Case Study

Case studies from clinical practices using URO17™ in the detection of bladder cancer

Introduction

Bladder cancer is one of the major cancers of the urinary system that is one of the most expensive cancers to treat due to a high recurrence rate [1-4]. Typically, routine monitoring of bladder cancer is performed by cystoscopic examination that is invasive, painful, and expensive. Cystoscopy is often augmented by a non-invasive laboratory method such as urine cytology, UroVysion, or NMP22 tests. However, these tests lack adequate sensitivity or specificity to significantly improve the treatment and diagnosis of bladder cancer patients [3].

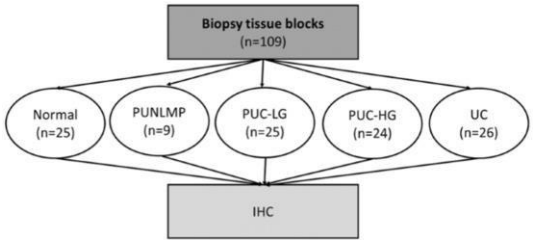
URO17™ ™ Bladder Cancer Test

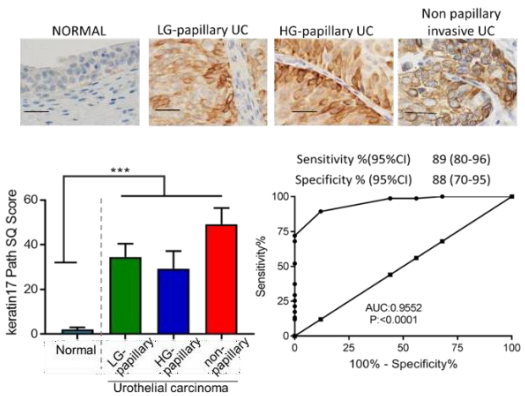
The URO17™ test (or "URO17™") is a non-invasive test that detects the presence of bladder cancer cells from a patient's urine sample. The URO17™ test has reported a sensitivity of 100% and specificity of 96% in early studies for detecting the presence of bladder cancer cells in urine samples, which makes it the most sensitive and specific non-invasive test for bladder cancer [5]. Since URO17™ (utilizing Keratin 17 biomarker detection) is shown to detect all stages and grades of urothelial cancers, [5] it could improve the identification of early-stage cancers that can be overlooked by cystoscopy and other current urine tests for bladder cancer. URO17™ would likely also enhance the detection of the spread of urothelial cancer into an upper urinary tract that cannot be detected by cystoscopy- thus improving the detection rate of recurrent cancer at an earlier stage where it can be treated more effectively. Additionally, URO17™ can detect urothelial cancer in patients who cannot have cystoscopy due to other medical conditions.

URO17™ is based on well-established immunoassay chemistry that can be performed on any of the immunohistochemical instrumentation that is already installed in most of the clinical laboratories, which makes the test cost-effective to perform. Furthermore, the URO17™ test utilizes the same samples that are routinely used in urine cytology for bladder cancer monitoring and are read by the same cytopathologist who performs the urine cytology examination. Thus, the application of URO17™ fits in seamlessly into the existing bladder cancer management clinical routines, which makes it easily adaptable to clinicians and the laboratories.

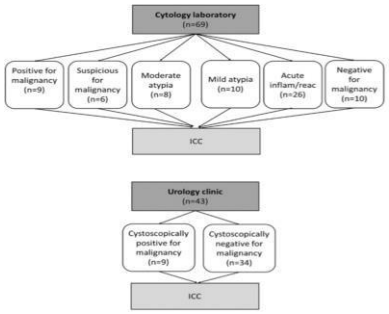
Data

STUDY 1: Initial study [5] examining the expression of K17 in urothelial cancer utilizing 109 tissue samples that were stained for K17 using IHC.





The data showed significant overexpression of K17 in both low-grade and high-grade lesions and invasive urothelial cancer. The study also examined K17 expression in 112 urine samples with immunocytochemistry.



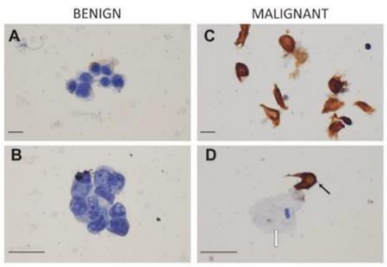


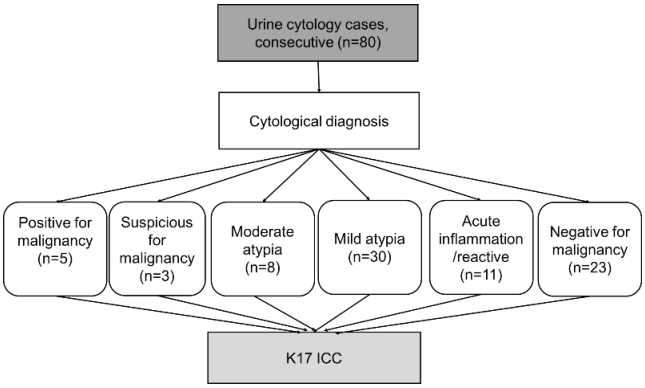
Table 1 Urine specimens: Keratin 17 immunocytochemistry has a higher sensitivity and specificity than cytologic examination for urothelial carcinoma

Test	Cytology[a] % (95%CI)	K17 ICC[b] % (95%CI)
Sensitivity[c]	80 (61–91)	100 (90–100)
Specificity[c]	93 (82–98)	96 (89–99)
PPV	87 (68–95)	91 (79–97)
NPV	89 (77–95)	100 (95–100)

A. Benign urothelial cells; B. Normal urothelial cells; C. K17 positive urothelial cells; D. K17 positive urothelial cells adjacent to benign squamous cell (white arrow)

The results showed that K17 is expressed in urothelial carcinoma with 100% sensitivity and 96% Specificity, and PPV of 91% and NPV of 100%.

STUDY 2: A follow up study [6] was conducted on 80 urine samples that included samples from patients with hematuria (n = 40), under surveillance for bladder cancer recurrence (n = 20), and other benign clinical conditions (n = 20).



TEST	CYTOLOGY (n=80) % (95%CI)	K17 ICC (n=80) % (95%CI)
Sensitivity	41 (27-57)	100 (91-100)
Specificity	100 (91-100)	90 (77-96)
Positive Predictive Value	100 (80-100)	90 (78-96)
Negative predictive value	64 (51-75)	100 (90-100)

The results showed that K17 was expressed in all 39 cases of clinically confirmed urothelial carcinoma (100%). K17 was also positive in 8 of 40 cases with hematuria with no prior history of bladder cancer, and 6 of the 8 K17 positive samples had biopsy-confirmed urothelial cancer. These data confirm the original findings and show that the URO17™ test utilizing K17 biomarker can be used to identify bladder cancer in patients with hematuria with no prior history of bladder cancer.

STUDY 3: A third study [7] examined 145 urine specimens from patients with hematuria and surveillance for urothelial carcinoma.

TOTAL DATA

URO17	Cancer	Benign
Positive	**56**	**12**
Negative	**0**	**77**

SENSITIVITY = 100% SPECIFICITY = 87%

The results showed that K17 is expressed in urothelial carcinoma with 100% sensitivity and 87% specificity, which again confirms the highly sensitive and specific nature of the URO17™ test in identifying bladder cancer.

Case Studies

URO17™ test has been available as a laboratory developed test for clinical application in selected reference laboratories in the U.S. The following are some of the case studies based on urologists who have applied URO17™ in their clinical practice in bladder cancer management.

Case Study 1

Urine sample collected from a 56-yr. old male subject with a history of bladder cancer during a routine monitoring visit. The URO17™ test result was positive despite a normal workup with no evidence of disease on CT and cystoscopy. On further evaluation in a subsequent visit, a retrograde pyelogram was done which detected a ureteral tumor (cancer that has spread to ureter between the bladder and the kidney), pathologically confirmed as ureteral transitional cell carcinoma.

Case Study 2

Urine sample collected from a 68-yr. old man with a history of bladder cancer during a routine monitoring visit. The URO17™ test result was positive but there was no evidence of disease on the routine white light cystoscopy. The patient was followed up with a blue light cystoscopy to examine the patient in a subsequent visit, where the presence of urothelial carcinoma was detected.

Case Study 3

Urine sample collected from a 76-yr. old male subject with gross hematuria. Ultrasound and cystoscopy were normal, but URO17™ was positive. A subsequent CT scan was then done which suggested a renal calyceal mass. Ureteroscopic evaluation demonstrated a urothelial tumor in the upper segment of the kidney collecting system.

Discussion

Data from the studies outlined above and other ongoing studies confirm extremely high sensitivity of URO17™ in detecting bladder cancer through urine, which translates into a uniquely high negative predictive value (NPV) for ruling out the presence of bladder cancer. High NPV means that URO17™ can likely provide highly confident assurance that a patient with a negative URO17™ result does not have bladder cancer. The data also suggests that the test has relatively high specificity in the range of 87%-96%, which translates into high positive predictive value (PPV) so that there is an increased chance that a patient with a positive URO17™ result has bladder cancer that needs to be followed up with cystoscopy or additional diagnostic methods. These data indicate that the application of URO17™ in the management of bladder cancer could provide significant benefits to the patients.

The clinical application of URO17™ can be divided into two areas: (1) Surveillance, or monitoring, for recurrent bladder cancer, and (2) Triaging patients with hematuria into cystoscopy or imaging. It is recommended that the surveillance or monitoring for recurrent bladder cancers be performed quarterly for patients with bladder cancer [2]. These examinations are usually performed with cystoscopy. Urine cytology is routinely used for monitoring but with limited utility due to its poor sensitivity in detecting bladder cancer. Although cystoscopy is a sensitive and specific test for bladder cancer, it is invasive and expensive and could still miss cancer that has spread to the ureter, or low-grade flat lesions that could be difficult to detect by visual inspections. Thus, the addition of the URO17™ test in conjunction with cystoscopy could significantly increase the detection of cancer and/or increase a confidence level in determining that cancer has not recurred.

Conclusion

The URO17™ Bladder Cancer Test is a highly effective urine test for bladder cancer with, in current studies, a reported extremely high sensitivity and specificity for detecting the presence of bladder cancer. The URO17™ is a non-invasive test that detects the presence of bladder cancer cells from a patient's

urine sample. Thus, the test causes no additional pain or hardship for the patient. And, while URO17™ is not a replacement for cystoscopy, it may be the case that fewer cystoscopies will be performed during the clinical management of bladder cancer if there is access to a non-invasive urine test such as URO17™ with increased sensitivity and specificity. Further, with its high sensitivity in detecting all stages and grades of bladder cancer, URO17™ should significantly increase the accuracy of bladder cancer detection, even in early-stage cancers that are difficult to detect by traditional means. Earlier detection of bladder cancer recurrence by URO17™ should lead to more effective control and treatment of cancer, thus improving patient outcome and long- term cost savings. Furthermore, since the URO17™ is a urine test that could detect cancer cells throughout the urinary tract, it can detect the spread of urothelial cancer into an upper urinary tract that cannot be viewed by cystoscopy. Lastly, since the URO17™ test utilizes traditional immunoassay chemistry and platforms, the test will be a cost-effective way to significantly improve patients' clinical outcome.

References

1. Siegel RL, Miller KD, Jemal A, et al., Cancer statistics, 2018. CA Cancer J Clin. 2018;68:7–30.
2. Chang SS, Bochner BH, Chou R, et al., Treatment of Non-Metastatic Muscle-Invasive Bladder Cancer: AUA/ASCO/ASTRO/SUO Guideline. J Urol. 2017 Sep;198(3):552-559.
3. Miyake M, Owari T, Hori S, et al., Emerging biomarkers for the diagnosis and monitoring of urothelial carcinoma. Res Rep Urol. 2018 Dec 14;10:251-261.
4. Mariotto AB, Noone AM, Howlader N, et al., Cancer survival: an overview of measures, uses, and interpretation. J Natl Cancer Inst Monogr. 2014;2014:145–86.
5. Babu S, Mockler DC, Roa-Peña L, et al., Keratin 17 is a sensitive and specific biomarker of urothelial neoplasia. Mod Pathol. 2019 May;32(5):717-724.
6. Babu S, Roa-Peña L, Chan I, et al., Validation of a Novel Cytologic Biomarker for Urothelial Carcinoma, Bladder Cancer: Transforming the Field, 2019 AACR meeting.
7. Kody LM, Babu S, Roa-Pena L. et al., Demonstration of K17 ICC Biomarker for Urothelial Carcinoma Detection in the university and community urology practices. 2019 Western Section of Urological Association of America Annual meeting

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