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Mini Review

The Role of Liquid Biopsy in the Detection, Risk Stratification, and Surveillance of Non-muscle-invasive Bladder Cancer: A Mini Review

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Abstract

Non-muscle-invasive bladder cancer (NMIBC) is characterized by a high recurrence rate and a substantial long-term surveillance burden. However, current detection and surveillance strategies rely largely on invasive cystoscopy and urine cytology, which are limited by patient discomfort, suboptimal adherence, and insufficient sensitivity, particularly for low-grade disease. This mini review examines the role of liquid biopsy in the detection, risk stratification, and surveillance of NMIBC. It summarizes current evidence on circulating tumor DNA, circulating tumor cells, exosomes and extracellular vesicles, urinary tumor DNA, and DNA methylation and protein biomarkers in blood or urine. For detection, urine-based molecular assays complement cystoscopy and cytology in the noninvasive assessment of patients with suspected bladder cancer. For risk stratification, molecular detection of residual disease and longitudinal biomarker changes help identify patients at increased risk of recurrence or progression. During surveillance, urine-based assays support earlier recurrence detection and, in selected settings, help reduce the frequency of cystoscopy. Overall, liquid biopsy is a promising minimally invasive complement to conventional NMIBC management although technical standardization and prospective clinical validation are required before routine implementation.

Introduction

Bladder cancer is the tenth most common cancer worldwide, with approximately 75% of patients presenting with non-muscle-invasive bladder cancer (NMIBC; stages Ta, T1, and carcinoma *in situ*). Although transurethral resection of bladder tumor (TURBT) plus adjuvant intravesical therapy can control local disease, NMIBC has a 5-year recurrence rate of 50–70% and a 10–20% risk of disease progression.[1-3] For high-risk disease, repeat TURBT is recommended to reduce understaging and adverse oncological outcomes. Consequently, prolonged surveillance is required, with cystoscopy and urine cytology typically scheduled every 3 months during the first 2 postoperative years.

Cystoscopy with histopathological confirmation remains the diagnostic gold standard for bladder cancer, but its limitations include invasiveness, cost, patient discomfort, and the risk of urinary tract infection. Urine cytology has good sensitivity for high-grade tumors, but its sensitivity falls below 40% for low-grade lesions.[4,5] Over the past two decades, multiple noninvasive modalities, including urinary tumor protein assays and fluorescence *in situ* hybridization (FISH), have been developed to provide accurate, high-throughput, patient-friendly diagnostic tools for bladder cancer.[6,7] More recently, advances in next-generation sequencing (NGS) have facilitated the development of liquid biopsy, a minimally invasive molecular testing strategy, as a potential adjunct across several stages of NMIBC management.[8-10]

Circulating tumor DNA (ctDNA) has been validated as a predictive biomarker for guiding adjuvant immunotherapy in muscle-invasive bladder cancer (MIBC), but its role in NMIBC remains incompletely defined. Notably, urine is in direct contact

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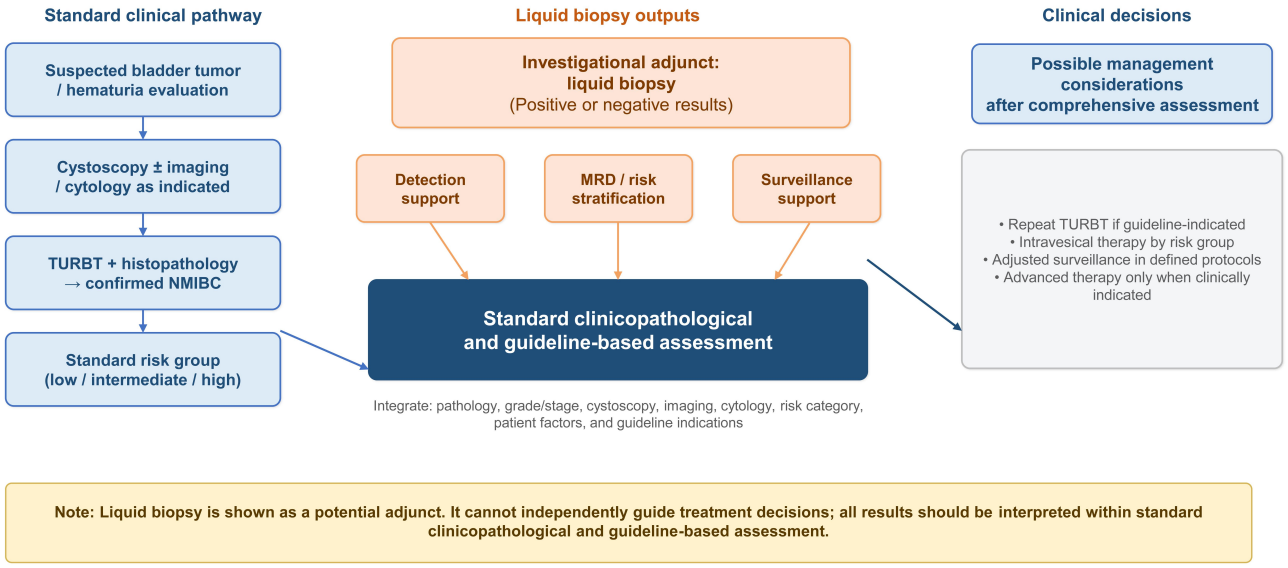

Fig. 1. Potential adjunctive roles of liquid biopsy in NMIBC management. The dark blue refers standard clinicopathological and guideline-based clinical decision, and bright orange refers investigational adjunct based on liquid biopsy, which cannot independently guide treatment decisions. MRD, minimal residual disease; NMIBC, non-muscle-invasive bladder cancer; TURBT, transurethral resection of bladder tumor.

with urothelial lesions and can be collected less invasively than blood.[11,12] This mini review examines the applications of liquid biopsy in NMIBC detection, risk stratification, and surveillance and discusses how molecular testing may inform future clinical decision-making (Fig. 1).

Technical platforms and core biomarkers of liquid biopsy for NMIBC

Unlike blood samples, which primarily reflect systemic tumor invasion or metastatic potential, urine is a particularly relevant specimen for NMIBC liquid biopsy because it is in direct contact with bladder tumors. Major liquid biopsy biomarkers evaluated in NMIBC research include the following:

FISH: Identifies aneuploidy of chromosomes 3, 7, and 17 and loss of the 9p21 locus.

Tumor-associated proteins: Classic urinary markers include NMP22 and BLCA-1/4 but have suboptimal diagnostic specificity.

Circulating tumor cells (CTCs): Have low detection rates in localized NMIBC but may be associated with the risk of tumor progression.

DNA methylation markers: Aberrant hypermethylation of genes such as *GDF15*, *VIM*, and *ZNF582* has been reported in NMIBC tissues and paired urine specimens.

Exosomes/extracellular vesicles: Contain tumor-derived RNA, proteins, lipids, and DNA and may enable dynamic monitoring of tumor-associated molecular changes.

Plasma ctDNA: Captures tumor-specific somatic mutations (e.g., *FGFR3*, *TERT*, and *PIK3CA*) that characterize the genomic landscape of urothelial carcinoma.

Urinary tumor DNA (utDNA): May more sensitively reflect the genomic profile and tumor burden of localized bladder lesions than blood-derived circulating nucleic acids.

These platforms have distinct technical strengths and potential clinical applications, as summarized in Table 1.

Clinical application of liquid biopsy in bladder cancer detection and primary diagnosis

Early detection and diagnostic evaluation

Although cystoscopy is the diagnostic gold standard for bladder cancer, the procedure is invasive, costly, and time-consuming and may limit acceptability as an initial diagnostic assessment in some patients. An ideal noninvasive biomarker should reliably distinguish bladder cancer from benign causes of hematuria and other urinary tract conditions with minimal patient burden.

Urinary methylation profiling is among the most mature translational approaches in this field. A prospective cohort of 254 patients (146 with newly diagnosed bladder cancer) compared the diagnostic performance of Bladder EpiCheck, a panel of 15 methylation biomarkers, with routine urine cytology.[13] Bladder EpiCheck yielded a sensitivity of 73% and a specificity of 99%, substantially outperforming conventional cytology. The UriFind assay detects ONECUT2 and *VIM* methylation; in a prospective trial of 175 participants (109 with confirmed bladder cancer), it achieved 91.7% sensitivity and 77.3% specificity, suggesting potential as a screening assay.[14]

AssureMDx integrates mutations in several genes (*FGFR3*, *TERT*, *OTX1*, etc.) and epigenetic alterations and has reported a negative predictive value (NPV) of up to 93% for ruling out bladder cancer in patients with hematuria. A separate multitarget urine DNA study reported an NPV of 93.33%, which may help reduce unnecessary cystoscopy referrals.[15,16] The Xpert Bladder

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Table 1. Characteristics of various liquid biopsy biomarkers

Biomarker	Technical platform	Advantages	Limitations	Applicable scenarios
DNA mutation markers	Next-generation sequencing (NGS)	Directly assesses tumor-associated driver alterations and may provide high specificity	Low tumor DNA fraction in NMIBC may result in false-negative findings	Postoperative surveillance
DNA methylation markers	Bisulfite conversion, methylation-sensitive restriction enzymes, or other methylation-specific amplification or sequencing methods	High tissue specificity and greater stability than mutation detection	Provides epigenetic information only; may require integration with mutation data for comprehensive screening and surveillance	Evaluation of patients with hematuria; postoperative surveillance
ctDNA	Tumor-informed patient-specific panels based on tumor profiling or fixed tumor-naïve panels for plasma analysis	Captures tumor-specific somatic alterations and may provide high specificity	Primarily reflects systemic tumor burden and has low sensitivity for low-burden NMIBC	Postoperative recurrence and progression surveillance
utDNA	Tumor-informed or fixed panels for analysis of tumor-derived DNA in urine	Relatively simple, noninvasive urine sampling	Reflects intravesical tumor burden and shows interindividual variability in detection performance	Initial diagnostic evaluation and postoperative surveillance
CTCs	Enrichment and detection of tumor cells from whole blood based on size, morphology, or surface markers	May reflect invasive and metastatic potential	Low detection rate and variable sensitivity in NMIBC	Assessment of tumor progression risk
EV-related markers	Detection of DNA, mRNA, miRNA, proteins, and lipids derived from extracellular vesicles	Provides multi-omic tumor information and may reflect tumor biology and the microenvironment	Lack of standardized detection and analytical workflows	Emerging research for comprehensive tumor evaluation
Protein markers	Enzyme-linked immunosorbent assay (ELISA)	Simple, rapid, and low-cost detection	Limited diagnostic specificity and susceptibility to interference from urinary inflammation	Initial diagnostic evaluation and surveillance
FISH	Detection of aneuploidy of chromosomes 3, 7, and 17 and loss of 9p21 in urinary exfoliated cells	Established adjunctive assay with available clinical evidence	Low sensitivity for low-grade tumors and dependence on adequate numbers of intact exfoliated cells or nuclei	Adjunctive diagnostic evaluation and surveillance

ctDNA, circulating tumor DNA; CTCs, circulating tumor cells; EVs, extracellular vesicles; FISH, fluorescence *in situ* hybridization; mRNA, messenger RNA; miRNA, microRNA; NMIBC, non-muscle-invasive bladder cancer; utDNA, urinary tumor DNA.

Cancer Monitor measures five messenger RNA (mRNA) targets (*ABL1*, *CRH*, *IGF2*, *UPK1B*, and *ANXA10*) and was evaluated in a cohort of 828 patients with hematuria, with diagnostic performance benchmarked against cystoscopy and histopathology as well as cytology and UroVysion FISH.[17] Xpert achieved an overall sensitivity of 78%, an NPV of 98%, and a specificity of 84%, supporting its potential to identify low-risk patients who might be candidates for reduced cystoscopy after further validation. Despite the promising diagnostic performance of several commercial urine assays, standardized operating procedures and clinical interpretation thresholds remain lacking for routine use.

By contrast, protein biomarkers and CTCs generally have lower sensitivity for early bladder cancer detection. Urinary NMP22 and bladder tumor antigen assays have reported sensitivities of 50–65% for bladder cancer diagnosis. The CellSearch platform has reported 71.4% sensitivity for metastatic urothelial carcinoma but detects CTCs in only 20% of localized NMIBC cases.[6,18-20] FISH has moderate sensitivity, ranging from 59.4% to 72.0%.[21] The multiplex urinary protein assay Oncuria-Detect has shown encouraging preliminary diagnostic performance.[22] Among 292 patients with microscopic hematuria (22 with confirmed bladder malignancies), Oncuria-Detect achieved 82.0% sensitivity and a 97.5% NPV, compared with BladderChek (NMP22; 9.3% sensitivity and 95.4% NPV) and urine cytology (44.8% sensitivity and 97.2%

Table 2. Selected studies of urinary biomarkers for initial bladder cancer detection

Study	Biomarker	No. of patients enrolled	No. of patients with bladder cancer	Results	Comparator
Xpert[17]	5 mRNAs	828	59	Sensitivity: 78%; Specificity: 84%; Positive predictive value: 27%; Negative predictive value: 98%	Cytology and UroVysion
Oncuria-Detect[22]	10 proteins	292	22	Sensitivity: 82.0%; Specificity: 37.8%; Positive predictive value: 6.5%; Negative predictive value: 97.5%	BladderChek™ and cytology
EpiCheck[13]	15 methylation biomarkers	254	146	Sensitivity: 73%; Specificity: 99%	Cytology
UriFind[14]	2 methylation biomarkers	175	109	Sensitivity: 91.7%; Specificity: 77.3%; Positive predictive value: 87.0%; Negative predictive value: 85%	Cytology and FISH
AssureMDx[15]	3 mutations and 3 methylations	200	97	Sensitivity: 93%; Specificity: 86%; Positive predictive value: 87%; Negative predictive value: 93%	Cystoscopy (reference standard)
mt-utDNA[16]	2 mutations and 2 methylations	947	417	Sensitivity: 91.37%; Specificity: 95.09%; Positive predictive value: 93.61%; Negative predictive value: 93.33%	Cytology, the NMP22 test, and UroVysion FISH

FISH, fluorescence *in situ* hybridization; mRNA, messenger RNA; mt-utDNA, multitarget urinary tumor DNA; NMP22, nuclear matrix protein 22.

NPV). Although protein biomarkers generally have lower sensitivity than epigenetic and nucleic acid assays, their rapid turnaround, low cost, and accessible sample processing may offer practical advantages. Selected studies of NMIBC detection are summarized in Table 2.[13-17,22]

Advances in NGS have positioned ctDNA as a potential diagnostic modality for bladder cancer. Available evidence suggests that utDNA may have higher detection sensitivity than plasma ctDNA for localized NMIBC.[23-26] Nevertheless, utDNA sequencing remains costly, whereas multiplex protein immunoassays are more accessible and less expensive. Cystoscopy with histopathological biopsy remains the definitive diagnostic standard for primary bladder cancer, although flexible cystoscopy may reduce procedural discomfort. Given its high throughput, rapid turnaround, and minimal invasiveness, liquid biopsy may have value in the diagnostic evaluation of selected high-risk or symptomatic populations.

Auxiliary molecular staging for pathological evaluation

Approximately 10–20% of initial TURBT specimens may be inaccurately staged, predominantly because of understaging of T1 lesions. Liquid biopsy may provide additional molecular information to refine pathological risk assessment. Plasma ctDNA positivity exceeds 80% in MIBC but ranges from 10% to 30% in NMIBC. Accordingly, a positive plasma ctDNA result may indicate occult muscle-invasive or otherwise high-risk disease and may prompt further clinicopathological assessment; treatment decisions should not be based on ctDNA status alone.[24,27] CTC detection may provide similar adjunctive information when differentiating invasive from noninvasive urothelial tumors.[20] These findings suggest that liquid biopsy may help identify clinically silent advanced disease that appears localized on cross-sectional imaging. However, large prospective trials are required before liquid biopsy can be routinely integrated into standardized NMIBC management algorithms.

Liquid biopsy for NMIBC risk stratification

Postoperative minimal residual disease (MRD) detection to guide repeat TURBT

Residual tumor after initial TURBT is common in NMIBC, with reported residual lesion rates of 31.6% for Ta tumors and 44.5% for T1 tumors.[28] Major international guidelines, including those from the European Association of Urology and the American Urological Association/Society of Urologic Oncology, recommend repeat TURBT for high-risk patients with suspected residual disease, particularly those with T1 or multifocal tumors.[2,3]

Postoperative MRD is an important predictor of NMIBC recurrence, but molecular detection becomes more difficult at low residual tumor burdens after resection.[29] One prospective analysis enrolled 50 candidates for repeat TURBT, 22 of whom had histologically confirmed residual disease; preoperative Bladder EpiCheck methylation testing yielded 78.6% specificity and a 73.3% NPV for residual tumor prediction.[30] A prospective multicenter Chinese study evaluating OncoUrine, which combines mutation and methylation biomarkers, reported 77% sensitivity, 78% specificity, and an 88% NPV, with positive OncoUrine results independently predicting postoperative recurrence.[31] Collectively, these studies suggest that liquid biopsy may help refine candidate selection for repeat TURBT in research settings. For this

proposed application, specificity and NPV may be clinically informative; however, a negative molecular result should not override guideline-based indications for repeat resection.

In a potential future workflow, utDNA testing could help identify postoperative MRD, supporting risk-adapted evaluation after TURBT. Meanwhile, plasma ctDNA profiling may provide information on the risk of tumor progression and distant metastasis in selected NMIBC cohorts. Multiple prospective trials investigating utDNA-guided risk-adapted therapy are currently underway (www.chictr.org.cn: ChiCTR2600128255, Beijing Hospital; ClinicalTrials.gov: NCT07187635, The Second Hospital of Tianjin Medical University). In NCT07187635, patients with positive utDNA undergo repeat TURBT, whereas those with negative utDNA may omit repeat TURBT and proceed with guideline-based treatment or surveillance.

Prognostic biomarkers for recurrence and progression risk stratification

Conventional clinicopathological risk scores may not fully individualize treatment stratification, highlighting the potential value of molecular profiling for prognostic refinement. As in auxiliary staging, persistent ctDNA positivity may reflect subclinical metastatic disease that is not detected by conventional imaging.

Available studies suggest that postoperative utDNA positivity is associated with an increased risk of recurrence, although testing time points, specimen types, and assay designs vary.[29] Both tumor-informed and tumor-naïve approaches have shown prognostic potential, but direct comparisons remain limited. A cohort of 52 patients with high-risk NMIBC found that longitudinal tumor-informed ctDNA monitoring identified individuals at increased risk of pathological upstaging.[32] A separate study of the tumor-naïve UroAmp utDNA panel associated positive utDNA status with tumor recurrence and enabled longitudinal response monitoring during intravesical bacillus Calmette-Guérin therapy.[33] Existing evidence is limited by retrospective designs and small sample sizes; large prospective treatment-focused trials are needed to validate liquid biopsy-guided NMIBC management strategies.

Dynamic postoperative surveillance guided by liquid biopsy

Approximately half of patients with NMIBC experience tumor recurrence within 5 years of TURBT, with approximately 70% of recurrences occurring within the first 2 postoperative years. Early detection and treatment of recurrence may help prevent disease progression, supporting intensive surveillance schedules for high-risk patients. However, cystoscopy and cross-sectional imaging may miss microscopic residual or recurrent lesions, and repeated cystoscopy imposes a substantial physical and psychological burden on patients.

Early detection of recurrent lesions during surveillance

Urinary methylation assays are increasingly studied for molecular recurrence monitoring, analogous to their role in primary diagnosis. Some studies suggest that molecular recurrence signals may precede abnormalities detected by imaging or cystoscopy, but the lead time varies by assay and population.[29] Tumor-informed panels (e.g., Signatera), which generate patient-specific somatic mutation profiles from primary tumor tissue, have shown potential for NMIBC recurrence surveillance.[27] A key limitation of tumor-informed sequencing is its inability to capture novel subclonal mutations that emerge during treatment or recurrence; tumor-naïve broad-spectrum panels may partly address this limitation by covering a wider range of recurrent clones.

A prospective study compared Bladder EpiCheck, a 15-methylation-biomarker panel, with combined cystoscopy and cytology, with recurrence confirmed histopathologically.[13] In the surveillance cohort, the assay showed an overall sensitivity of 55% and a specificity of 91%; sensitivity for high-grade recurrence was 87%.

The Xpert Bladder Cancer Monitor mRNA panel was prospectively evaluated before surveillance cystoscopy, with performance compared with urine cytology and UroVysion FISH.[34] Xpert achieved an overall sensitivity of 74% (95% confidence interval [CI]: 60–85) and a sensitivity of 83% (95% CI: 64–93) for high-grade lesions; the overall NPV was 93% (95% CI: 89–96), the high-grade-specific NPV was 98% (95% CI: 94–99), and overall specificity was 80% (95% CI: 73–85). Xpert had higher sensitivity and NPV than both cytology and FISH in this study.

The Oncuria-Monitor multiplex protein panel measures 10 urinary biomarkers (A1AT, APOE, ANG, CA9, IL8, MMP9, MMP10, PAI1, SDC1, and VEGF) for recurrence surveillance.[35] The study enrolled 300 patients who provided 1,248 serial urine samples; 93 patients experienced 143 recurrence events. Oncuria-Monitor achieved 85.6% sensitivity (95% CI: 78.1–92.2%) and a 93.0% NPV (95% CI: 89.2–96.4%), compared with BladderChek (NMP22; 20.0% sensitivity and 88.0% NPV) and conventional cytology (36.9% sensitivity and 91.6% NPV). Several studies have reported higher sensitivity or NPV for nucleic acid and multiplex protein assays than for cytology or FISH, although cross-study comparisons are limited by heterogeneous populations and study designs (Table 3).[13,34-36]

Collectively, utDNA, mRNA, and multiplex protein urine assays have shown potential for early detection of recurrent disease. Nevertheless, the clinical significance of early molecular recurrence remains incompletely defined. A phase 3 randomized trial in colorectal cancer found that adjuvant chemotherapy initiated for ctDNA-positive patients without radiographically visible lesions did not improve disease-free survival, illustrating that molecular positivity alone should not serve as an independent indication for early intensified treatment; however, extrapolation of these findings to NMIBC is uncertain.[37] Key questions requiring prospective validation include (1) whether liquid biopsy-enabled early recurrence detection improves long-term oncological outcomes and (2) which intensified treatment strategies, if any, benefit patients with subclinical molecular recurrence.

De-escalation of cystoscopy frequency based on negative liquid biopsy results

Frequent long-term cystoscopy can adversely affect patient quality of life, particularly in men. The high NPV reported for some assays provides a rationale for evaluating biomarker-guided reductions in cystoscopy within defined clinical protocols.[36,38] However, negative biomarker results alone do not currently establish a general schedule for reducing cystoscopy frequency.

The 2026 National Comprehensive Cancer Network Bladder Cancer Guidelines acknowledge urinary biomarkers as an adjunctive surveillance tool within prospective clinical trial frameworks.[12] The prospective randomized UroFollow trial

Table 3. Selected studies of urinary biomarkers for bladder cancer surveillance

Study	Biomarker	Study population/samples	Recurrence data	Results	Comparator
Xpert[34]	5 mRNAs	239	43	Sensitivity: 74%; Specificity: 80%; Positive predictive value: 44%; Negative predictive value: 93%	Cytology and UroVysion
Oncuria-Monitor[35]	10 proteins	300 patients; 1,248 serial urine samples	93 patients; 143 recurrence events	Validation cohort: Sensitivity: 85.6%; Specificity: 32.6%; Positive predictive value: 17.6%; Negative predictive value: 93.0%	BladderChek, cytology
Marker-guided[36]	Marker-guided surveillance algorithm	105 patients in marker-guided arm; 214 randomized overall	29 recurrences in marker-guided arm; 30 in standard arm	Marker-guided algorithm sensitivity: 81.5%	Standard cystoscopy-based surveillance
EpiCheck[13]	15-methylation biomarker	138 patients; 161 urine samples	116 recurrence-positive samples	Sensitivity: 55%; Specificity: 91%; High-grade sensitivity: 87%	Cystoscopy and cytology

mRNA, messenger RNA.

compared standard cystoscopy-only surveillance with biomarker-guided surveillance for low- and intermediate-risk NMIBC.[36] Standard-of-care cystoscopy achieved 96.5% sensitivity, whereas biomarker-guided surveillance achieved 81.5% sensitivity (P = 0.1); no high-grade progressive lesions were missed in either arm, with one low-grade Ta tumor missed in the standard group and five in the biomarker group. The long-term oncological impact of missed low-grade Ta lesions remains uncertain; these findings suggest that this marker-guided surveillance algorithm may reduce cystoscopy use in selected patients with low- or intermediate-risk disease, but broader applicability requires further study.

The DaBlaCa-15 randomized noninferiority trial compared alternating Xpert urine testing and cystoscopy with quarterly standard cystoscopy in patients with high-risk NMIBC.[39] After a median follow-up of 24–25 months, 43 high-grade recurrences were detected, with no apparent difference in recurrence-free survival risk between groups; the biomarker-guided arm required significantly fewer surveillance cystoscopies. Longer follow-up and larger multicenter cohorts are needed to confirm sustained noninferior oncological outcomes.

These randomized trials provide preliminary evidence supporting further evaluation of biomarker-guided reductions in cystoscopy. Multiplex protein urine assays may offer practical advantages in accessibility and cost compared with utDNA sequencing. However, no liquid biopsy platform has achieved universal consensus for standardized routine use. Tumor-informed sequencing requires paired profiling of primary tumor tissue, and standardized protocols for specimen processing, testing workflows, and result interpretation remain lacking across commercial panels.

Clinical challenges and future perspectives

Despite its potential across the NMIBC care continuum, widespread clinical adoption of liquid biopsy faces several translational barriers:

Suboptimal analytical sensitivity: Low-grade and small-volume NMIBC lesions may shed little tumor-derived nucleic acid into urine or blood, resulting in false-negative results; utDNA testing may partly mitigate this limitation.

Clonal hematopoiesis interference: False-positive plasma ctDNA findings can arise from benign hematopoietic somatic mutations (e.g., *DNMT3A* and *TET2*), necessitating matched leukocyte sequencing for signal correction.

Absence of standardized workflows: Consensus is lacking regarding preanalytical processing (urine collection and preservation), detection technology (NGS vs. droplet digital polymerase chain reaction), testing strategy (tumor-informed vs. tumor-naïve), and uniform result-interpretation thresholds.

Insufficient high-level clinical evidence: Most existing studies are retrospective and single-center; large prospective randomized controlled trials are required to determine whether biomarker-guided surveillance is noninferior to standard surveillance.

Future translational research priorities for NMIBC liquid biopsy include the following:

Develop multi-omics predictive models integrating somatic mutations, DNA methylation, proteomic, single-cell sequencing, and radiomic data to evaluate whether integration improves diagnostic accuracy.

Develop home-based urine sampling kits and point-of-care testing devices to support remote longitudinal monitoring.

Establish industry-wide standardized preanalytical, analytical, and postanalytical workflows together with unified criteria for interpreting molecular results.

Evaluate incorporation of liquid biopsy into international NMIBC diagnosis and treatment guidelines as a complementary surveillance tool rather than a replacement for cystoscopy.

Evaluate artificial intelligence and machine-learning algorithms for individualized recurrence-risk prediction and early warning.

In addition, many advanced liquid biopsy assays are costly;

formal health economic and cost-effectiveness analyses are needed to define appropriate clinical scenarios for targeted use across the NMIBC care continuum.

Limitations

This mini review has several limitations. As a narrative review, it may be subject to literature-selection bias, and no formal quality assessment of the included studies was performed. Heterogeneity in patient populations, specimen types, assay platforms, positivity thresholds, and clinical endpoints limits direct comparisons across studies. In addition, some evidence comes from retrospective studies, small cohorts, or preliminary reports, and findings from MIBC or other tumor types may not be directly generalizable to NMIBC.

Conclusions

Liquid biopsy may complement current approaches to the detection, risk stratification, and surveillance of NMIBC. At the primary diagnostic stage, selected assays may help refine evaluation and, in some patients with hematuria, reduce unnecessary cystoscopy. During postoperative surveillance, MRD testing may support risk-stratified follow-up. For recurrence-risk assessment, liquid biopsy may provide additional molecular information but should not independently direct treatment. Because challenges remain regarding technical standardization and high-level prospective clinical validation, routine implementation remains premature.

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Conflict of interest

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Author contributions

Conceptualization and manuscript design (YLY); literature retrieval and data collation (YMG, TXC, HTL); drafting the manuscript (YMG, TXC, HTL); interpretation of the evidence and critical revision of the manuscript (YLY); and approval of the final manuscript (YMG, TXC, HTL, YLY).

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