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Paper Alert

Do All Low Risk Microhematuria Patients Require Cystoscopy?

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The vast majority of bladder cancer (BC) patients are initially diagnosed because they have hematuria, usually microhematuria (MH). However, only 2–5% of patients who have MH have BC [1]. This means that ≥95% of patients with MH who are evaluated and undergo cystoscopy as part of the workup do not have BC. While the purpose of cystoscopy as part of the MH evaluation is to determine the cause of hematuria, clearly the major condition it is looking for is BC; the risk for which is incorporated into the AUA's risk group stratification [1, 2]. The AUA guidelines are structured to minimize the likelihood that any patient with life threatening BC is overlooked with the appropriate evaluation (including cystoscopy) [1]. The vast majority of MH patients undergo an unpleasant, costly (including out-of-pocket expenses for travel, time off from work for patients and families, etc.) and occasionally morbid procedure with little benefit except to know they (currently) do not have BC. Lotan and colleagues have tried to determine whether a marker-based test, Cx bladder triage (CxbT) could be used to decide which patient at low risk for harboring BC could safely forgo cystoscopy without overlooking any serious or potentially life-threatening BCs [3]. The test measures five mRNAs associated with BC or inflammation combined with questions on gender, age, smoking history, and history of gross hematuria with an algorithm that produces a score (1–10) [4].

Lotan et al., whose study antedated the publication of The AUA MH guidelines, defined "lower risk" for MH as having <30 RBC/high power field (HPF) on microscopic urinalysis, <10 pack year history of cigarette smoking, and no "current" gross hematuria; and "not lower risk" as having ≥30 RBC/HPF and/or ≥10 pack year smoking history (but still no hematuria currently visible). They assigned all subjects to have a CxbT test. If the test was negative, lower risk patients were randomized (2 : 1) to being informed of their test results and choosing if they wanted to undergo cystoscopy after a discussion with their urologist, vs not knowing their test results and being requested to undergo cystoscopy as standard of care (SOC)- a control arm. Those informed of their CxbT results and elected not to have a cystoscopy would have periodic follow-up urinalyses, CxbT tests, urinary cytologies, and bladder ultrasounds for up to two years. Those participants who were "not lower risk" would be evaluated by SOC (including cystoscopy) and would not be told their CxbT results. All participants regardless of risk category underwent standard upper tract imaging [3].

In the "control" arm of lower risk patients, who did not know their CxbT results, 67% underwent the SOC

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cystoscopy, and 80% of lower risk patients who had a positive CxbT test (CxbT+) and knew their results chose to be cystoscoped. However, in those lower risk patients who were CxbT- and knew their test result, less than 20% chose to undergo cystoscopy. Of the 48 CxbT- lower risk patients who chose not to have cystoscopy and underwent follow-up one patient, 13 months later had a CxbT test that turned positive, and cystoscopy showed a single high grade non muscle invading BC.

All in all, in the lower risk MH group the rate of cystoscopy dropped from 67% (in the lower risk MH patients who did not know their test results and were advised to undergo standard work up) to 27% in the lower risk MH patients who knew their negative or positive test results (a relative decrease of 60%), confirming that when given a choice most patients do not want to undergo cystoscopy. Perhaps most importantly the performance of CxbT in lower risk hematuria patients who had cystoscopy ($N = 75$) was confirmed: sensitivity 100% (37%–100%), specificity 77% (66%–86%). negative predictive value (NPV) 100% (94%–100%) and positive predictive value 5.6% (0.17%– 270%). Admittedly, these performance characteristics must be understood in the context that 14% of lower risk patients who knew their negative CxbT results and chose not to be cystoscoped did not have any follow-up at all, and for many others follow-up was not complete (even for one year).

So, what we have learned from this study is that the CxbT test has a very low false negative rate, particularly in lower risk MH patients, and if confirmed in larger studies (with fewer dropouts), perhaps such individuals can safely forgo cystoscopy if they are willing to be followed carefully with repeat testing (CxbT tests, urinalyses, cytologies and bladder USs). Whether this can eventually change SOC when only a minority of patients with hematuria are referred to a urologist, and among those who are many don't get thoroughly evaluated is another issue [1, 2]. Additionally, in a separate study it was estimated that using Cx bladder Detect (using the same 5 mRNAs) would reduce the cost of the hematuria work up by $559 per patient, on average, without reducing the number of cancers detected [5]. Importantly, triaging with CxbT might reduce the large number of negative (for BC) cystoscopies urologists do on lower risk MH patients when the backlog of cystoscopy slots in most outpatient clinics is considerable (as exemplified in an editorial comment to this paper [6]).This would permit more efficient and timely management of patients who really could benefit from cystoscopy.

CONFLICTS OF INTEREST

The author has no conflicts of interest to report.

REFERENCES

[1] Barocas DA, Boorjian SA, Alvarez RD, et al. Microhematuria: AUA/SUFU guideline. J Urol. 2020;204:778-86.

[2] Woldu SL, Ng CK, Loo RK, et al. Evaluation of the new American Urological Association guidelines risk classification for hematuria. J Urol. 2021;205(5):1387-93.

[3] Lotan Y, Daneshmand S, Shore N, et al. A multicenter prospective randomized controlled trial comparing Cxbladder triage to cystoscopy in patients with microhematuria trial. J Urol. 2024;212:41-51.

[4] Kavalieris L, O'Sullivan PJ, Suttie JM, et al. A segregation index combing phenotypic (clinical characteristics) and genotypic (gene expression) biomarkers from a urine sample to triage out patients presenting with hematuria who have a low probability of urothelial carcinoma. BMC Urol. 2015;15:23.

[5] Tyson MD, Abouassaly R, Durant A, et al. Budgetary Impact of Including the Urinary Genomic Marker Cxbladder Detect in the Evaluation of Microhematuria Patients. Urol Pract. 2024;11:54-60.

[6] Richards KA. Editorial Comment to Lotan Y, et al. J Urol. 2024;212:41-51.