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*Review Article*

# Clinical Utility Of Bladder Cancer Biomarkers.

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**Abstract**

An estimated 550000 cases of bladder cancer are diagnosed globally each year, and the disease is thought to be the cause of about 200000 fatalities. Bladder cancer is one of the most costly cancers to treat because it requires regular follow-up, invasive procedures like cystoscopy, repetitive procedures like transurethral resection of bladder tumors and intravesical instillation therapy in non-muscle invasive stages, and systemic treatment with or without radical local treatment in advanced stages. The treatment algorithms for bladder cancer could be drastically altered by prognostic and predictive biomarkers, which could lead to better oncological outcomes and patient comfort as well as a reduction in the disease's socioeconomic burden.

The first treatment for this illness that targets a particular mutation (fibroblast growth factor receptor) was just approved by the U.S. Food and Drug Administration as a result of extensive study. However, despite their therapeutic success, many aspects of bladder cancer diagnosis and treatment have not changed in decades. Particular concerns for the various illness phases and contexts should be kept in mind when integrating biomarkers into clinical practice patterns. (Urine-)biomarkers may be helpful, particularly in the context of screening, hematuria work-up, and patient surveillance for non-muscle invasive bladder cancer. However, they must exhibit a high enough sensitivity to detect a cancer diagnosis or recurrence and enable simple management. (ideally in a point-of-care context) and appropriate cost-benefit analyses, in addition to offering supplementary data for a comprehensive work-up. It would be very helpful to have a biomarker to identify individuals with muscle invasive bladder cancer who require neoadjuvant therapy and are likely to respond to it. Improved patient care in later stages of the disease will depend heavily on early diagnosis of progression or recurrence, as well as biomarkers that inform treatment choices among the current systemic medicines.

Introduction

**Keywords** : *Biomarkers, bladder cancer, muscle invasive bladder cancer, non-muscle invasive bladder cancer, neoadjuvant therapy, hematuria, cystoscopy, risk stratification, clinical decision-making.*

## INTRODUCTION

Bladder cancer accounts for almost 200,000 fatalities globally in 2018 and is diagnosed in roughly 550000 new cases annually [1]. Bladder cancer is one of the most costly cancers to treat because it requires frequent follow-up, invasive procedures like cystoscopy, repetitive procedures like transurethral resection of bladder tumors and intravesical instillation therapy in non-muscle invasive stages, and systemic treatment with or without radical local treatment in advanced stages [2]. Prognostic and predictive biomarkers could revolutionize bladder cancer treatment algorithms, potentially improving oncological outcomes and patient comfort while reducing the disease's socioeconomic burden. Recently, the U.S. Food and Drug Administration authorized the first medication for this illness that addresses a particular mutation [3]. However, despite their therapeutic success, many aspects of bladder cancer diagnosis and treatment have not improved in decades. Particular concerns for the various illness phases and contexts should be kept in mind when integrating biomarkers into clinical practice patterns

## CONSIDERATIONS FOR BIOMARKERS FOR BLADDER CANCER SCREENING

There is currently no indication for bladder cancer screening due to the low incidence of bladder cancer in the general population (and even in high-risk populations)[4]. Generally speaking, a dichotomous point-of-care test may be readily conducted in an ambulatory context for screening purposes in daily routine and should offer an initial risk assessment that could be used to customize the need for additional clinical inquiry. The most promising resource for this kind of test is undoubtedly urine.To guarantee that individuals at risk are not overlooked, a urine-based biomarker test needs to have a high sensitivity and negative predictive value (NPV). However, in order to avoid needless (invasive) evaluation due to false positive results, the test must also have a high specificity and positive predictive value (PPV) despite the low incidence. Furthermore, because it uses a urine marker as a

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screening tool, test analysis expenses need to be minimal and shouldn't significantly surpass those associated with a typical diagnostic work-up for bladder cancer. Lastly, a substantial improvement in oncological outcomes should ideally be shown by an earlier discovery following test analysis.Given the known substantial differences in survival between non-muscle invasive bladder cancer (NMIBC) and muscle invasive bladder cancer (MIBC), a decrease in the rates of invasive disease may act as a surrogate parameter, as it appears to be challenging to show an overall survival benefit in the general—or even high-risk—population. The majority of urine markers on the market now have PPVs that are too low to warrant their usage because the number of pointless tests will much outnumber the number of cancer detections.Although targeted screening of extremely high-risk groups may lead to a sufficiently high incidence of cancer, prospective research will be required to show a benefit in survival or at the very least a decrease in muscle invasive disease. Male sex, advanced age, and the length and severity of smoking are known to be linked to an increased risk of bladder cancer. According to a study analyzing these variables and the incidence of bladder cancer in the National Lung Screening Trial (NLST) and the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, incidence rates for men over 70 with ≥ 30 pack-years of smoking exposure were as high as 5.23 (NLST) and 11.92 (PLCO) per 1000 person-years [5].Bladder cancer and family history are not strongly correlated. However, screening for bladder cancer can be warranted if there are unique single-nucleotide polymorphisms linked to a high risk of the disease. Up to 28% of patients with known Lynch syndrome develop upper tract urothelial cancer. In addition to normal urine analysis and screening, these individuals might benefit from further testing based on the American Urological Association's recommendation of ≥ 3 red blood cells per high power field [6].tract disease typically manifests earlier in life, is more common in women, and is more likely to be bilateral.

## DIAGNOSIS IN PATIENTS WITH HEMATURIA

Hematuria patients require additional clinical work-up because they have a much higher risk of bladder cancer (gross 10% to 40%, depending on other risk factors, or microscopic 2% to 5%) [7, 8]. This work-up includes upper urinary tract contrast-enhanced imaging and cystoscopy with cytology [4]. These operations are unpleasant, intrusive, or expensive. In order to save patients who do not require a comprehensive evaluation, it would be preferable to substitute them with a biomarker test. Once more, in this situation, urine appears to be the most suitable medium for a biomarker test.Numerous genetic and protein markers, along with clinical and demographic characteristics, have been used to stratify risk in hematuria patients [4]. It appears that semiquantitative or dichotomous tests that assess a person's risk of bladder cancer are appropriate for advising physicians to proceed with more testing or not. To make sure a tumor is not overlooked, a high sensitivity and NPV are required, much like in screening. Although a high specificity and PPV are also preferred to avoid needless examinations for false positive test results, they are not as crucial as in screening because there are fewer of these "quasi"-prescreened individuals and associated expenses.Finding high-risk patients who require evaluation at all times is crucial since the cancer rate in hematuria patients is significantly higher than the rate in screening cohorts. According to a number of studies, the risk of developing cancer rises with age, male sex, and excessive hematuria [9, 10]. Regretfully, a large number of patients with high-risk conditions do not receive enough evaluation [11–13]. However, the prevalence of urothelial carinoma in individuals Patients with microscopic hematuria may benefit from risk stratification in the selection of patients for work-up, as gross hematuria already warrants examination. Improved risk stratification of patients may be the aim of markers, allowing higher risk patients to be assessed. However, it is also possible to determine which lower risk patients require examination and which may be safely monitored without intrusive testing [14,15]. Patients are randomized according to clinical risk and marker status in an ongoing prospective randomized trial (NCT03988309).Patients in the marker arm will undergo a clinical risk stratification, whereas those in the control arm will receive a standard evaluation. This means that patients with a negative marker and low clinical risk will only receive follow-up; patients with a positive marker or higher risk based on clinical factors will receive a standard evaluation along with cystoscopy. To alter the recommendations for guidelines, more research of this kind will be required.

## SURVEILLANCE OF PATIENTS WITH NON-MUSCLE INVASIVE BLADDER CANCER

Frequent cystoscopies are typically part of the follow-up treatment for patients with low- to intermediate-risk NMIBC in order to rule out recurring or progressive illness, particularly in those receiving intravesical instillation therapy. Many patients find these tests to be inconvenient, and they are often very expensive. As an alternative to intrusive diagnostic techniques, researchers have concentrated on biomarkers to precisely identify the existence or lack of a recurrence. The objectives for a biomarker must be taken into account because low- to intermediate-risk NMIBC has a low probability of progression (<15% at 5 years), but a significant risk of recurrence.A biomarker with a high specificity will cut down on the number of cystoscopies that are done due to false positive results, whereas one with a low sensitivity might overlook recurrences [16]. Since low-grade recurrences

are unlikely to progress, this might be acceptable in order to decrease the number of cystoscopies. Some researchers have suggested alternating cystoscopy with a marker as a substitute. This makes more sense because most indicators are more sensitive to high-grade disease and are therefore more likely to detect the infrequent occurrence of a low-grade tumor that spreads. Additionally, patients and urologists would be reassured by routine cystoscopy that the cancer would be discovered at a later evaluation even if a marker missed a low-grade recurrence.For instance, the UroFollow research was created as a prospective randomized trial to evaluate routine cystoscopy vs a noninvasive, urine marker-guided follow-up for patients with pTa G1-2 low-grade NMIBC [17].However, the chance of recurrence is higher for patients with a history of high-risk bladder cancer (50% at 5 years) [16]. To avoid missing any high-grade recurrence that could lead to the progression to muscle-invasive stages, a meaningful biomarker test must therefore have a high sensitivity and NPV. Even a decrease in test specificity could result from this. White light cytoscopy is known to overlook some high-grade malignancies, particularly carcinoma in situ, hence it would be ideal if a marker could identify tumors that are missed by this method [18].Urine marker investigations, regrettably, are not intended to determine whether a patient with a positive marker and a normal cystoscopy has a real positive or false positive result. Therefore, it is unclear what to do in this case if a marker test comes up positive.Molecular markers may potentially help clinicians estimate how well patients with NMIBC will respond to intravesical therapy. Patients who are unlikely to improve from BCG bacillus Calmette-Guérin and who need early radical treatment may be identified by including a biomarker test in a routine work-up. However, because bladder cancer is a diverse illness and the intravesical medicines employed are not specific to a particular biological target for which testing would be feasible, this problem is challenging to address in clinical trials. As a result, it will continue to be difficult to forecast how well intravesical therapy will work. This is further compounded by the fact that chemoinstillation and BCG immunotherapy cause inflammatory changes that might occasionally affect test results or make it more difficult to diagnose a tumor recurrence.However, early detection of patients who may need more drastic therapy and are unlikely to benefit from BCG may be possible by including a biomarker test in a routine work-up [19]. Additionally, groups at higher risk may be able to be chosen for clinical trial recruitment based on indicators [20].

## BIOMARKERS WITH MUSCLE INVASIVE BLADDER CANCER

Biomarkers have the potential to solve a number of specific issues in MIBC. Recurrence and progression rates vary among patients with AJCC stages 2 and 3. Additionally, 40% or so of patients are understaged [21]. Neoadjuvant chemotherapy (NAC) has level 1 evidence for treatment, however its usage is underutilized because to safety concerns and a negligible survival benefit [22]. Finding those who are likely to have micrometastatic disease would be beneficial because NAC is more beneficial for those with non-organ confined disease. A marker to identify likely responders would be crucial to avoid giving hazardous medications to individuals who are unlikely to benefit from them, as there is also varied response to NAC Mutations in the DNA repair genes ATM, RB1, and FANCC, [23], excision repair crosscomplementation group 2 (ERCC2) gene, [24,25], protein biomarkers, [26], and RNA subtyping of bladder cancer are among the several potential biomarkers that have been identified.Additionally, trimodality therapy is a viable alternative for certain individuals, even if cystectomy is the primary treatment for MIBC, and it would be helpful to forecast a patient's responsiveness to this kind of treatment. Adjuvant therapy may be useful for patients with non-organ confined illness who do not get NAC [29].Furthermore, because histopathological risk factors identified in radical cystectomy (RC) specimens have a significantly higher correlation to survival than histological parameters obtained by transurethral resection of bladder tumors, proponents of an adjuvant approach contend that there is a significant risk of overtreatment with NAC [30,31]. It has been observed that 40–50% of patients had a pathological complete or partial response (downstaging to non-muscle invasive tumor stages) with NAC, which is linked to improved survival [32]. Conversely, following RC, most patients will have persistent muscle-invasive disease (≥ ypT2), which is linked to poor outcomes [32]. In this context, a predictive biomarker should be able to identify individuals who require systemic treatment as well as those whose tumors respond well to systemic treatment (maybe even specifying which treatment in the future). In order to accurately predict response, biomarker expression levels inside the tumor lesion should be uniform due to the significant degree of intratumoral heterogeneity of MIBC [33]. To avoid undertreating MIBC patients, a biomarker evaluated in the transurethral resection material should ideally have a greater sensitivity than specificity. On the other hand, underuse of neoadjuvant treatment may arise from a high specificity but poor sensitivity; however, this could be mitigated if a safe and effective adjuvant treatment is accessible, especially for patients with comorbidities (such as reduced renal function).If there is no downstaging effect following neoadjuvant therapy, the currently available histopathological parameters (tumor and nodal stage) can be deemed accurate enough to determine the need for adjuvant treatment; nonetheless, a biomarker may be useful in identifying the best treatments going forward [34]. Given the extremely poor prognosis for the group of > ypT2 patients

following RC, it is important to have a biomarker with even higher specificity than the (primary) neoadjuvant setting in order to predict response in the adjuvant setting following the failure of a neoadjuvant strategy [32].A prognostic biomarker that indicates which patients will experience recurrence and which will not, as well as a predictive biomarker of which treatment might be associated with the best response, may be beneficial for patients with a locally advanced tumor following RC who have not previously received neoadjuvant therapy.

## METASTATIC BLADDER CANCER

To make sure patients in this extremely aggressive disease state are not receiving useless medications, predictive biomarkers are desperately needed in metastatic cancer/ disease to identify which tumor will likely respond to which treatment. These biomarkers are probably derived from tissue or blood. Since tumors, particularly metastases, change over time, it is ideal for biomarkers to be evaluated successively by blood draw to avoid requiring the patient to have multiple biopsies and to ensure that the biomarker accurately represents tumor features. Although the genetic characterisation of bladder cancers has laid the groundwork on several fronts, there aren't many verified biomarkers. Biomarkers are essential for forecasting how well a treatment will work. For metastatic bladder cancer, a targeted therapy that targets mutations in the fibroblast growth factor receptor has already been approved [35]. Although controversial, indicators like programmed death receptor ligand 1 (PD-L1) can sometimes be used to predict how well checkpoint drugs will work. While data from a randomized trial supports the use of, for instance, pembrolizumab in an unscreened population of platinum-pretreated patients, the use of PD-L1 inhibitors is currently only authorized after PD-L1 testing in firstline cisplatin-ineligible patients who are eligible for carboplatin [36,37]. Combining PD-L1 inhibitors with additional targeted drugs will be crucial to enhance response because of the modest response rates in both settings (25% full and partial remissions).However, it is anticipated that in the future, marker expression will be used to determine whether to employ single-agent or multiagent targeted therapy in any line of systemic therapy. The crucial concern is whether the tissue taken at original diagnosis can accurately reflect the tumor biology following numerous lines of systemic treatment, given the high mutational burden and heterogeneity of response to treatment in metastasized cancers. Therefore, a deeper comprehension of the molecular mechanisms involved in the course of metastatic disease will be necessary before the deployment of robust biomarkers in the various metastatic situations. To systematically evaluate changes in tumor biology during the metastasis development process, well-designed biopsy studies will be necessary.

## CONCLUSION

Biomarkers can be crucial in enhancing clinical decision-making in a number of bladder cancer-related areas. Most patients' outcomes cannot be accurately staged or predicted using the available data on disease grade and stage. Biomarkers may provide insight into the clinical characteristics of malignancies, enabling a more individualized approach to treatment. Improved knowledge of the disease's biology may also help identify which people require more extensive treatment and which treatments to employ.

### Abbreviations

BCG : bacillus Calmette-Guérin
MIBC : muscle invasive bladder cancer
NMIBC : non-muscle invasive bladder cancer
NAC : neoadjuvant chemotherapy
NLST : National Lung Screening Trial
NPV : negative predictive value
PD-L1 : programmed death receptor ligand 1
PLCO : Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial
PPV : positive predictive value
RC : radical cystectomy

## REFERENCES

1. Burger M, Catto JW, Dalbagni G, et al., Epidemiology and risk factors of urothelial bladder cancer. Eur Urol 2013; 63: 234–241.

2. Elias K, Svatek RS, Gupta S, et al., High-risk patients with hematuria are not evaluated according to guideline recommendations. Cancer 2010; 116: 2954–2959.

3. Garg T, Pinheiro LC, Atoria CL, et al., Gender disparities in hematuria evaluation and bladder cancer diagnosis: a population based analysis. J Urol 2014; 192: 1072–1077.

4. Ghandour R, Freifeld Y, Singla N, Lotan Y. Evaluation of hematuria in a large public health care system. Bladder Cancer 2019; 5: 119–129.

5. Lotan Y, Svatek RS, Krabbe LM, et al., Prospective external validation of a bladder cancer detection model. J Urol 2014; 192: 1343–1348.

6. Lotan Y, Capitanio U, Shariat SF, et al., Impact of clinical factors, including a point-of-care nuclear matrix protein-22 assay and cytology, on bladder cancer detection. BJU Int 2009; 103: 1368–1374.

7. Sylvester RJ, van der Meijden AP, Oosterlinck W, et al., Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol 2006; 49: 466–465; discussion 475–467.

8. Benderska-Soder N, Hovanec J, Pesch B, et al., Toward noninvasive follow-up of low-risk bladder cancer—Rationale and concept of the UroFollow trial. Urol Oncol 2020.

9. Daneshmand S, Patel S, Lotan Y, et al., Efficacy and safety of blue light flexible cystoscopy with hexaminolevulinate in the surveillance of bladder cancer: a phase III, comparative, multicenter study. J Urol 2018; 199: 1158–1165.

10. Kamat AM, Willis DL, Dickstein RJ, et al., Novel fluorescence in situ hybridization-based definition of bacille Calmette-Guerin (BCG) failure for use in enhancing recruitment into clinical trials of intravesical therapies. BJU Int 2016; 117: 754–760.

11. Lotan Y, Inman BA, Davis LG, et al., Evaluation of the fluorescence in situ hybridization test to predict recurrence and/or progression of disease after bacillus calmette-guerin for primary high grade nonmuscle invasive bladder cancer: results from a prospective multicenter trial. J Urol 2019; 202: 920–926.

12. Shariat SF, Palapattu GS, Karakiewicz PI, et al., Discrepancy between clinical and pathologic stage: impact on prognosis after radical cystectomy. Eur Urol 2007; 51: 137–149; discussion 149–151.

13. Alfred Witjes J, Lebret T, Comperat EM, et al., Updated 2016 EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer. Eur Urol 2017; 71: 462–475.

14. Plimack ER, Dunbrack RL, Brennan TA, et al., Defects in DNA repair genes predict response to neoadjuvant cisplatin-based chemotherapy in muscle-invasive bladder cancer. Eur Urol 2015; 68: 959–967.

15. Liu D, Plimack ER, Hoffman-Censits J, et al., Clinical validation of chemotherapy response biomarker ERCC2 in muscle-invasive urothelial bladder carcinoma. JAMA Oncol 2016; 2: 1094–1096.

16. Van Allen EM, Mouw KW, Kim P, et al., Somatic ERCC2 mutations correlate with cisplatin sensitivity in muscle-invasive urothelial carcinoma. Cancer Discov 2014; 4: 1140–1153.

17. Baras AS, Gandhi N, Munari E, et al., Identification and validation of protein biomarkers of response to neoadjuvant platinum chemotherapy in muscle invasive urothelial carcinoma.PLoS One 2015; 10: e0131245.

18. Choi W, Porten S, Kim S, et al., Identification of distinct basal and luminal subtypes of muscle-invasive bladder cancer with different sensitivities to frontline chemotherapy. Cancer Cell 2014; 25: 152–165.

19. Seiler R, Ashab HA, Erho N, et al., Impact of molecular subtypes in muscle-invasive bladder cancer on predicting response and survival after neoadjuvant chemotherapy. Eur Urol 2017.

20. Advanced Bladder Cancer Meta-analysis C. Adjuvant chemotherapy in invasive bladder cancer: a systematic review and meta analysis of individual patient data Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Eur Urol 2005; 48: 189–199; discussion 199–201.