SUFU Guideline (2025)

Daniel A. Barocas,[1] Yair Lotan,[2] Richard S. Matulewicz,[3] Jay D. Raman,[4] Mary E. Westerman,[5] Erin Kirkby,[6] Lauren J. Pak,[6] and Lesley Souter[7]

2

Why ???



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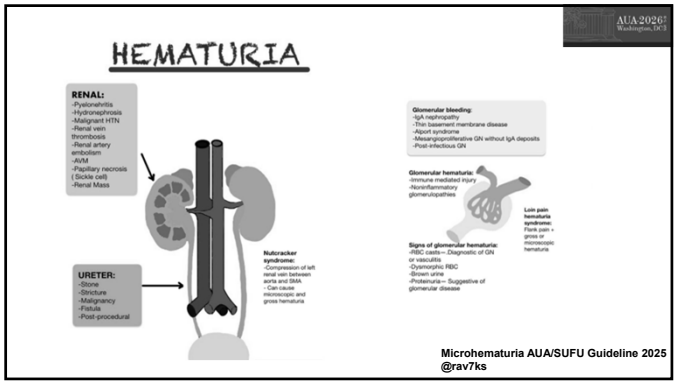
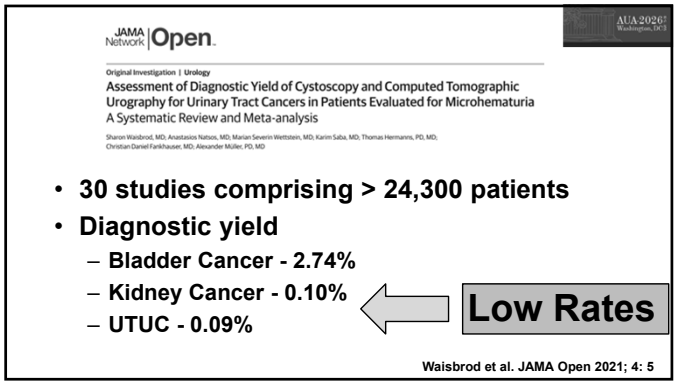
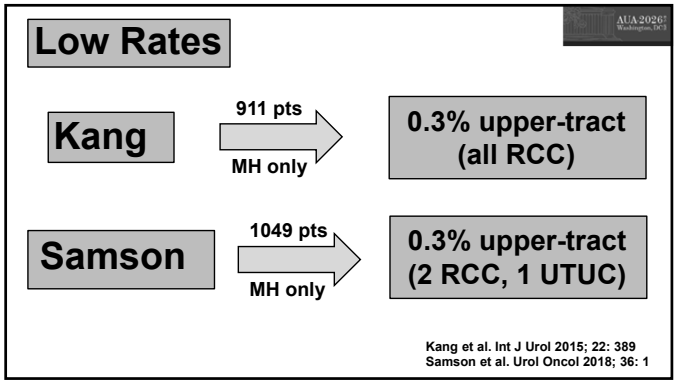

HEMATURIA
RENAL:
-Pyelonefritis
-Hydronephrosis
-Malignant HTN
-Renal vein thrombosis
-Renal artery embolism
-AVM
-Papillary necrosis (Sickle cell)
-Renal Mass
URETER:
-Stone
-Stricture
-Malignancy
- Fistula
-Post-procedural
Nutcracker syndrome:
-Compression of left renal vein between aorta and SMA
- Can cause microscopic and gross hematuria
Glomerular bleeding:
-IgA nephropathy
- Thin basement membrane disease
-Alport syndrome
-Mesangioproliferative GN without IgA deposits
-Post-infectious GN
Glomerular hematuria:
-Immune mediated injury
-Noninflammatory glomerulopathies
Loin pain hematuria syndrome:
Flank pain + gross or microscopic hematuria
Signs of glomerular hematuria:
-RBC casts-- Diagnostic of GN or vasculitis
-Dysmorphic RBC
-Brown urine
-Proteinuria-- Suggestive of glomerular disease
Microhematuria AUA/SUFU Guideline 2025
@rav7ks

4


JAMA Network Open.
Original Investigation | Urology
Assessment of Diagnostic Yield of Cystoscopy and Computed Tomographic Urography for Urinary Tract Cancers in Patients Evaluated for Microhematuria
A Systematic Review and Meta-analysis
• 30 studies comprising > 24,300 patients
• Diagnostic yield
– Bladder Cancer - 2.74%
– Kidney Cancer - 0.10%
– UTUC - 0.09%
Low Rates
Waisbrod et al. JAMA Open 2021; 4: 5

5


Low Rates
Kang
911 pts
MH only
0.3% upper-tract (all RCC)
Samson
1049 pts
MH only
0.3% upper-tract (2 RCC, 1 UTUC)
Kang et al. Int J Urol 2015; 22: 389
Samson et al. Urol Oncol 2018; 36: 1

6

Higher Rates …

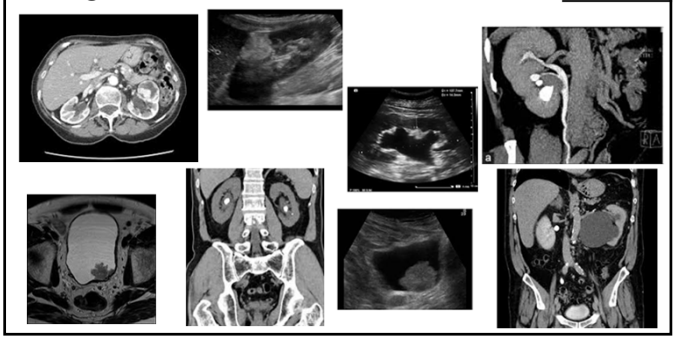
Fankhauser

- 432 pts → MH → < 1% upper-tract (3 RCC)
- 415 pts → GH → 1.7% upper-tract (7 RCC, 4 UTUC)

Fankauser et al. World J Urol 2021; 39: 97

7

When ???



8

When ???

9

Who ??? IR & HR pts

Low/Negligible (patients meet all criteria	Intermediate (patients meets one or more of these criteria)	High (patients meets one or more of these criteria)
• 3-10 RBC/HPF • Women age <60 years; Men age <40 years • Never smoker or <10 pack years • No risk factors for urothelial cancer	• 11-25 RBC/HPF • Women age ≥60 years; Men age 40-59 years • 10-30 pack years • Low/Negligible risk patient with no prior evaluation and 3-25 RBC/HPF on repeat urinalysis • Any additional Risk factors for urothelial cancer	• > 25 RBC/HPF • History of gross hematuria • Men age ≥ 60 years • Women not categorized as high-risk solely based on age • > 30 pack years • One or more of above plus any additional Risk factors for urothelial cancer

Risk factors for UCC: Irritative LUTS; Prior Pelvic Radiotherapy; Certain Prior Chemotherapy agents; Occupational Exposure; Indwelling foreign body; Family History of Urothelial CA

Microhematuria AUA/SUFU Guideline 2025
Strong Recommendation; Evidence Level C

10

47 year old female with 5 RBC/HPF, never smoker, no risk factors for urothelial CA; family hx of tuberous sclerosis

Risk stratification = LOW

Evaluation = at a minimum, some type of upper-tract imaging needed

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Genetic syndromes

- **Patients with MH with family hx of RCC or known renal tumor syndrome should get upper-tract imaging**

Table 5: *Known Genetic Renal Tumor Syndromes**

Known genetic renal tumor syndrome
1. von Hippel-Lindau
2. Birt-Hogg-Dube
3. Hereditary Papillary Renal Cell Cancer
4. Hereditary Leiomyomatosis Renal Cell Cancer
5. Tuberous sclerosis

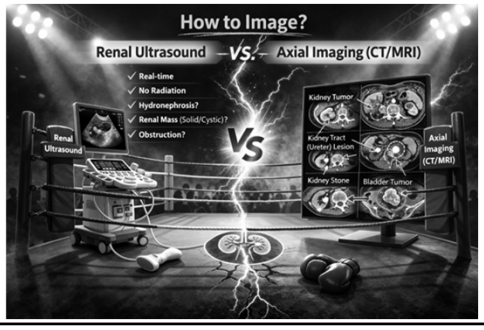
* The Panel recognizes that this list is not exhaustive.

- **Irrespective of MH risk strata**
- **Imaging type = provider discretion**

Barocas et al. J Urol 2020; 204: 778

12

How ???



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Guideline Statement

Clinicians should recommend cystoscopy and renal ultrasound in patients with MH categorized as intermediate risk for malignancy.

Microhematuria AUA/SUFU Guideline 2025
Strong Recommendation; Evidence Level C

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RUS vs. CT

RUS	CT
Less expensive	More expensive
No ionizing radiation	Ionizing radiation
No IV contrast	IV contrast
Identifies cortex lesions	Identifies cortex lesions
Operator dependent	Operator independent
Low sensitivity for UTUC	High sensitivity for UTUC

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Why RUS for IR

- Risk for upper-tract cancer (kidney or UTUC) is low
- CT imaging has potential for unexpected incidental findings
- Performance characteristics of U/S are overall quite good

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Risk of Cancer

IR → 0.2% - 3.1%

HR → 1.3% - 6.3%

Sanci et al. Urology 2021; 154: 28
Woldu et al. J Urol 2021; 205: 1387
Saxon et al. Urology 2022; 160: 34

17

Assessing the Costs of Extraurinary Findings of Computed Tomography Urogram in the Evaluation of Asymptomatic Microscopic Hematuria

- 202 patients with MH
  - 2 pts (1%) with GU malignancy (RCC)
  - 60 pts (30%) with stones
  - 150 pts (74%) with extra-urinary findings

Lai et al. Urology 2016; 95: 34

18

Assessing the Costs of Extraurinary Findings of Computed Tomography Urogram in the Evaluation of Asymptomatic Microscopic Hematuria

Procedure Type	Number of Procedures	Total Cost for Procedures($)	Inpatient Days Needed
Colonoscopy	3	3915	
Endovascular aneurysm repair	2	7548	15
Esophagogastroduodenoscopy	2	3548	
Hysterectomy	2	7000	2
Gastrointestinal endoscopic ultrasound	1	1067	
Hemicolectomy	1	4817	3
Endometrial biopsy	1	848	
Fine needle aspiration of retroperitoneal cyst	1	993	
Adrenalectomy	1	5214	
Laparoscopic hepatic resection	1	5824	1
Vaginal sling	1	3449	1
Exploratory-laparotomy, removal of ovarian mass	1	2870	
Port placement	1	1505	5
Laparoscopic cholecystectomy	1	3627	
Attempted cannulation of left renal artery	1	2430	1

Total cost:
~ $140,000 USD

Per patient cost:
~ $700 USD

Lai et al. Urology 2016; 95: 34

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Diagnostic Imaging in the Evaluation of Asymptomatic Microhematuria: Systematic Review and Meta-analysis

Jacob I. Taylor,[1] Lesley H. Souter,[2] Daniel A. Barocas,[3] Stephen A. Boorjian,[4] Jay D. Raman,[5] and Yair Lotan[1]*

- **For detection of RCC or UTUC, RUS performance characteristics**
  - **Sensitivity – 14 - 96%** (low certainty of evidence)
  - **Specificity – 99 - 100%** (moderate certainty of evidence)

Taylor et al. J Urol 2023; 209: 1099

20

Diagnostic Imaging in the Evaluation of Asymptomatic Microhematuria: Systematic Review and Meta-analysis

Jacob I. Taylor,[1] Lesley H. Souter,[2] Daniel A. Barocas,[3] Stephen A. Boorjian,[4] Jay D. Raman,[5] and Yair Lotan[1]*

	Positive likelihood ratio	Post-test probability of UTUC/RCC based on positive test result	Negative likelihood ratio	Post-test probability of UTUC/RCC based on negative test result
US in MH and GH patients[c]				
Low-risk patients: 0.5% pre-test probability	126.38	47.0%	0.28	0.1%
Intermediate-risk patients: 2.0% pre-test probability		78.3%		0.6%
High-risk patients: 10.0% pre-test probability		95.1%		3.0%

Taylor et al. J Urol 2023; 209: 1099

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Oncology

Assessing the Diagnostic Performance of Renal Ultrasound in Microhematuria Evaluation: Validation of the AUA Microhematuria 2020 Guidelines

Emily Bochner, Chidera Ibezue, Dev Banerji, Sarah Attia, Jacob Taylor, Yair Lotan

- **5167 patient with MH who underwent CT, RUS, or both**
  - **Potpourri of imaging … retrospective**
  - **RUS missed**
    - **1 bladder, 2 UTUC, 5 RCC**

Bochner et al. Urology 2026; 207: 196

22

Guideline Statement

Clinicians should perform cystoscopy and axial upper tract imaging in patients with MH categorized as high-risk for malignancy

Microhematuria AUA/SUFU Guideline 2025
Strong Recommendation; Evidence Level C

23

Upper Tract Imaging Options for HR MH

If there are <u>no</u> contraindications to use, clinicians should perform multiphasic CT urography

Microhematuria AUA/SUFU Guideline 2025
Moderate Recommendation; Evidence Level C

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Preferred study

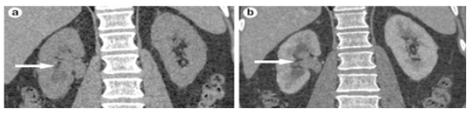
- **Multiphasic CT urography should include imaging of the urothelium**
- **Triphasic (essential)**
  - **Non-contrast**
  - **Nephrographic phase (100 seconds)**
  - **Excretory phase (10 – 15 minutes)**

Vikram et al. AJR Am J Roentgenol 2009; 192: 6

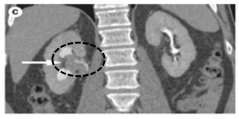
25

CT Urography

Non-contrast **Nephrographic**



Excretory or Pyelographic



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CT Urography

Table 2 | CT urography for diagnosing UUT-UCC and bladder cancer

Study	*n*	Site	Se	Sp	PPV	NPV	Indications	Bolus	Maneuvers
Fritz *et al.* (2006)[31]	41	UUT	1.00	NR	NR	NR	Histologically verified UUT-UCC	Single (1.5 ml/kg)	None
Chow *et al.* (2007)[32]	8	UUT	1.00	0.99	0.80	1.00	Painless hematuria	Double	oral water; compression
Sudakoff *et al.* (2008)[33]	11	UUT	0.82	0.98	0.50	1.00	Unspecified hematuria		None
Wang *et al.* (2009)[34]	39	Renal pelvis	0.94	0.99	NR	NR	Visible hematuria		(120 ml)
Wang *et al.* (2009)[34]	39	Ureter	0.67	0.98	NR	NR		Single	
Maheshwari *et al.* (2010)[35]	9	UUT	1.00	0.99				Double	1,000 ml oral water; log roll on table; partially empty bladder
Jinzaki *et al.* (2011)[36]	46	UUT	0.94	0.99			Hematuria	Single (2 ml/kg)	400–500 ml oral water
Cowan *et al.* (2007)[33]	32	UUT (RUS)	0.96	0.97	0.89	0.99	Hematuria, equivocal or positive IVU, or persistent hematuria and negative IVU	Double (100 ml; 50 ml)	750–1,000 ml oral water; void before CT examination; walk and log roll
Cowan *et al.* (2007)[33]	32	UUT (RUS)	0.96	0.97	0.89	0.99	Hematuria, equivocal or positive IVU, or persistent hematuria and negative IVU	Double (100 ml; 50 ml)	750–1,000 ml oral water; void before CT examination; walk and log roll
Blick *et al.* (2011)[37]	156	Bladder (CTU)				0.98	Visible hematuria, ≥40 years; no infection	Double (100 ml; 50 ml)	750–1,000 ml oral water; void before CT examination, walk and log roll
Blick *et al.* (2011)[37]	156	Bladder (FC)			0.80	0.99	Visible hematuria, ≥40 years; no infection	Double (100 ml; 50 ml)	750–1,000 ml oral water; void before CT examination, walk and log roll
Sadow *et al.* (2008)[38]	54	Bladder (CTU)	0.83	0.94	0.71	0.97	Visible hematuria	Single (100 ml)	900 ml oral water, void before CT examination; 250 ml intravenous saline
Sadow *et al.* (2008)[38]	54	Bladder (FC)	0.94	0.93	0.69	0.99	Visible hematuria	Single (100 ml)	900 ml oral water, void before CT examination; 250 ml intravenous saline

Abbreviations: CTU, CT urography; FC, flexible cystoscopy; IVU, intravenous urography; NPV, negative predictive value; NR, not reported; PPV, positive predictive value; RUP, retrograde ureteropyelography; Se, sensitivity; Sp, specificity; UUT, upper urinary tract; UUT-UCC, upper urinary tract urothelial cell carcinoma.

Sensitivity ~ 90%
Specificity > 95%

Raman et al. AJR Am J Roentgenol 2013; 201: 6

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CT Urography

Table 1. *Pooled Sensitivities and Specificities Based on Imaging Modality*

Imaging modality	Sensitivity for UTUC/RCC detection	Specificity for UTUC/RCC detection
CTU in solely MH patients	80%; 95%CI, 28%-99%[a]	86%; 95%CI, 70%-95%[a]
CTU in MH and GH patients	94.2%; 95%CI, 83.8%-98.1%[b]	99.1%; 95%CI, 96.6%-99.8%[b]
US in MH and GH patients	Range 14%-98%[c]	Range 99%-100%[c]
MRU in MH and GH patients	83%; 95%CI, 69%-93%[d]	86%; 95%CI, 67%-96%[d]

Performance characteristics are notably better for GH than MH

Taylor et al. J Urol 2023; 209: 6

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Low Dose Protocol

Split Dose Protocol

Dual Energy

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Split Dose CTU

Standard single dose	Split dose protocol
• Non-contrast CT – 300mg/ml contrast – 2.5 ml/sec injection – 90 mL bolus • Nephrographic images after 90s • Excretory images at 10 min	• Non-contrast CT – 300mg/ml contrast – 2.5 ml/sec injection – 50 mL bolus followed by 80mL bolus 9 min later • Nephrographic and excretory images 90s after 2nd bolus

Maheshwari et al. AJR Am J Roentgenol 2010; 194: 2

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Iodine Contrast Induced Nephropathy


ORIGINAL RESEARCH • STATEMENTS AND GUIDELINES

Radiology

Use of Intravenous Iodinated Contrast Media in Patients with Kidney Disease: Consensus Statements from the American College of Radiology and the National Kidney Foundation

Matthew S. Davenport, MD • Mark A. Perazella, MD • Jerry Yee, MD • Jonathan R. Dillman, MD, MS • Derek Fine, MD • Robert J. McDonald, MD, PhD • Roger A. Rudity, MD • Carolyn L. Wang, MD • Jeffrey C. Weinreb, MD

Risk of contrast nephropathy is low!

Davenport et al. Radiology 2020; 294: 3

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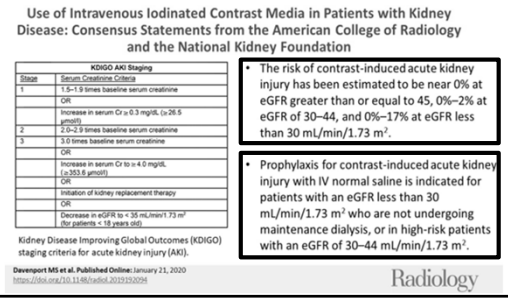
Iodine CIN


Use of Intravenous Iodinated Contrast Media in Patients with Kidney Disease: Consensus Statements from the American College of Radiology and the National Kidney Foundation

KDIGO AKI Staging	
Stage	Serum Creatinine Criteria
1	1.5–1.9 times baseline serum creatinine
	OR
	Increase in serum Cr ≥ 0.3 mg/dL (≥ 26.5 μmol/l)
2	2.0–2.9 times baseline serum creatinine
3	3.0 times baseline serum creatinine
	OR
	Increase in serum Cr to ≥ 4.0 mg/dL (≥ 353.6 μmol/l)
	OR
	Initiation of kidney replacement therapy
	OR
	Decrease in eGFR to < 35 mL/min/1.73 m² (for patients < 18 years old)

Kidney Disease Improving Global Outcomes (KDIGO) staging criteria for acute kidney injury (AKI).

- The risk of contrast-induced acute kidney injury has been estimated to be near 0% at eGFR greater than or equal to 45, 0%–2% at eGFR of 30–44, and 0%–17% at eGFR less than 30 mL/min/1.73 m^2.
- Prophylaxis for contrast-induced acute kidney injury with IV normal saline is indicated for patients with an eGFR less than 30 mL/min/1.73 m^2 who are not undergoing maintenance dialysis, or in high-risk patients with an eGFR of 30–44 mL/min/1.73 m^2.

Davenport MS et al. Published Online: January 21, 2020
https://doi.org/10.1148/radiol.2019192094

Radiology

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CT Urography

- **Contraindications (none absolute)**
  - **Chronic kidney disease (CKD)**
  - **Allergy to iodine-based contrast**
  - **Pregnancy**
    - **Few pts fall into high-risk group**
    - **Renal U/S during pregnancy; consider CT or MRI after delivery**

Microhematuria AUA/SUFU Guideline 2025

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Upper Tract Imaging Options for HR MH

If there are contraindications to multiphasic CT urography, clinicians may use magnetic resonanace urography (MRU)

Microhematuria AUA/SUFU Guideline 2025
Moderate Recommendation; Evidence Level C

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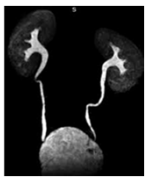
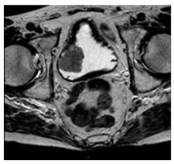
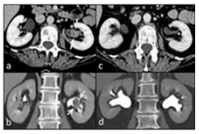
MRU has adequate sensitivity for renal cortical tumors and UTUC; lower for nephrolithiasis

Microhematuria AUA/SUFU Guideline 2025
Moderate Recommendation; Evidence Level C

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MR Urography

- **Advantages**
  - **Maintain upper-tract parenchymal and excretory system visualization**
  - **Obviates radiation exposure of CT**
  - **Liberal renal function thresholds**

Microhematuria AUA/SUFU Guideline 2025
Moderate Recommendation; Evidence Level C

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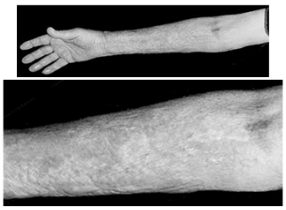
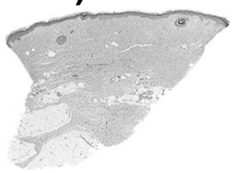
Nephrogenic Systemic Fibrosis (NSF)



Hardened skin with fibrotic nodules and plaques



Dermal fibroblasts, dendritic cells, collagen, elastin, and mucin

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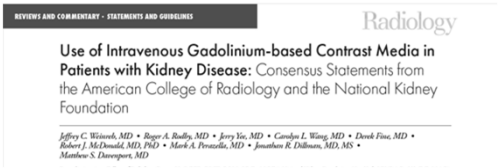
Gadolinium and CKD



REVIEWS AND COMMENTARY • STATEMENTS AND GUIDELINES

Radiology

Use of Intravenous Gadolinium-based Contrast Media in Patients with Kidney Disease: Consensus Statements from the American College of Radiology and the National Kidney Foundation

Jeffrey C. Weinreb, MD • Roger A. Rodby, MD • Jerry Yee, MD • Carolyn L. Wang, MD • Derek Fine, MD • Robert J. McDonald, MD, PhD • Mark A. Perazella, MD • Jonathan R. Dillman, MD, MS • Matthew S. Davenport, MD

Group II/III agents with very low risk of nephrogenic systemic fibrosis

Weinreb et al. Radiology 2021; 298: 1

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Gadolinium and CKD

TABLE 1. ACR Manual Classification of Gadolinium-Based Agents Relative to Nephrogenic Systemic Fibrosis

Group I: Agents associated with the greatest number of NSF cases:

Gadodiamide (Omniscan® – GE Healthcare)

Gadopentetate dimeglumine (Magnevist® – Bayer HealthCare Pharmaceuticals)

Gadoversetamide (OptiMARK® – Guerbet)

Group II: Agents associated with few, if any, unconfounded cases of NSF:

Gadobenate dimeglumine (MultiHance® – Bracco Diagnostics)

Gadobutrol (Gadavist® – Bayer HealthCare Pharmaceuticals; Gadovist in many countries) Gadoteric acid (Dotarem® – Guerbet, Clariscan – GE Healthcare)

Gadoteridol (ProHance® – Bracco Diagnostics)

Group III: Agents for which data remains limited regarding NSF risk, but for which few, if any unconfounded cases of NSF have been reported:

Gadoxetate disodium (Eovist – Bayer HealthCare Pharmaceuticals; Primovist in many countries)

ACR Manual On Contrast Media, 2023

39

MR Urography

- Contraindications
  - Pacemakers
  - Mobile (small) metal fragments (i.e. welders)

Microhematuria AUA/SUFU Guideline 2025

40

MR Urography

- Disadvantages
  - Significantly longer study than CT
  - Access
  - Claustrophobia
  - Cost: CT urogram (~473 USD) vs. MR urogram (~964 USD)

medicare.gov/procedure-price-lookup/

41

Upper Tract Imaging Options for HR MH

If there are contraindications to multiphasic CT and MR urography, clinicians may use retrograde pyelography

Microhematuria AUA/SUFU Guideline 2025
Moderate Recommendation; Evidence Level C

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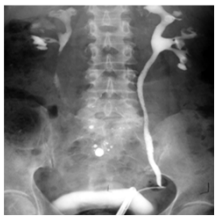
Other options

- Parenchymal imaging
  - CT non-contrast
  - MRI non-contrast
  - Renal ultrasound
- Excretory system imaging
  - Retrograde pyelography



43

Repeat ???

Yield of Urinary Tract Cancer Diagnosis With Repeat CT Urography in Patients With Hematuria

- 103 patients with negative CTU and persistent hematuria (gross and microscopic)
  - No new diagnoses of urothelial cancer within 3 years
- 45 patients with suspicious CTU
  - 4 (8.9%) malignancies

Mullen et al. AJR Am J Roentgenol 2015; 204(2) 318-323

44

Repeat ???

Clinical-Bladder cancer

Diagnostic yield of repeat evaluation for asymptomatic microscopic hematuria after negative initial workup

Jamie S. Pak M.D., Elizabeth Y. Wong B.A., M.P.H., Kevin Lee B.S., Luis A. Pino M.D., James M. McKiernan M.D., Christopher B. Anderson M.D.

- Of 1304 pts with negative MH workup, 637 with persistent MH
  - 317 with repeat upper tract imaging at median 39 months
    - 4 new renal masses (1.3%)

Pak et al. Urol Oncol 2021; 300: e1

45

Imaging Summary

- **Risk of upper-tract pathology is low … but not negligible**
- **RUS for IR; axial imaging for HR**
- **Low yield in repeating imaging in first few yrs after negative evaluation**

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Thank you

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Biomarkers and Microscopic Hematuria

Mary Beth Westerman, MD FACS
University of North Carolina - Chapel Hill

School of Medicine

1

Agenda

1. Pre-Test
2. Biomarker Basics
3. Biomarkers & the Guidelines
4. Practical Implementation
5. Conclusions

2

Clinical Scenario

A 65yo female with 5rbc/hpf and no other risk factors is referred to your clinic. Which of the following is an appropriate initial evaluation?

a) repeat UA within 6 months
b) urinary biomarker + renal ultrasound
c) cytology + CT Urogram
d) cystoscopy + CT Urogram
e) urinary biomarker + non contrast CT scan

3

Clinical Scenario

The patient prefers a urinary biomarker test rather than cystoscopy. Her biomarker test is positive. How likely are you to find bladder cancer on cystoscopy given these test characteristics?

Test Characteristics

Pre-test probability of bladder cancer: 2.5%	
Sensitivity	99%
Specificity	90%

a) 100%
b) 90%
c) 75%
d) 50%
e) 20%

4

Poll

Are you currently or planning to incorporate biomarkers in your microscopic hematuria evaluation pathway?

a) Yes - currently using biomarkers
b) Strongly considering using biomarkers
c) Maybe - Interested in learning more
d) No interest

5

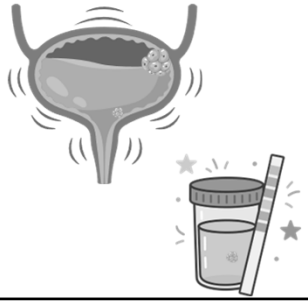
Transition slide - image

6

What is a biomarker?

NIH NATIONAL CANCER INSTITUTE

A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease



7

Urinary Biomarkers

Primary Care → Accelerate Referral

Specialist → Improve Risk Stratification

8

Urinary Biomarker for Bladder Cancer Detection

10%

prevalence of MH among adults

276.8 million

2026 US Adult population

Potential Market

27.6 million biomarker tests/year!

9

Vesica Health is positioned to lead in the $6 billion bladder cancer diagnostics market, with a mission to improve survival and patient care through earlier detection, precision diagnostics, and expanded access to noninvasive solutions. Learn more at: www.vesicahealth.com.

10

(Perfectly) Accurate Biomarker

High sensitivity

- All the patients who have bladder cancer get a positive result
  - *SNOUT: Sensitive test Negative rules OUT*
    - no false negatives

High specificity

- No patient without bladder cancer gets a positive result
  - *SPIN: Specific test Positive rule IN*
    - no false positives

(also cheap, can be done at home, easy to interpret results, no paperwork)

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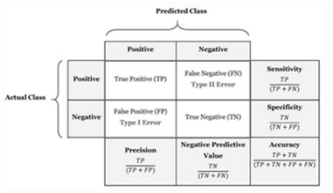
Unfortunately the perfect biomarker doesn't exist (yet)

Transition slide - image



So understanding test characteristics still matters

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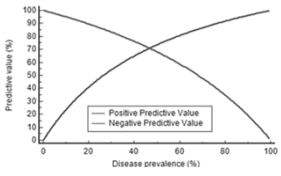
Test Characteristics

Population	Who are you using the test in
Prevalence	How many cases are present in a particular population at a given time?
Positive predictive value	If the test is positive how likely is it that the person has the disease?
Negative predictive value	If the test is negative how likely is it that the person does not have the disease

Bladder cancer prevalence is relatively low in MH patients
(0-6%)

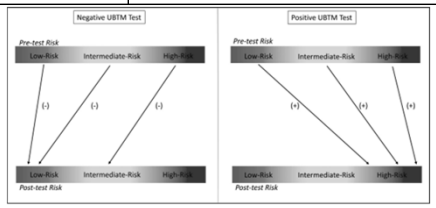


As prevalence goes down NPV goes up

13

Test characteristics

Pre-test Probability	probability patient has the disease before a diagnostic test (~prevalence)
Post-test probability	probability patient has the disease after a diagnostic test (~positive predictive value)



Woldu et al, Urol Oncol 2020; 38(11): 787

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High Risk MH Risk Stratification

(AssureMdX)

Probability of UC	Gross Hematuria	Microscopic Hematuria	High Risk MH
Pre-test	21%	4%	7%
Post-test (+)	36%	31%	42%
Post-test (-)	2%	0%	1%

de Jong, J. J. et al. Eur Urol Onc, 2022

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Transition slide - image

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(Original) Biomarkers for the Detection of Bladder Cancer

Assay	Hematuria Population	Total Patients (n)	Reported Negative Predictive Value	AUA Strength of Evidence
CxBladder Resolve	MH and GH	Total, n=548; MH, n=289	99.8%	B
CxBladder Triage	MH[C]	n=390	99%; 95%CI, 95-100%	A
	MH and GH	Total, n=571; MH, n=185	100%; 95%CI, 94-100%	C
NMP22 BladderChek (qualitative)	MH	n=876	95% - 100%	C
Urine cytology	MH	n=513	95.0% - 98.7%	C
	MH and GH	Total, n=4,497; MH, n=1,743	89.5% - 96.0%	C
UroVysion	MH and GH	Total, n=828 MH, n=384	97%	C
Xpert	MH and GH	Total, n=1,152 MH, n=597	98.0% - 99.6%	C

Barocas DA, Loton Y et al, 2025

17

American Urological Association

STATEMENT 13

IN APPROPRIATELY COUNSELED INTERMEDIATE RISK PATIENTS WHO ACCEPT THE RISK OF FORGOING DIRECT VISUAL INSPECTION OF THE UROTHELIUM CLINICIANS **MAY OFFER URINE CYTOLOGY OR VALIDATED URINE BASED TUMOR BIOMARKERS TO FACILITATE DECISION REGARDING CYSTOSCOPY**

CONDITIONAL RECOMMENDATION: LEVEL C

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STATEMENT 14

FOR PATIENTS WITH INTERMEDIATE-RISK MH WHO DO NOT UNDERGO CYSTOSCOPY BASED ON URINARY MARKER RESULTS, CLINICIANS SHOULD **OBTAIN A REPEAT UA WITHIN 12 MONTHS**. SUCH PATIENTS WITH PERSISTENT MH SHOULD THEN UNDERGO CYSTOSCOPY.

STRONG RECOMMENDATION: LEVEL C

19

STATEMENT 19

CLINICIANS SHOULD NOT ROUTINELY USE URINE CYTOLOGY OR URINE-BASED TUMOR MARKERS IN THE **INITIAL EVALUATION** OF LOW/NEGLIGIBLE- OR HIGH-RISK PATIENTS WITH MH.

STRONG RECOMMENDATION; EVIDENCE LEVEL C

20

STATEMENT 20

CLINICIANS SHOULD NOT ROUTINELY USE CYTOLOGY OR URINE-BASED TUMOR MARKERS AS **ADJUNCTIVE TESTS** IN THESETTING OF A NORMAL CYSTOSCOPY.

STRONG RECOMMENDATION; EVIDENCE LEVEL C

21

STATEMENT 21

CLINICIANS MAY OBTAIN URINE CYTOLOGY FOR HIGH-RISK PATIENTS WITH **EQUIVOCAL FINDINGS** ON CYSTOSCOPIC EVALUATION OR WITH PERSISTENT MICROHEMATURIA AFTER A NEGATIVE WORKUP WHO HAVE **IRRITATIVE VOIDING SYMPTOMS** OR RISK FACTORS FOR **CARCINOMA IN SITU**.

EXPERT OPINION

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Transition slide - image

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Criteria for inclusion

- NPV for the assay was reported in a purely MH population **or**
- MH patients comprised ≥25% of total hematuria population **and**
- Included ≥100 microhematuria patients.

ASSAYS IN INITIAL GUIDELINE PUBLICATION	SUBSEQUENT ADDITIONS
CxBladder	AssureMDx
Resolve	EarlyTectBCD
CXBladder Triage	
NMP22 qualitative	
Cytology	
Urovysion Fish	
Xpert	

Barocas, et al. J. Urol, 2025

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CYTOLOGY

Local Coverage Determination (LCD)

Bladder/Urothelial Tumor Markers

L36975

Urine cytology is not considered a bladder tumor marker.

	N (MH) prevalence	Sens	Spec	NPV	PPV
Feifer, 2010	149 3.3%	20%	100%	95%	100%
Pan, 2021	200 4%	0%	100%	96%	0%
vanValenberg, 2021	384 2.9%	36%	98%	98%	31%

FDA Approved: Yes
CMS Covered: Yes
Pathologic Interpretation
Medicare Reimbursement:
~$25

Feifer et al, Urology, 2010
Pan et al. Amer Journal Clin Exp Urol 2021
van Valenberg et al. EU Onc, 2021

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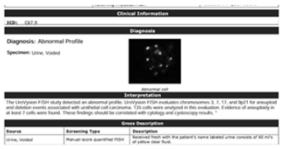
UROVYSION



FDA Approved: yes (2000)
CMS Status: Covered in certain circumstances*
CPT: 88120 or 88121 ($566-$822)
Must be billed by CLIA certified lab
Requires pathologist
Kit Storage: -20
35cc urine shipped immediately (ambient) or overnight if refrigerated
Turn around: 7 days

Local Coverage Determination (LCD)

Genetic Testing in Oncology: Specific Tests

L39367

To clarify indeterminate or nondiagnostic cytology results in patients with persistent gross or microscopic hematuria suspected of having urothelial cancer following a complete history and physical, cystoscopy, and imaging of the urinary tract in alignment with published, peer-reviewed specialty society guidelines[24,25,26] *OR*

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eau
European Association of Urology

Validation of an mRNA-based Urine Test for the Detection of Bladder Cancer in Patients with Haematuria

Franciscus Johannes P. van Valenberg[a,], Andrew M. Hiar[b], Ellen Wallace[b], Julia A. Bridge[c], Donna J. Mayne[d], Safedin Beqaj[e], Wade J. Sexton[f], Yair Lotan[g], Alon Z. Weizer[b],*

	N (MH) Prevalence	Sensitivity	Specificity	NPV	PPV
UroVysion	n=384 2.9%	64%	90%	99%	16%

van Valenberg et al. EU Onc, 2021

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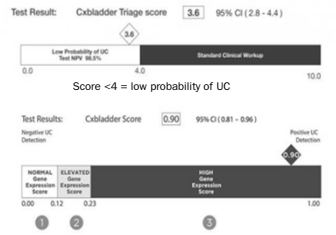
Cx bladder

PacificEdge CANCER DIAGNOSTICS



Score <4 = low probability of UC

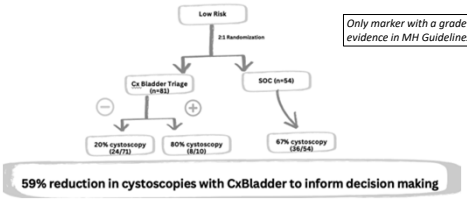
FDA Approved: No
CLIA certified: yes
CPT: 0363U: $760
5ml Urine
Send Out
No Refrigeration required
7-day turnaround
Can be integrated into EMR

28

A Multicenter Prospective Randomized Controlled Trial Comparing Cxbladder Triage to Cystoscopy in Patients With Microhematuria: The Safe Testing of Risk for Asymptomatic Microhematuria Trial

Yair Lotan,[1] Siamak Daneshmand,[2] Neal Shore,[3] Peter Black,[4] Kristen R. Scarpato,[5] Amit Patel,[6] Tony Lough,[7] Daniel A. Shoskes,[8] and Jay D. Raman[9]

THE JOURNAL of UROLOGY®



59% reduction in cystoscopies with CxBladder to inform decision making

Only marker with a grade "A" level of evidence in MH Guidelines

Lotan et al., J Urol, 2024

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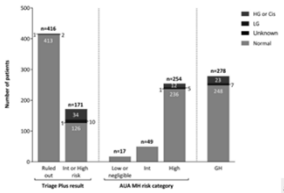
Original Article

Diagnostic performance of Cxbladder Triage Plus for the identification and stratification of patients at risk for urothelial carcinoma: The multicenter, prospective, observational DRIVE study

Stephen J. Savage, M.D.[a,*], Cesar E. Ercole, M.D.[b], George Hemstreet, M.D.[c], Andrew Leone, M.D.[d], Thomas Masterson, M.D.[e], Glen McWilliams, M.D.[f], Michael Risk, M.D.[g], Florian R. Schroeck, M.D.[h], Kelly Stratton, M.D.[i], Tony Lough, Ph.D.[j], Michel de Lange, Ph.D.[j], Kyoko Sakamoto, M.D.[j]

UROLOGIC ONCOLOGY



	N (MH) Prevalence	Sens	Spec	NPV	PPV
AUA HR	254 7.0%	89%	76%	98.9%	22%
AUA IR	49 0	NA	82%	100%	0

Combined performance characteristics for all MH not provided

Sep 10th, 2025
CMS Recommends US$1,328 Price for Triage Plus

Savage et al, 2026

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Abbott

NMP22™ BLADDERCHEK™

FDA Status: Approved
CMS Coverage for MH: No
CLIA waived
CPT: 86386

Point of Care
4 drops urine
30 minutes to results
Order in bulk from Abbott

National Average Reimbursement

$18.93	$13.10	$20.82	$60.20

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eau European Association of Urology

Platinum Priority – Bladder Cancer
Editorial by Brant A. Inman and Michael R. Abern on pp. 48–50 of this issue

Outcomes of a Bladder Cancer Screening Program Using Home Hematuria Testing and Molecular Markers

Chris H. Bangma*, Stacy Loeb*, Martijn Bosstra*, Xiaoye Zhu*, Samira El Bouazzaoui*, Jeanine Refos*, Kirstin A. Van Der Kwa*, Stephen Tjin*, Conja G.A.M. Franken*, Geert J.L.H. van Leenders*, Ellen C. Zwarthoff*, Monique J. Roobol*,*

	N (MH) Prevalence	Sens	Spec	NPV	PPV
NMP22	409 1.2%	25%	96.6%	99.2%	7.1%

Urologia Internationalis

Diagnostic Value of a Urine-Based Tumor Marker for Screening Lower Urinary Tract in Low-Risk Patients with Asymptomatic Microscopic Hematuria

Levent Sagnak Hamit Ersoy Osman Gucuk Ugur Ozok Hikmet Topaloglu

	N (MH) Prevalence	Sens	Spec	NPV	PPV
NMP22	164 1.2%	100%	85.2%	100%	7.7%

European Urology, 2013
Urologia internationalis, 2011

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EarlyTect BCD

promis DX

EarlyTect® Bladder Cancer Detection Test

Test	Results	Normal Reference Range
PENK DNA methylation	Positive**	Negative

FDA Status: Breakthrough Device Designation (2023)
Formal approval not required
CLIA certified: yes
PLA: 0452U
CPT: 81401
CMS CLFS: $192 (1/1/2025)

20ml urine
stable refrigerator/RT: 14 days
Results: 2-7 days

33

JAMA Oncology | Original Investigation

Urinary DNA Methylation Test for Bladder Cancer Diagnosis

promis DX

In Gab Jeong, MD, PhD; Sung-Cheol Yun, PhD; Hong Koo Ha, MD, PhD; Sung Gu Kang, MD, PhD; Sangchul Lee, MD, PhD; Sungchan Park, MD, PhD; Hyun Hwan Sung, MD, PhD; Sun Il Kim, MD, PhD; Eu Chang Hwang, MD, PhD; Kyung Cheol Moon, MD, PhD; Cheol Kwak, MD, PhD

EarlyTect BCD, a Streamlined *PENK* Methylation Test in Urine DNA, Effectively Detects Bladder Cancer in Patients with Hematuria

Bo-Ram Bang,[1] Jin Zhong,[1] Tae Jeong Oh,[1] Ji Yong Lee,[1] Yangyei Seo,[1] Min A Woo,[1] Jae Sung Lim,[1] Yong Gil Na,[1] Ki Hak Song,[1] Ju Hyun Shin,[1] Justin Jungsuk Lee,[1] Chan Su Im,[1] Seoyong Kim,[1] Safedin Beqaj,[1] Joseph D. Shirk,[1] Katelyn W. Ke, John Vallone,[1] and Sungwhan An[1]

	n(MH) prevalence	Sens	Spec	NPV	PPV
Jeong 2025	455 8.8%	87.5%	–	–	–
Bang 2024	82 8.5%	57.1%	93.3%	95.9%	44.4%

Not provided for MH only

Jama Onc, 2025
Journal of Molecular Dx, 2024

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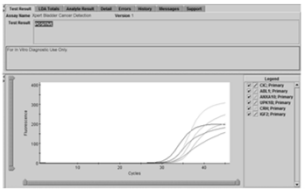
Xpert® Bladder Cancer Detection



FDA Approved: No
CPT: N/A ~5-20$/cartridge
Voided specimen
Cartridge use within 30 min
Decentralized Lab
90min turnaround

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European Association of Urology

Validation of an mRNA-based Urine Test for the Detection of Bladder Cancer in Patients with Haematuria

Franciscus Johannes P. van Valenberg[a,], Andrew M. Hiar[b], Ellen Wallace[b], Julia A. Bridge[c], Donna J. Mayne[d], Safedin Beqaj[e], Wade J. Sexton[f], Yair Lotan[g], Alon Z. Weizer[b],*

		Cystoscopy/histology		
		Pos	Neg	Total
Xpert detection of microhaematuria	Pos	8	59	67
	Neg	3	314	317
	Total	11	373	384

	N (MH) Prevalence	Sens	Spec	NPV	PPV
Xpert	n=384 2.9%	73%	84%	99%	12%

European Urology 2021

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AssureMDx™
Patient Result Report

Vesica Health®
Noninvasive. Early. Detection.

Patient Test Result: **Positive**

A positive AssureMDx test result is associated with a significantly increased risk of urothelial carcinoma. In clinical validation, the post-test cancer probability ranged from 31% to 42%, corresponding to a two- to eight-fold increase in risk compared to baseline, depending on hematuria type.[1,2]

Biomarker Status:

Biomarker	Category	Functional Role	Clinical Relevance	Result
TWIST1 [1,3]	DNA methylation	EMT/invasion regulator	When positive, indicates aggressive tumor biology with promoter hypermethylation significantly associated with progression, stage, grade, and recurrence potential.	Positive
OTX1 [1,3]	DNA methylation	Cell proliferation / differentiation	When positive, indicates proliferative dysregulation associated with urothelial tumorigenesis and predictive of future recurrence potential.	Negative
ONECUT2 [1,3]	DNA methylation	Epithelial differentiation	When positive, indicates altered epithelial differentiation associated with urothelial tumorigenesis.	Negative
FGFR3 [1,3,5]	Somatic mutation	Growth factor receptor, MAPK pathway	When positive, indicates activating mutation typical of low-grade NMIBC and predictive of future recurrence potential.	Negative
HRAS [1,3,4]	Somatic mutation	RAS/MAPK oncogene	When positive, indicates RAS pathway activation; complementary marker in multi-gene panels.	Negative
TERT [1,3,4,5]	Somatic mutation	Telomerase promoter driver	When positive, indicates early driver mutation detectable across stages and predictive of future recurrence potential.	Positive

FDA Approved : No
CLIA Certified: Yes
CMS Status: Investigational

PLA CODE: 0613U (1/1/2026)

30ml urine
Same day shipping (Fed ex)
Must be at lab within 5 days
Transfer from collection cup to transport tube with 15min
5-7 days for results

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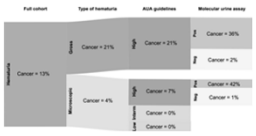
eau
European Association of Urology

A Urine-based Genomic Assay Improves Risk Stratification for Patients with High-risk Hematuria Stratified According to the American Urological Association Guidelines

Joep J. de Jong[a,], Olga M. Pijpers[a], Kim. E.M. van Kessel[a], Joost. L. Boormans[a], Wim Van Criekinge[b], Ellen C. Zwarthoff[c], Yair Lotan[d]*

Table 1 – Overview of the definition of low-, intermediate-, and high-risk microscopic hematuria used for stratification

Low risk	Intermediate risk	High risk
Male <40 yr Female <50 yr	Remaining patients	Presence of gross hematuria Age >60 yr male or female



	N (MH) Prevalence	Sens	Spec	NPV	PPV
AssureDx	381 3.4%	92.9%	92.1%	99.7%	30.9%

de Jong, J. J, et al. Eur Urol Onc, 2022

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Practical

	FDA Approved	CMS coverage for hematuria	Cost	Place of Service	Time to results	Company
AssureMDx	No	I/E		Send out	5-7 days	Vesica Health
~~CxBladder Resolve~~	~~No~~	~~I/E~~	~~—~~			~~Pacific Edge~~
CxBladder Triage	No	I/E	$760	Send out	7 days	Pacific Edge
EarlyTectBCD	No*	I/E	$192	Send out	2-7 days	PromisDx
Cytology	Yes	**Yes**	$25	Lab	48 hours	
UroVysion	Yes	**Select situations**	$800	Lab	4-7 days	Abbott Molecular
NMP22 BladderChek	Yes	I/E	<$50	**Home/clinic**	**30 minutes**	Alere
Xpert	No	I/E	5-20$/cartridge	clinic	**90 minutes**	Cephiad

CxBladder Triage Plus CMS price: $1328 (pending LCD)

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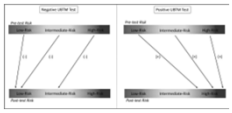
Circle back –

Pre-test Probability	probability patient has the disease before a diagnostic test (~prevalence)
Post-test probability	probability patient has the disease after a diagnostic test (~positive predictive value)



	Cancer Prevalence		Risk
Low/Negligible	0.0% - 0.4%	A positive test is most likely false (10% false positive rate)	Unnecessary workup
High Risk	1.3% - 6.3%	No data that a negative test is enough to forgo cystoscopy in high risk	Missed Cancer

Woldu et al, Urol Oncol 2020; 38(11): 787

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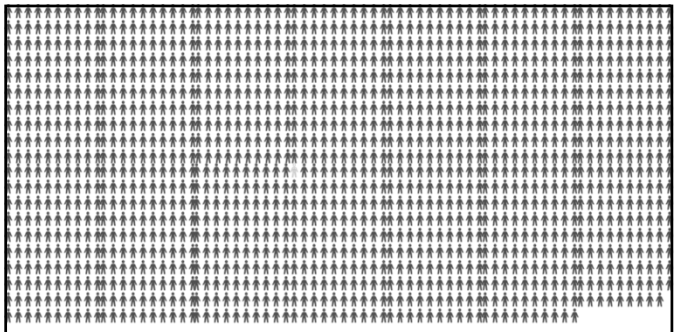

Cancers detection from cytology alone

Mishriki SF et al, J Urol 2013; 189(4): 1255-1258

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Key Take Home Points

Cystoscopy is the gold standard for diagnosis of bladder cancer

AUA guidelines support use in **intermediate risk microhematuria** patients who wish to avoid cystoscopy

- RCT demonstrated reduction in cystoscopies performed with incorporation of biomarker

No CMS coverage for biomarkers in hematuria evaluation – understand the cost implications for patients

- **Urine cytology is not classified as a biomarker by CMS**

The prevalence of the disease in the patient population impacts the test performance. In the microhematuria population (especially intermediate risk) the prevalence is low

The lower the prevalence the higher the negative predictive value of the test will be. Most patients with a positive test will not have bladder cancer

42

Conclusions & Challenges

Holy Grail Biomarker does not exist for microhematuria

Most patients with a positive biomarker will not have bladder cancer – workflow integration could be challenging for urology clinic workflow

No level 1 evidence showing a benefit to bladder cancer screening

Are biomarkers truly cost effective at a population or health system level?

Is this a solution in search of a problem?

43

BPH Related Bleeding

Mary Beth Westerman, MD

@drmbwesterman

UNC SCHOOL OF MEDICINE

1

78 YEAR OLD MALE PRESENTS WITH THREE EPISODES OF GROSS HEMATURIA.

Endorses baseline LUTS; denies tobacco exposure; denies risk factors for urothelial carcinoma

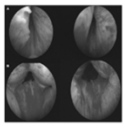
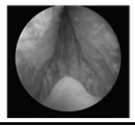
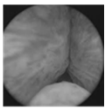
→ **Hematuria Evaluation**

2

CT Urogram → **no filling defects prostatomegaly (75cc)**

Cytology → **Negative**

Cystoscopy →

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4

PROSTATE BLEEDING

- BENIGN PROSTATIC HYPERPLASIA
- INFECTION (PROSTATITIS)
- INFLAMMATION
- CANCER/MALIGNANCY

5

BPH AND HEMATURIA

20%
only pathologic condition identified in hematuria evaluation

#1 men over 60
most common cause of gross hematuria

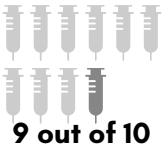
#1 prostate related bleeding
most common cause

Borth CS et al. Urology 2001; 57: 1082-1085
Lynch TH et al. Br J Urol 1994; 74: 732-732

6

7

5a–Reductase Inhibitors



9 out of 10
SYMPTOM IMPROVEMENT OR RESOLUTION

2 weeks - 9 months

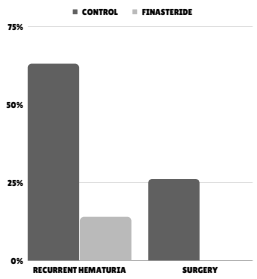
Onset of action
(cessation of bleeding)

Puchner PJ et al. J Urol 1995; 154: 1779-1782
Carlin BI et al. Prostate 1997; 31: 180-182

8

Finasteride Efficacy

- PROSPECTIVE RCT (N=57)
- BPH–RELATED HEMATURIA
- FINASTERIDE VS PLACEBO



Foley SJ et al. J Urol 2000; 163: 496-498

9

“

AFTER EXCLUSION OF OTHER CAUSES OF HEMATURIA, 5-ARIS MAY BE AN APPROPRIATE AND EFFECTIVE TREATMENT ALTERNATIVE IN MEN WITH REFRACTORY HEMATURIA PRESUMABLY DUE TO PROSTATIC BLEEDING.

EXPERT OPINION

Sandu et al. AUA BPH Guideline Amendment, 2023

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“

CLINICIANS MAY CONSIDER 5-ARIS AS A TREATMENT OPTION TO REDUCE INTRAOPERATIVE BLEEDING AND PERI- OR POSTOPERATIVE NEED FOR BLOOD TRANSFUSION AFTER TURP OR OTHER SURGICAL INTERVENTION FOR BPH.

EXPERT OPINION

Sandu et al. AUA BPH Guideline Amendment, 2023

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PATIENT PLACED ON 5ARI WITH BLEEDING CESSATION X 6 MONTHS.

Recurrence of gross hematuria. Urinary clot retention x 1. No infection or new exposures.

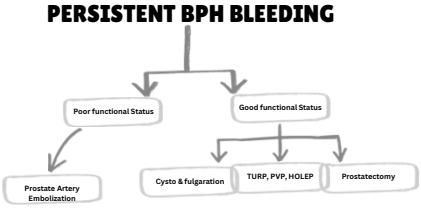
→ Repeat Hematuria Evaluation

Oozy friable prostate. No other findings

12

PATIENT WITH RECURRENT PROSTATE BLEEDING, ON 5-ARI, ECOG 3 ON OXYGEN

PERSISTENT BPH BLEEDING



Poor Functional Status

13

ROLE OF PAE IN THE MANAGEMENT OF REFRACTORY HEMATURIA IS EVOLVING… THE ABILITY TO BOTH DECREASE PROSTATE VOLUME AND DECREASE VASCULAR INFLOW MAKES PAE A POTENTIAL ADJUNCT IN MANAGEMENT OF REFRACTORY HEMATURIA

Sandu et al. AUA BPH Guideline Amendment, 2023

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PAE MAY BE OFFERED FOR THE TREATMENT of LUTS/BPH. PAE should be performed by clinicians trained in this interventional radiology procedure following a discussion of the potential risks and benefits. (Grade C)

Sandu et al. AUA BPH Guideline Amendment, 2023

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Prostate Artery Embolization for Bleeding

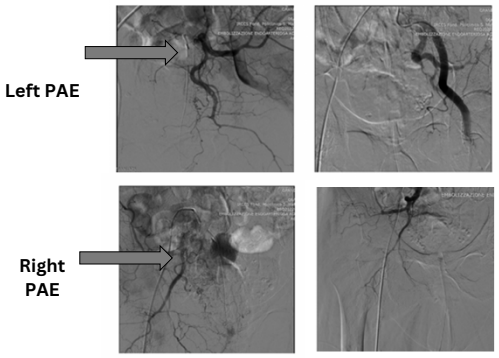
Table 1 Studies Investigating the Use of Prostatic Artery Embolization (PAE) in Treating Refractory Hematuria in Prostatic Origin (RHPO)

Author, year	No. of Patients	Etiology	Vessel Embolized	Embolic Material	Unilateral/ Bilateral	Technical Success	Initial Clinical Success	3 Month Clinical Success	12-Month Clinical Success	Complications
Ayyagari, 2020	55	BPH	Prostatic	100-300 μm Embosphere particles (Merit Medical Systems, South Jordan, UT)	Bilateral = 100%	100%	96%	94%	100%	NA
Tian, 2019	20	BPH	Prostatic	90-180 μm or 180-300 μm Polyvinyl alcohol particles (Cook Incorporated)	Bilateral = 100%	100%	100%	85%	80%	Minor: Gluteal pain, nausea, and fever
Tapping, 2018	12	BPH	Prostatic	200 μm PVA particles (180-300 μm Cook Incorporated, Bloomington, IN) or Embospheres 300-500 μm (Merit Medical, Roissy en France, France)	Bilateral = 100%	100%	100%	100%	92%	NA

Resolution: 1-5days

Kaply I et al. Tech Vasc Interventional Rad 2020 Sep;23(3):10069

16



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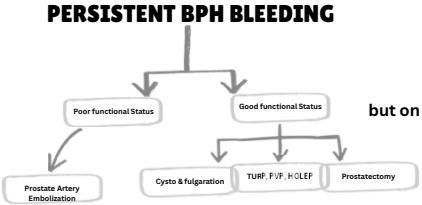
PATIENT WITH RECURRENT PROSTATE BLEEDING, ON 5-ARI, MARATHON RUNNER

PERSISTENT BPH BLEEDING



Good Functional Status

but on anticoagulation that you can not stop

18

HOLEP, PVP, AND THULEP SHOULD BE CONSIDERED AS TREATMENT OPTIONS IN PATIENTS WHO ARE AT HIGHER RISK OF BLEEDING.
(Grade C)

Sandu et al. AUA BPH Guideline Amendment, 2023

19

ORIGINAL ARTICLE

Emergency holmium laser enucleation of the prostate (HoLEP): a novel approach in the management of refractory hematuria for patients with benign prostatic hyperplasia (BPH): a single-institution experience

Hazem Elmansy[1] · Amr Hodhod[1] · Moustafa Fathy[1,2] · Philippe D. Violette[3] · Ahmed Elshafei[1] · Ahmed S. Zakaria[1] · Ryan Kelly[1] · Radu Rozenberg[4] · Amer Alaref[4] · Loay Abbas[1] · Ruba Abdul Hadi[1] · Ahmed Kotb[1] · Walid Shahrour[1]

- **40 patients with refractory hematuria**
  - **67.5% on anticoagulation**
  - **Median gland size 110gm**
- **Time to HOLEP 1.5 days**

92.5%

Discharged without Foley POD 1

95%

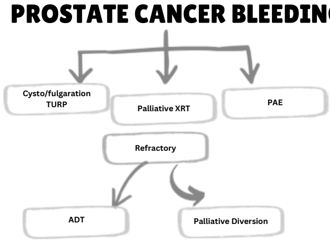
Complete resolution of bleeding

Elmansy et al. World Journal of Urology, 2023

20

80 M WITH RECURRENT PROSTATE BLEEDING FROM LOCALIZED PROSTATE CANCER, ON 5-ARI/ADT

PROSTATE CANCER BLEEDING



Marshall S et al. J Urol 1993; 149:1553-1554
Kaya E et al. Prostate Cancer Prostatic Dis 2004; 7: 311-315
Din OS et al. Radiother Oncol 2009; 93: 192-196
Barbieri A et al. Urol Int 2002; 69: 318-320
Chen JW et al. J Vasc Interv Radiol 2017; 28: 295-301

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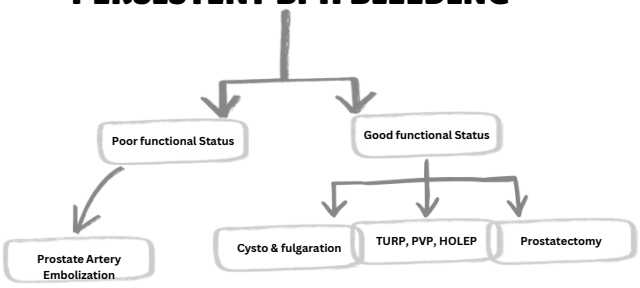
PERSISTENT BPH BLEEDING



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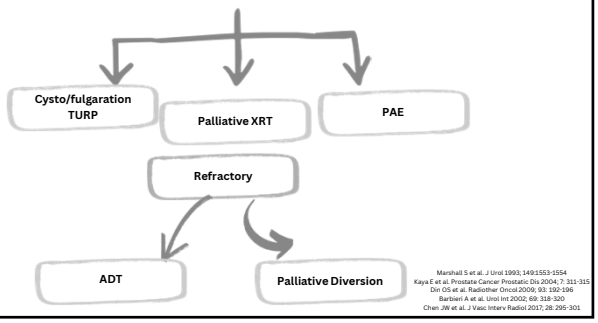
PROSTATE CANCER BLEEDING



Marshall S et al. J Urol 1993; 149:1553-1554
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Barbieri A et al. Urol Int 2002; 69: 318-320
Chan JW et al. J Vasc Interv Radiol 2017; 28: 295-301

23

- BPH most common cause of prostate bleeding – treat with 5ARI
- Surgery as salvage option for refractory prostatic bleeding
- Radiographic interventions for refractory bleeding in comorbid patient

24

HEMORRHAGIC CYSTITIS

Stephen A. Boorjian, MD
Carl Rosen Professor of Urology
David and Anne Luther Chair, Department of Urology
Director, Urologic Oncology Fellowship

1

HEMORRHAGIC CYSTITIS

- Intractable bleeding localizing to the bladder
- Diffuse inflammation and bleeding from the bladder mucosa
- WIDE RANGE IN SEVERITY OF CONDITION
  - Quickly resolving after conservative therapy
  - Life-threatening condition
- Estimated annual US incidence=60,000-100,000 cases
  - For perspective: 82,000 cases kidney cancer and 82,000 cases bladder cancer/year

Li KD et al, BJU Int 2023

2

PROBLEMS WITH THE MANAGEMENT OF HEMORRHAGIC CYSTITIS

- Data to date from small retrospective case series
- Most frequently occurs in elderly/comorbid patients
- Lack of prospective, randomized trials and established clinical guidelines (due in part to heterogeneity of the condition)
  - …spoiler alert…help is on the way (AUA 2027…)

3

KEY PRINCIPLE FOR THE MANAGEMENT OF HEMORRHAGIC CYSTITIS:

BALANCE OF RISK

- Treatment escalation risk– "will I make things worse?"
  - May be reluctant to be aggressive for "benign" indication
- No treatment escalation risk– "will the patient get worse?"
  - Continued bleeding, readmission, deconditioning

4

CLINICAL CASE

- 77 yo man p/w intermittent gross hematuria with passages of clots over past 6-8 weeks
- No LUTs, no flank pain, no systemic symptoms
- SH: (-) smoking
- PMH/PSH:
  - Prostate cancer, s/p RP + sRT, PSA now undetectable
  - CAD, s/p MI; cardiomyopathy (EF 46%)
  - Mitral valve replacement (mechanical), on warfarin (INR 3)

5

HEMORRHAGIC CYSTITIS = DIAGNOSIS OF EXCLUSION

- Evaluate gross hematuria with CT urogram, cystoscopy, voided urine cytology
  - Pelvic XRT = risk factor for bladder cancer *and* hemorrhagic cystitis
  - Consider cysto in OR to allow for biopsy/fulguration
- In case here:
  - CTU and cytology negative
  - Cystoscopy - clots evacuated, diffuse oozing seen from bladder mucosa

6

INITIAL MANAGEMENT OF HEMORRHAGIC CYSTITIS

- Sequential approach, dependent on severity
- Treat correctable causes - infection, coagulopathy
- Supportive management
  - Increase urine output – hydration, diuresis
  - Transfusion prn
- Bladder drainage +/- continuous irrigation
- Cystoscopy with clot evacuation +/- fulguration/biopsy
  - May use laser (potassium titanyl phosphate) fulguration

7

…AND WHAT ABOUT THE ANTICOAGULATION?

- No “one size fits all” answer for managing anticoagulation in patients with gross hematuria
- Factors to consider:
  - Severity of bleeding: clots in urine, Hb, vitals
  - Indication for anticoagulation: mechanical valve versus recent VTE versus a-fib
  - Type of anticoagulation: anti-platelet versus anticoagulation; ½ life of agent; oral versus IV

8

ETIOLOGIES OF HEMORRHAGIC CYSTITIS: VIRAL

- Most often in children, immunosuppressed adults
  - i.e. bone marrow transplant
- BK virus (member of polyomavirus family) = most common virus associated with hemorrhagic cystitis
- Adenovirus (types 11, 35) - children, renal transplant
- Treatment = hydration, continuous bladder irrigation
  - +/- antiviral therapy

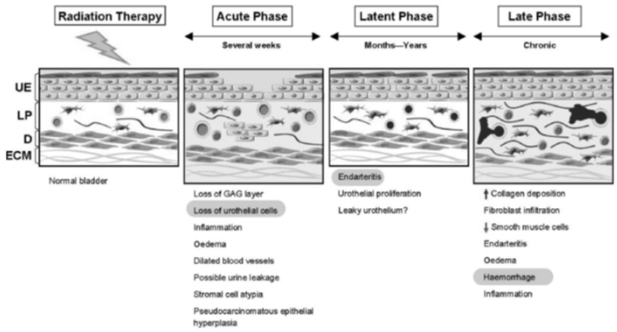
Rastinehad AR et al, AUA Update, 2007

9

CHEMICAL ETIOLOGIES

- Oxazaphosphorine chemotherapeutic agents
  - **Cyclophosphamide**/ifosfamide
  - HC develops in 2-40% of treated patients
  - Due to renal excretion of metabolite **acrolein**
  - Preventative measures (potential)
    - Mesna (2-mercaptoethane sulfonate) – IV agent that binds acrolein (recommended by ASCO guidelines)
    - Hyperhydration with forced diuresis
  - Rule out 2˚ malignancy (bladder cancer)

10



- Rule out 2˚ malignancy (bladder cancer)

Goucher G et al, Can Urol Assoc J 2019
Li KD et al, BJU Int 2023

11

Admission Rates, Healthcare Utilization, and Inpatient Cost of Radiation Cystitis in the United States

Sohrab Arora, Irene Chen, Chandler Bronkema, Giuseppe Chiarelli, Marco Finati, Giuseppe Ottone Cirulli, Sami E. Majdalany, Ivan Rakic, Akshay Sood, Quoc-Dien Trinh, Craig G. Rogers, James O. Peabody, Mani Menon, and Firas Abdollah

- Nationwide Inpatient Sample 2008-2014
- 61% of patients underwent at least 1 procedure
  - 25% > 1 procedure
- Median length of stay = 4.5 days
- Cost per admission = $9207
- Cumulative cost = $63.5 million

Urology 2024

12

…AND NOW BACK TO OUR PATIENT…

- Re-presents to ER one month later in clot retention
- Hemoglobin = 7.2
- Next steps = OR for clot evacuation, transfusion of PBRC, and ???
  - Intravesical alum?
  - Intravesical formalin?
  - Hyperbaric oxygen?
  - Other?

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ALUM

- 1% solution (50 gm alum in 5 L sterile water)
- Irrigate bladder at 200-300 cc/hour
  - No requirement for anesthesia
- Treatment success variable and modest (40-80%)
- Toxicity low
  - Rare absorption → aluminium toxicity (neuro changes) in patients with renal insufficiency
- **FIRST-LINE INTRAVESICAL THERAPY**

Choong SKS et al, BJU Int 2000
Abt D et al, Int J Urol 2013

14

Safety and efficacy of intravesical alum for intractable hemorrhagic cystitis: a contemporary evaluation

Mary E. Westerman [1], Stephen A. Boorjian [1], Brian J. Linder [1]

- 40 patients treated 1997-2014
  - Median age = 76.5 yrs
  - 38/40 received prior pelvic radiation
- Most common adverse event = bladder spasms (35%)
  - No clinical evidence of aluminum toxicity
- Treatment success (no further tx) in 18 pts (45%)
  - 8 pts (20%) without further tx at 15.5 mo. follow-up
- **Safe, but efficacy limited, and not durable!**

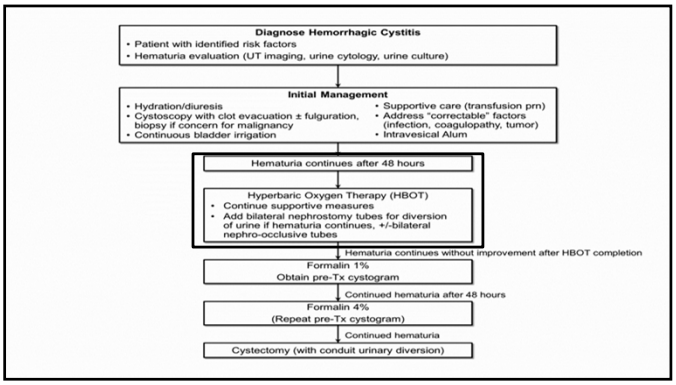
Int Braz J Urol 2016

15

…SO THREE WEEKS AFTER ALUM…

- Patient re-admitted with clot retention
  - OR clot evacuation performed
- What now?
  - Hyperbaric oxygen?
    - +/- percutaneous nephrostomy tubes
  - Intravesical formalin?
  - Cystectomy?

16



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HYPERBARIC OXYGEN

- Administration of 100% O_2 at pressure of 2-3 atmospheres
  - Delivered in special chamber
  - 90 minutes/session; daily (5-7 days/week)
  - Given over 30-40 sessions (8 weeks of treatment)
- Increase local tissue oxygen tension
  - Decrease edema
  - Promote neovascularization
  - Improve wound healing

Bevers RFM et al Lancet 1995
Del Pizzo JJ et al J Urol 1998
O'Reilly KJ et al AUA Update 2002
Chong KT et al Urology 2005

18

HYPERBARIC OXYGEN

- Particularly indicated in cases 2° to **prior radiation** or cyclophosphamide
- Response rate = 80-90%
  - However – varied data on durability of response
- Complications
  - Claustrophobia (confinement anxiety)
  - Otalgia, myopia, barotrauma
  - Oxygen toxicity (seizures (rare))

Bevers RFM et al Lancet 1995
Del Pizzo JJ et al J Urol 1998
O'Reilly KJ et al AUA Update 2002
Chong KT et al Urology 2005
Cardinal J et al Curr Urol Rep 2018

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Radiation-induced cystitis treated with hyperbaric oxygen therapy (RICH-ART): a randomised, controlled, phase 2–3 trial

Nicklas Oscarsson, Bernd Müller, Anders Rosén, Pär Lodding, Johan Mölne, Daniel Giglio, Karin M Hjelle, Guro Vaagbø, Ole Hyldegaard, Michael Vangedal, Lisbeth Salling, Anders Kjellberg, Folke Lind, Otto Ettala, Olli Arola, Helén Seeman-Lodding

- 87 patients randomized to HBOT or no
- Primary outcome = change in patient-perceived urinary symptoms at 6-8 months (per EPIC)
- Caveat – trial excluded patients with ongoing bleeding requiring > 500 ml transfusion in past 4 wks
- Trial not really assessment of HBOT for bleeding control, more for symptom resolution

Lancet Oncol 2019

20

Radiation-induced cystitis treated with hyperbaric oxygen therapy (RICH-ART): a randomised, controlled, phase 2–3 trial

Nicklas Oscarsson, Bernd Müller, Anders Rosén, Pär Lodding, Johan Mölne, Daniel Giglio, Karin M Hjelle, Guro Vaagbø, Ole Hyldegaard, Michael Vangedal, Lisbeth Salling, Anders Kjellberg, Folke Lind, Otto Ettala, Olli Arola, Helén Seeman-Lodding

- Patients treated with HBOT had significantly greater increase in EPIC score

Change from visit 1 to visit 4 (6-8 mo. after randomized)	Hyperbaric oxygen therapy group	p value within group	Standard care group	p value within group	p value between groups	Mean difference between groups (95% CI)
EPIC						
Urinary total	17·8 (18·4)	<0·0001	7·7 (15·5)	0·0049	0·013	-10·1 (-18·1 to -2·2)

- HBOT relieved symptoms of radiation cystitis

Lancet Oncol 2019

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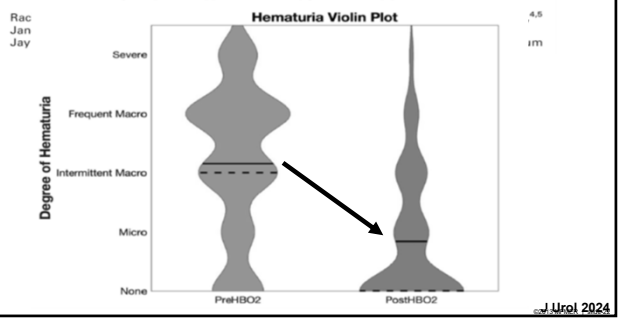
Patient-Reported Outcome Measures Following Hyperbaric Oxygen Therapy for Radiation Cystitis: Early Results From the Multicenter Registry for Hyperbaric Oxygen Therapy



J Urol 2024

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UNDERSEA & HYPERBARIC MEDICINE

Controlled CMS Data Demonstrates a Cost and Clinical Advantage for Hyperbaric Oxygen for Radiation Cystitis

John J. Feldmeier, DO[1]; John P. Kirby, MD[2]; Helen B. Gelly, MD[3]; Marc Robins, DO[4]; John Peters, FACHE[5]; Peter Gruhn, MA[6]; Sarmistha Pal, PhD[6]

- 3,309 Medicare patients with radiation cystitis 2014-2019
  - 1030 received HBOT
- Treatment with HBOT:

Table 2. Average Total Annual Patient Medicare Authorized Payments

total spending	pre-treatment (phase 1)	follow-up at one year follow-up (phase 3)	difference post-pre-treament	difference post-pre-treament for 40 treatments
study (HBO_2)	$31,293	$26,234	-$5,059 (any hyperbaric treatment)	-$11,548 (40 or more hyperbaric treatments
control	$29,130	$31,496	+$2,366	+$2,366

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Table 5. Overview of Additional Clinical Results with Increasing Number of Treatments

	base model hyperbaric treatments ≥ 1	hyperbaric treatments ≥ 20	hyperbaric treatments ≥ 30	model at recommended dose hyperbaric treatments ≥ 40
hyperbaric study group (N)	1,030	695	693	330
comparison group (N)	2,279	2,279	2,279	2,279
dependent variables	percentage difference	percentage difference	percentage difference	percentage difference
total spending	-$3,267 (10% ↓ *)	-$8,274 (27% ↓ ***)	-$10,868 (34% ↓ ***)	-$11,548 (37%↓ ***)
inpatient spending	-$3,188 (22% ↓ **)	-$6,686 (46% ↓ ***)	-$8,221 (55% ↓ ***)	-$9,222 (60%↓ ***)
physician spending	-$1,114 (14% ↓ **)	-$1,358 (17% ↓ ***)	-$1,760 (22% ↓ ***)	-$1,149 (15%↓ ***)
endoscopic treatment [Y/N]	(30% ↓ ***)	(33% ↓ ***)	(31% ↓ ***)	(34%↓ ***)
number of endoscopic procedures	(44% ↓ ***)	(37% ↓ ***)	(33% ↓ ***)	(39%↓ ***)
urinary bleeding (with radiation cystitis dx) [Y/N]	(27% ↓ ***)	(31% ↓ ***)	(31% ↓ ***)	(36%↓ ***)
blood transfusion [Y/N]	- (not significant)	(57% ↓ ***)	(91% ↓ ***)	(78%↓ **)
mortality [Y/N]	(18% ↓ **)	(46% ↓ **)	(56% ↓ ***)	(53%↓ ***)

Feldmeier JJ et al, Undersea Hyperb Med 2024

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OUR STORY CONTINUES…

- Patient treated with HBOT
  - After first several treatments, bilateral nephrostomy tubes placed for urinary diversion as patient had continued to bleed

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SUPRA-VESICAL URINARY DIVERSION

- Intention = decrease exposure of the bladder to urokinase → thereby facilitate hemostasis
- Bilateral nephrostomy tube insertion
  - +/- ureteral occlusion catheters for continued bleeding
    - Minimizes but does not completely eliminate exposure of bladder to urine

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BETWEEN A ROCK AND A HARD PLACE

- 3 weeks after completing HBOT, nephrostomy tubes capped → patient re-presents with clot retention + anemia
- Now what???
  - Intravesical formalin?
  - Bladder angioembolization?
  - Cystectomy?
  - Other?

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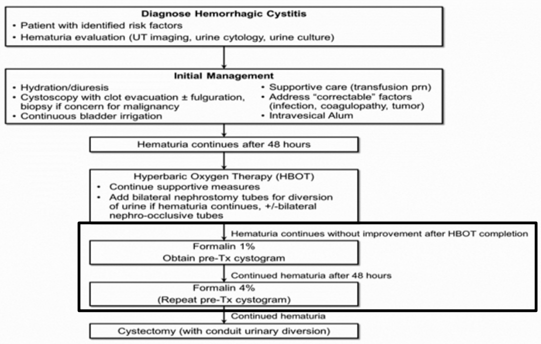

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FORMALIN

- Solution of formaldehyde
- Instilled intravesically
- Induces cellular protein precipitation + capillary occlusion

- **Control of bleeding in 80-90% of cases**
  - Small series, limited f/u

Choong SKS et al, BJU Int 2000
Abt D et al, Int J Urol 2013

29

FORMALIN

- Administer under general (or spinal) anesthesia
  - Instillation may (+) significant pain

- Complications of formalin treatment:
  - Bladder fibrosis → decreased capacity
  - Ureteral stricturing
    - **Pre-treatment cystogram** to r/o reflux, perforation
      - If reflux → place occlusive ureteral catheters

Choong SKS et al, BJU Int 2000
Abt D et al, Int J Urol 2013

30

FORMALIN

- Start with low concentration (1%)
  - May increase dose up to 10%
- Irrigation done under gravity
  - Catheter no more than 15 cm above pubis
  - Volume up to 300cc/bladder capacity
  - 10-15 minutes of contact time

Choong SKS et al, BJU Int 2000
Abt D et al, Int J Urol 2013

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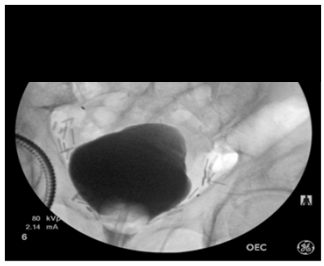
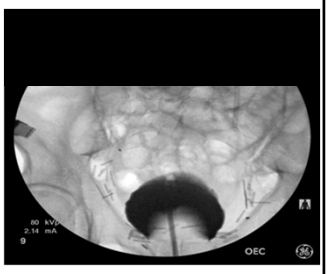
POTENTIAL TOXICITY OF FORMALIN: *BLADDER FIBROSIS/CONTRACTURE*



Pre-treatment cystogram



1 wk post-treatment cystogram

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CLINICAL CASE (con't)

- Cystogram (-) → formalin given
- Patient remains CBI-dependent, continues to require transfusions
- Next step?
  - Urinary diversion only (conduit, etc)?
  - Cystectomy + urinary diversion?
  - Other?

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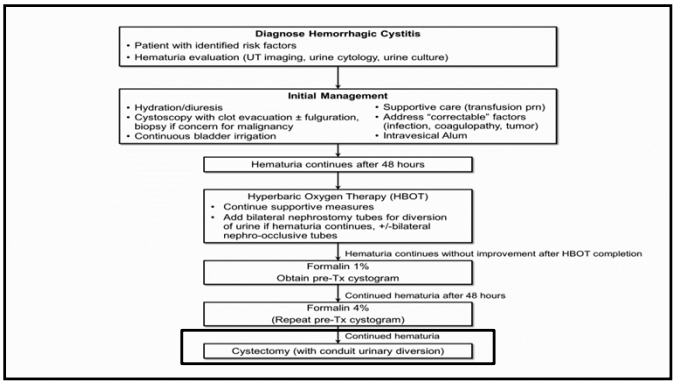

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WHAT ABOUT URINARY DIVERSION ALONE (WITHOUT CYSTECTOMY)?

Fate of the Leftover Bladder After Supravesical Urinary Diversion for Benign Disease

Tajammul Fazili,* Tahir R. Bhat, Shikohe Masood, John H. Palmer and G. R. Mufti

- 24 patients
- 13 (54%) experienced complications
  - 11 (46%) infectious complications
    - 8 (33%) – frank pyocystis
- 6 (25%) ultimately treated with cystectomy

J Urol 2006

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Cystectomy for Refractory Hemorrhagic Cystitis: Contemporary Etiology, Presentation and Outcomes

Brian J. Linder, Robert F. Tarrell and Stephen A. Boorjian*

From the Departments of Urology (BJL, SAB) and Health Sciences Research (RFT), Mayo Clinic, Rochester, Minnesota

- 21 patients (median age = 77; median ASA = 3)
- Median preoperative hemoglobin = 10.2 gm/dl
- Median length of stay postoperatively = 10 days
- Clavien III-V complications in 42%
- 90-day mortality = 16%
- 3-year overall survival = 52%

J Urol 2014

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CASE FOLLOW-UP

- Cystectomy/ileal conduit diversion performed
  - Post-op course included:
    - NSTE MI, CHF exacerbation
    - Prolonged (16 day) hospital stay
  - **A product of presurgical deconditioning?**
- Patient remained without recurrent bleeding now at 9 months post-cystectomy follow-up

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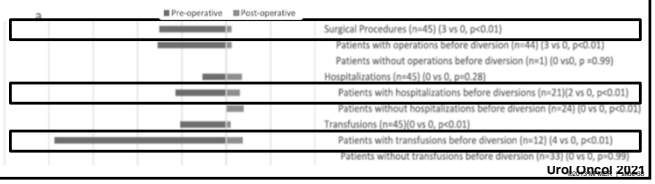
Definitive surgical therapy for refractory radiation cystitis: Evaluating effectiveness, tolerability, and extent of surgical approach

Isamu Tachibana, MD[a,*], Adam C. Calaway, MD[b], Zain Abedali, MD[a], Konrad M Szymanski, MD[a], Matthew J Mellon, MD[a], Timothy A. Masterson, MD[a], Clint Cary, MD[a], Hristos Z. Kaimakliotis, MD[a], Ronald S. Boris, MD[a]

- 31 patients treated with cystectomy/diversion + 14 treated with diversion alone



Urol Oncol 2021

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TAKE-HOME MESSAGES

- Stepwise approach to hemorrhagic cystitis management
  - Irrigate until clot free
    - +/- under anesthesia in case biopsy/fulguration
  - Alum = 1st line intravesical therapy
    - Safe but ? efficacy
    - Beware if renal insufficiency

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TAKE-HOME MESSAGES

- Consider expeditious/ “aggressive” treatment
  - Avoid prolonged delays with continued bleeding/patient deconditioning
- Hyperbaric Oxygen
  - +/- bilateral nephrostomy tubes for diversion

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TAKE-HOME MESSAGES

- 2nd line, non-bladder preserving therapies
  - Formalin
    - Cystogram first
    - Under anesthesia
    - Toxicity
- Cystectomy/Urinary diversion
  - Counsel regarding morbidity
- Balance risks of next treatment vs risks of delay – continued bleeding, continued de-conditioning

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THANK YOU

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