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Review article

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Low-grade non-muscle-invasive bladder cancer: molecular landscape, treatment strategies and emerging therapies

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Abstract

Low-grade non-muscle invasive bladder cancer is a specific category of bladder cancer with a favourable prognosis; however, its management presents several challenges. The risk of stage progression is very low, but approximately half of patients will experience recurrence within the first 5 years after diagnosis. This high propensity for recurrence, coupled with the threat of progression, mandates ongoing surveillance. However, the optimal frequency and duration of follow-up monitoring remain undefined. Current management strategies for low-grade non-muscle invasive bladder cancer rely heavily on routine office cystoscopy, with few advances in diagnostic and treatment options over the past 25 years. Our basic understanding of disease biology has substantially advanced. However, at present, considerable variations in clinical practice exist, with implications for increased financial and treatment burden for patients and health care systems. Molecular signatures and biomarker discoveries are crucial to understand disease behaviour and inform novel treatment strategies. Emerging therapies, such as advanced drug-delivery systems, immunomodulatory agents and targeted therapies, offer the potential to improve patient outcomes, streamline management and reduce the need for surveillance cystoscopies. Actionable avenues for future research in the field include prospective validation of novel biomarkers and therapies with the ultimate aim of optimizing patient care and reducing health care costs.

Sections

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Key points

- Tumour grade is one of the most important prognostic features in non-muscle invasive bladder cancer (NMIBC) and low-grade disease accounts for half of patients with NMIBC at presentation. Low-grade tumours are characterized by a high propensity to recur, with a lifetime average of 6.6 recurrences per patient. The risk of recurrence is highest within the first 5 years following diagnosis and reduces thereafter. This feature of disease contributes to the overall high cost of bladder cancer care.

- Low-grade NMIBC is associated with a low rate of progression to an increased stage or grade (3–19%). Risk of progression to muscle-invasive bladder cancer is 1.6% overall but can be as high as 8.3% in patients who have multiple risk factors as defined by the International Bladder Cancer Group intermediate-risk NMIBC scoring system.

- Current management challenges in low-grade NMIBC reflect the lack of consensus of the most optimal surveillance frequency and intensity. High use of surveillance cystoscopy results in escalating health care costs without affecting disease outcome.

- Low-grade NMIBC exhibits relative molecular homogeneity and low tumour mutational burden compared with high-grade NMIBC and MIBC, with increased prevalence of gain-of-function alterations in *FGFR3*, *RAS* and *PIK3CA*. Low-grade NMIBC lacks molecular aberrations in commonly mutated genes prevalent in advanced disease (*TP53*, *CDKN1A*, *RB1*, *ERCC2*, *ERBB3* and *FBXW7*). These differences highlight distinct pathways of oncogenesis and hint at differences in therapeutic strategies.

- Bladder cancer is unique in that tumour cells and associated proteins are continuously in contact with and shed into the urine, which can be leveraged using non-invasive urine-based biomarkers. Urine cytology remains one of the only biomarkers endorsed by professional guidelines in NMIBC surveillance algorithms, but has low sensitivity, especially for low-grade disease.

- Emerging therapies and innovations in drug delivery, immunomodulation and targeted treatments offer promising avenues to enhance the efficacy of treatment while potentially reducing the need for invasive follow-up procedures.

Introduction

Bladder cancer ranks as the 10th most commonly diagnosed cancer globally, with 573,000 new cases reported in 2020 and a projected rise to 991,000 by 2040 (ref. 1). Local tumour staging for bladder cancer is based on the depth of invasion, with ~75% of cancers presenting as non-muscle invasive bladder cancer (NMIBC)[2,3]. Tumour grade is one of the most important prognostic factors amongst all clinicopathological features of bladder cancer[2,3]. Low-grade tumours comprise ~50–60% of NMIBCs[3]. These tumours have a relatively low likelihood of progression, but a high propensity to recur following primary resection[4,5]. Within the control arm of the Southwest Oncology Group (SWOG) 0337 trial enrolling patients with clinically low-grade NMIBC, stage-progression to muscle-invasive bladder cancer (MIBC) was 1.6%, whereas 54% of patients experienced recurrence during a median follow-up duration of 4 years[6].

Bladder cancer is one of the most expensive malignancies to manage[7]. The high propensity for recurrence has led to current recommendations for frequent surveillance for NMIBC[8,9]. However, guideline adherence in patients with low-grade NMIBC is poor, with a trend towards oversurveillance in the past decades. A 2022 SEER–Medicare database analysis showed that among patients diagnosed with low-grade NMIBC, the rates of surveillance cystoscopies, upper tract imaging, and urine cytology all increased considerably from 2004 to 2013 in the USA, leading to a rise in the total annual median cost from $34,792 to $53,986 (ref. 10). Furthermore, the mandated surveillance, continued treatment and the perceived threat of cancer progression together confer insidious negative effects on the patients' quality-of-life, including mental health, possibly to a greater degree than that attributed to cancer progression[11,12]. Thus, substantial efforts have been made to improve understanding of low-grade NMIBC in order to reduce treatment burden while optimizing oncological control[13–15].

In this Review, we summarize the biological features of low-grade NMIBC, the clinical risk stratification and the evidence supporting currently used treatment strategies. Furthermore, we highlight contemporary developments in monitoring and therapeutic technologies with the promise of revolutionizing how we manage low-grade NMIBC.

Definition and risk stratification

Previously, the WHO 1973 classification system for bladder cancer stratified papillary urothelial cancers into three grades[16]: Grade 1 (G1) comprises well-differentiated tumours showing mild cellular atypia, necrosis and few mitotic activities; grade 3 (G3) tumours were characterized by poor differentiation with marked nuclear pleomorphism, increased mitotic activity and disordered maturation from urothelial basal to luminal cell layers. The remaining tumours with 'moderate' differentiations were classified as grade 2 (G2). An unintended consequence of this division was a disproportionate and heterogenous mix of tumours being placed in G2, resulting in low utility for clinical decision making. Subsequently, the WHO and the International Society of Urological Pathology adopted an alternative, two-tiered classification system in 1998, designating tumours as either low grade or high grade[16]. Under the new two-tier system, G1 tumours were generally placed into the low-grade category and G3 tumours into the high-grade category, whereas 40% of the G2 tumours were reclassified as high grade and the remaining classified as low grade. Additionally, the most indolent G1 tumours were regrouped as papillary urothelial neoplasms with low malignant potential. The new WHO 1998–2004 two-tiered system aligned better with the cytological diagnostic terminology of The Paris System for Reporting Urine Cytology than the old system, and reduced clinical ambiguity[17]. Conversely, the European Association of Urology (EAU) maintains a recommendation of simultaneous use of both the WHO 1973 and the WHO 2004 classification systems in parallel, which demonstrated superior prognostic value to using either system alone[4].

To further reduce interobserver variability, the WHO Classification of Tumours series for urinary tumours was updated in 2022, so that tumours with <5% high-grade component can now be reported as low grade[16]. The numerical cut-off of 5% was based on similar methods employed in the grading of prostate cancers[18]. This definition was supported by results from a small retrospective review of 31 patients with mixed-grade papillary NMIBC, which demonstrated no significant differences in overall recurrence (53.8% and 45.2%, $P = 0.40$) and grade progression (18.3% and 12.9%, $P = 0.35$) between those

with pure low-grade histology and those with 5% or less high-grade disease[19]. This update has since been adopted by intermediate-risk NMIBC clinical trials to expand patient accrual in this disease space (NCT06319820)[20].

In parallel, efforts to optimize risk-adapted treatment decision making based on risk of recurrence and progression led to the designation of risk groups based on various clinicopathological features including tumour grade, stage, size, multiplicity, and the frequency and timing of recurrence, or into groups using disease progression as the primary end point (Table 1). Generally, low-grade NMIBC is placed in the low-risk or intermediate-risk category. However, the specific definitions vary between guideline committees, resulting in heterogeneity in practice pattern. For instance, the EAU recognizes age >70 years as a risk factor used to stratify patients into four risk groups, whereas the AUA does not consider age as a metric and stratifies patients into only three risk groups[8,9]. To simplify clinical trial design and enrolment, the International Bladder Cancer Group (IBCG) defines intermediate-risk NMIBC as any recurrent pTa low-grade or G1, newly diagnosed pTa low-grade or G1 with multifocality and/or tumour ≥3 cm, and newly diagnosed or recurrent pTa G2 tumours. Intermediate-risk low-grade tumours are characterized by a number of associated risk factors, including multiple tumours; early recurrence <1 year; frequent recurrence >1/year; tumour size ≥3 cm; and recurrence despite previous intravesical treatment[21]. In turn, the number of risk factors dictate recommended treatment. For example, administration of single-dose postoperative chemotherapy is advised for those with no risk factors versus adjuvant induction intravesical therapy for those with one to two risk factors. Since its introduction, the IBCG intermediate-risk NMIBC risk scoring system has been independently validated, demonstrating clinically meaningful differences in recurrence-free survival (RFS) and progression-free survival (PFS) across risk groups[22,23]. In an international multicentre retrospective analysis, patients with IBCG intermediate-risk NMIBC disease with no risk factors had recurrence rates of 10.7% at 1 year and 29.5% at 3 years, with no observed disease progression. By contrast, patients with one to two risk factors had recurrence rates of 13.1% at 1 year and 36.9% at 3 years, with progression rates of 0.6% and 2%, respectively. Those with ≥3 risk factors had markedly increased recurrence rates — 33.5% at 1 year and 67.5% at 3 years — as well as progression rates of 2.6% and 8.2%, respectively[23].

Risk of recurrence and progression

High rate of recurrence and the threat of progression are the two major challenges in the management of low-grade NMIBC. Recurrence rates are highest within the first 5 years following initial diagnosis (18.4% at 1 year, and 40.8% at 5 years), tapering off to 13% thereafter[24]. Median time to first recurrence is 14–18 months, with an average of 6.6 recurrences per patient over a median follow-up period of 8 years[25]. The recurrence rate varies depending on the number of IBCG risk features,

Table 1 | Risk categories based on AUA, EAU, IBCG and NICE guidelines

Guidelines	Low-risk disease	Intermediate-risk disease	High-risk disease	Very high-risk disease	Additional considerations
AUA	Solitary low-grade Ta ≤3 cm papillary urothelial neoplasm of low malignant potential	Low-grade Ta recurrence within 1 year Solitary low-grade Ta >3 cm Multifocal low-grade Ta High-grade Ta ≤3 cm Low-grade T1	High-grade T1 Recurrent high-grade Ta High-grade Ta >3 cm (or multifocal) Carcinoma in situ Any BCG failure in patients with high-grade disease Any variant histology	NA	NA
EUA	Primary, solitary low-grade Ta or T1 <3 cm Primary, low-grade Ta orT1 with at most one additional risk factor[a]	Patients without carcinoma in situ who are not in low-risk, high-risk or very-high risk group	T1 high-grade without carcinoma in situ[b] All patients with carcinoma in situ[b] Low-grade Ta with three risk factors[a] High-grade Ta or low-grade T1 with two risk factors[a]	High-grade Ta and carcinoma in situ with three risk factors[a] Low-grade T1 and carcinoma in situ with two risk factors[a] High-grade T1 and carcinoma in situ with one risk factor[a] High-grade T1 without carcinoma in situ with three risk factors[a]	Risk factors: 1. Age >70 2. Multifocal 3. Tumour >3 cm
IBCG	Primary, solitary low-grade Ta	Low-grade Ta, recurrent Low-grade Ta ≥3 cm or multifocal Low-grade T1, primary or recurrent	Any high-grade Any carcinoma in situ Variant histology	NA	Risk factors: 1. Early recurrence (<1 year) 2. Multifocal 3. Frequent recurrence (>1/year) 4. Tumour >3 cm 5. Failure of previous intravesical treatment
NICE	Solitary low-grade Ta ≤3 cm low-grade TaG2 Papillary urothelial neoplasm of low malignant potential	All tumours not defined as low-risk or high-risk	High-grade Ta Any T1 carcinoma in situ Aggressive variants of urothelial cell carcinoma	NA	NA

AUA, American Urological Association; EAU, European Association of Urology; IBCG, International Bladder Cancer Group; NA, not applicable; NICE, National Institute for Health and Care Excellence. [a]See additional considerations. [b]Except those in the very high-risk group.

with patients in the highest risk group having a recurrence rate of 67.5%, compared with 29.5% in those classified as having the lowest risk at the 3-year follow-up[23]. In addition to the clinicopathological features used to risk stratify patients with NMIBC, tumour recurrence at the initial 3-month surveillance cystoscopy enables prediction of near-certain propensity for further recurrence[26,27]. Accordingly, both the AUA and EAU recommend performance of the first surveillance cystoscopy at 3 months following initial resection[8,14]. However, disagreement exists regarding the optimal subsequent surveillance frequency and duration. By contrast, low-grade NMIBC has relatively low rates of grade and stage progression (3–19%). In a retrospective cohort of 215 patients with low-grade NMIBC, progression was reported to be 8% at a median follow-up duration of 8 years[26]. In a subsequent retrospective cohort of 577 patients with low-risk NMIBC, a 5-year high-risk recurrence rate (defined as grade progression to high-grade or stage progression to ≥T1) was 5.2%[24]. After 5 years, the high-risk recurrence rate further diminishes to 2.8%[24]. In a separate multicentre validation cohort of 677 patients with G1–G2 Ta or T1 intermediate-risk NMIBC, the rate of progression to muscle-invasive or non-organ-confined disease was 2.6% at 1 year and as high as 8.2% at 3 years for patients classified within the highest IBCG risk category[23]. By contrast, increased rates of disease progression have been described in active surveillance cohorts. In a prospective study of carefully selected patients with low-grade NMIBC on active surveillance, 18.7% of the 124 patients experienced grade progression (including conversion from G1 to G2) and 14.8% had stage progression to T1 (ref. 28). In the low-grade Ta population on active surveillance within this cohort, none progressed to muscle invasion at a median follow-up duration of 6 years. However, four patients with G2T1 disease progressed to muscle-invasive disease[28].

In general, the frequent recurrences incidentally detected during surveillance can lead to undue anxiety and are often managed with multiple repeated surgical resections[12]. The benefit-to-risk ratio of such procedures is unproven, especially given substantial perioperative risks related to concurrent comorbidity commonly observed in patients with bladder cancer, with 44% of patients experiencing at least one complication with 30 days of transurethral resection of bladder tumour (TURBT)[29]. In addition, rigorous surveillance and treatment protocols incur high health care costs and treatment burden on patients and society[10].

Molecular pathogenesis

The cell of origin of bladder tumours is a much-debated topic (Fig. 1). The urothelium is composed of basal, intermediate and superficial cells[30]. The superficial cells are large, multi-nucleated, post-mitotic cells that specialize in the synthesis of uroplakins – proteins that are assembled into plaques that coalesce to form the waterproof urothelial barrier[31]. Superficial cells are also bound together by tight junctions formed by claudins and zona occludens, restricting the paracellular flow of small molecules[32]. Intermediate cells make up 5% of the urothelium and populate the suprabasal and luminal layers of the urothelium and basal cells are characterized by expression of keratin 5 and make up 90% of the urothelium[33].

Basal cells were found to be the progenitors for carcinoma in situ (CIS) and MIBC in genetically engineered mouse models[34]. Subsequent studies further narrowed the cell of origin to keratin 14-expressing basal cells[35]. On the other hand, UPK2-expressing intermediate cells were described to be the progenitors of non-invasive papillary tumours[36]. Furthermore, shared gene expression of the urothelial

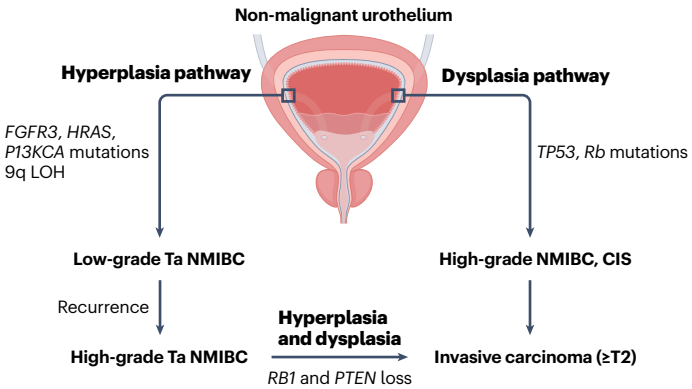

Fig. 1 | Genetic pathway for low-grade and high-grade non-muscle-invasive bladder cancer. The two-pathway model explains the divergent pathways between low-grade bladder cancer and carcinoma in situ (CIS) or invasive bladder cancer. Low-grade tumours are papillary and arise owing to genetic alterations that promote the hyperplasia pathway. NMIBC, non-muscle-invasive bladder cancer.

differentiation-associated markers GATA3, FOXA1 and PPARG in both Ta G2 tumours and intermediate cells suggests a common lineage[37,38]. These two seemingly contradictory findings were reconciled by a set of elegant experiments that demonstrated the necessity for basal-cell activation to elicit carcinogenesis in a rat model, which is dependent on the metabolism of *N*-nitrosodibutylamine into active metabolite (*N*-nitrosobutyl(4-hydroxybutyl)amine, BBN)[31]. However, obligatory *PPARG* expression and signalling drive a luminal differentiation programme in the activated basal-cell-derived cancer progenitors, resulting in the formation of luminal tumours[39]. An increase in *PPARG* activity owing to gene amplification or activating mutations in its binding partner RXR occurs in 10–20% of luminal tumours, whereas expression levels are downregulated in basal and squamous tumour subtypes[40]. Together, these data strongly point to *PPARG* as a key regulator of the development of luminal fate, most commonly observed amongst papillary low-grade tumours[41].

Clinically, stimulation of the *PPARG* signalling pathway was once thought to be carcinogenic owing to the observed association between increased incidence of bladder cancer and the use of thiazolidinedione (TZD), a known *PPARG* agonist[36]. However, increased follow-up duration of the PROactive trial and KPNC longitudinal cohort study showed equilibration over time of the observed cancer rates between patients treated with TZD and those who were not[42,43]. Furthermore, a retrospective study demonstrated no compromise in cancer-related outcomes in patients with diabetes and MIBC taking TZD in the perioperative setting after radical cystectomy[43]. Thus, *PPARG* activation is no longer proposed to be oncogenic; instead, pathway signalling is now hypothesized to act as a tumour suppressor in basal tumours. Emerging preclinical data suggest that the combination of MEK inhibition and PPARG stimulation can lead to profound tumour elimination and might be clinically active in muscle-invasive basal and squamous tumours[44].

Unlike in MIBC, transcriptomic profiling of papillary low-grade NMIBC revealed relative molecular homogeneity and is devoid of cancer stem-cell-associated gene expression[41]. Thus, low-grade NMIBCs are frequently classified as 'Urobasal A' per the Lund taxonomy[45] and 'Class 1' and 'Class 3' in the UROMOL NMIBC classification[38]. Interestingly, one exception to the molecular homogeneity is observed in mTORC1

signalling, thought to be directly related to the loss of *TSC1* (a negative regulator of mTORC1) residing in the chromosome 9q region in a subset of Ta G2 tumours. Tumours with *TSC1* loss demonstrate high expression of genes involved in the unfolded protein response, cholesterol homeostasis, and glycolysis, all of which are influenced by upregulated mTORC1 signalling[46]. The deregulated protein folding and synthesis from constitutive mTORC1 expression and the resulting endoplasmic reticulum stress generates a vulnerable state that can be exploited through synthetic endoplasmic reticulum stress inducers, pushing the cancer cell towards apoptosis[46]. These findings highlight the existence of genomic variations in low-grade NMIBC, offering a potential avenue for the application of targeted therapies.

The loss of chromosome 9q in these tumours reflects increased copy-number alterations observed on low-pass whole-genome sequencing, distinguishing these tumours (genomic subtype 2) from those with no or few alterations (genomic subtype 1)[41]. On Cox proportional hazard modelling, genomic subtype 2 tumours occur more frequently in men, tend to have increased histological grading, and demonstrate a trend towards worse RFS[41]. On first inspection, the frequency of chromosome 9q loss within the cancer cells as well as tumour-adjacent regions of non-malignant-appearing urothelium suggests that it might precede malignant transformation[47]. However, as few isolated incidences of chromosome 9q loss were observed, it could also be the most common event within a constellation of chromosomal changes, rather than an early event in bladder-cancer development.

Loss of the Y chromosome (LOY) is also common in early-stage bladder cancer with potential clinical implications[48]. Evidence has shown that LOY, specifically loss of the chromatin modifiers *KDM5D* and *UTY*, confer an aggressive phenotype to bladder cancer through the evasion of adaptive immune response. Tumours with LOY exhibited increased tumour-associated macrophage infiltration, high levels of immune-checkpoint molecules and $CD8^+$ T cell exhaustion[48]. Consequently, these tumours responded favourably to anti-PD-1 and PD-L1 rescue. Analysis of LOY in a large cohort of patients with NMIBC, however, did not show any influence on disease outcome — both in diploid tumours and in tumours with whole-genome doubling. Furthermore, it did not correlate with increased T cell exhaustion. Thus, the overall implications of LOY in the context of NMIBC remain elusive.

Consistently, low-grade papillary tumours show lower tumour mutational burden (TMB) than high-grade and muscle-invasive tumours (median TMB: 1.9 to 3.8 versus 5.8)[41,49]. As in MIBC, the contribution from the activity of the APOBEC family of cytidine deaminases accounts for the majority of single-nucleotide mutations[41]. Genomic analyses indicate that low-grade papillary lesions were generally characterized by gain-of-function alterations, most frequently affecting key oncogenic drivers, including *FGFR3*, *RAS* and *PIK3CA*[41] (Table 2). However, notably absent were mutations affecting *TP53*, *CDKN1A*, *RB1*, *ERCC2*, *ERBB3* and *FBXW7* (ref. 41). *FGFR3* alterations are found in up to 70% of low-grade NMIBCs, but also in 10–15% of MIBCs[25]. *FGFR3* alterations are known to occur frequently in precancerous lesions (urothelial hyperplasia, papilloma and papillary urothelial neoplasms with low malignant potential) so they are thought to contribute to early oncogenesis[49]. The most common activating missense mutations, including FGFR3S249C (48.1%) and FGFR3R248C (9.2%) in the extracellular domain and FGFR3Y375C (13.2%) in the transmembrane domain[50], induce cysteine-mediated disulfide bond formation, leading to ligand-independent dimerization and auto-activation. In turn, receptor-mediated signalling through the phospholipase Cγ (PLCγ), phosphoinositide 3-kinase (PI3K)–AKT and RAS–MAPK signalling cascades confer many of the physiological functions associated with *FGFR* activation. Gene fusion has also been described, such as coupling the carboxy terminus of *FGFR3* with *TACC3* (2%)[51]. This fusion results in escape from microRNA targeting the 3′ untranslated region of *FGFR3*, followed by TACC3-mediated dimerization and activation of *FGFR3* (ref. 52). In vitro, *FGFR3* mutations led to increased cellular proliferation and viability, conferring selective advantage in the urothelium leading to cellular overgrowth at confluence[53]. From a prognostic perspective, tumours harbouring *FGFR3* alterations are typically of relatively low grade and stage[54,55]. Beyond this well-established link, evidence regarding whether *FGFR3* alterations confer reduced[56] or increased recurrence probability[55] in low-grade NMIBC is inconsistent. However, given its high prevalence, interest in targeting FGFR3 signalling for therapeutic purposes is increasing, with several inhibitors currently under clinical investigation.

Downstream of the FGFR3–RAS–MAPK axis, *RAS* mutations have been described in 10–15% of NMIBCs[57]. Interestingly, from a comprehensive screen of 98 low-grade NMIBC tumour samples and 31 bladder-cancer cell lines, *FGFR3* and *RAS* mutations were found to be mutually exclusive, suggesting functional redundancy in bladder-cancer pathogenesis[57]. Of the different *RAS* oncogenes, *HRAS* is most extensively studied. Expression of a constitutively active *Ha-ras* in transgenic mouse urothelium elicited early-onset hyperplasia in 24 mice examined at 3–8 months of age[58]. By 10–26 months of age, 10 of the 16 mice examined had developed superficial papillary tumours, suggesting that the hyperplasia pathway preceded superficial NMIBC development[58]. Furthermore, carcinogenesis was found to be dose dependent on the number of copies of the transformed *Ha-ras*[59]. These tumours strongly resembled those found in humans phenotypically and did not progress to high-grade disease over time. Similarly, early-onset low-grade NMIBC occurs in patients with germline *HRAS* mutations[60]. Given the mutual exclusivity observed between *FGFR3* and *RAS* mutations, the two together are estimated to account for the vast majority of low-grade NMIBCs[1]. Indeed, in the largest genomic datasets on Ta NMIBCs, the incidence of *FGFR3* or *HRAS* alterations was found in 70 to 91.5% of the tumours[41,61].

Another gene found to be frequently altered in low-grade NMIBC is *PIK3CA*, which encodes the catalytic subunit of phosphatidylinositol 3 kinase (PI3K). In an analysis of 87 unselected bladder tumours, alterations in *PIK3CA* were found to be most prevalent in Ta tumours (16%) and inversely correlated with increasing tumour stage[62]. *PIK3CA* alterations often co-occur with alterations in *FGFR3* or *RAS*, so non-overlapping functions from the activation of the PI3K and MAPK signalling pathways

Table 2 | Frequently mutated genes in low-grade non-muscle-invasive bladder cancer

Gene	Prevalence in low-grade non-muscle-invasive bladder cancer (%)	Gene function
KDM6A	44	Histone modification
FGFR3	80	Cell proliferation
RAS	30	Cell proliferation
STAG2	33	Cell division and DNA repair
PI3KCA	20–50	Activates the PI3K–mTOR pathway

mTOR, mechanistic target of rapamycin; PI3K, phosphoinositide 3-kinase.

might occur in tumorigenesis. Interestingly, data from patients whose disease develops clinical resistance to FGFR3-targeted therapy indicate that *PIK3CA* mutations might compensate for the inhibition of the *FGFR3* signalling[63]. These findings emphasize the need to further explore combinatorial or sequential targeting strategies in tumours harbouring both *FGFR3* and *PIK3CA* alterations.

Finally, epigenetic changes including DNA methylation, histone modification, microRNA regulation and nucleosome positioning all contribute to distinct clinical features specific to NMIBC[64]. Tumour-specific DNA hypermethylation patterns have been detected in adjacent-non-malignant urothelial tissues, suggesting that DNA methylation might be an early event in carcinogenesis[64]. The different epigenetic patterns observed in cancer are linked to frequent alterations found in chromatin remodelling genes in NMIBC samples[61]. A report on Ta NMIBC revealed that one or more components of the COMPASS-like complex, an enzymatic complex recruited to enhancers to influence transcriptional activation, was mutated in 65% of samples. Along with 34% being inflicted with mutations in *CREBBP* or *EP300* (two key acetyltransferases and transcriptional co-factors), a total of 73% of the tumours expressed mutations predicted to alter enhancer activation[61], pointing to its prevalence and importance in the oncogenic pathway.

The most studied of these alterations is *KDM6A*, which encodes a histone 3 lysine 27 dimethyl and trimethyl (H3K27me2/me3) demethylase, which complexes with KMT2C/D to create permissive chromatin environments at enhancer regions[65]. These alterations demonstrate sexual dimorphism, with an increased incidence of *KDM6A* mutations in women with NMIBC (74%) compared with men with NMIBC (42%)[41]. *KDM6A* supports the transcription of several genes that are important for luminal-cell fate[66]. By contrast, *FGFR3* activation is associated with reduced expression of these luminal genes[67]. Mutations in *KDM6A* and *FGFR3* frequently co-occur, so *KDM6A* loss is hypothesized to induce a plastic and aberrant epigenetic background that supports activation of *FGFR3* and the ensuing tumorigenesis[67]. Understanding the precise mechanisms underlying the interaction between epigenetic changes resulting from *KDM6A* loss and *FGFR3* activation might enhance the efficacy of targeted therapeutic strategies.

Low-grade non-muscle invasive bladder cancer biomarkers

Urothelial malignancy is unique in that cancer cells and their constituent nucleic acids and proteins continuously interface with urine, enabling the diverse application of urine-based assays aimed at high-fidelity cancer detection (Table 3). Despite this promise, only urine cytology is currently endorsed by the AUA, whereas the EAU guidelines mention of a few biomarkers such as Epicheck and CxBladder, without definitive recommendations in the management of bladder cancer[8,68]. The application of voided urine cytology was first described by Papanicolaou in 1945 and relies on the visual interpretation of shed-cell morphology by trained cytopathologists[69]. However, interpretation can be complicated by factors such as specimen processing, interobserver variability and inflammatory processes that can mimic early cytological malignant changes[70,71]. Additionally, visual inspection of urinary-cell morphology cannot reliably distinguish between malignancies of different histological subtypes originating from the genitourinary tract[72]. These variables contribute to the overall low sensitivity (36–48%) of urine cytology in detecting bladder cancer[73,74]. Importantly, urine cytology is especially poor at detecting low-grade tumours (sensitivity 16%)[74]. Routine use of urine cytology in the surveillance of patients with low-grade NMIBC is generally discouraged, but its real-world clinical use remains high, approaching 60% in the USA in a 2013 SEER–Medicare-based dataset[10]. In a subsequent survey of practice patterns conducted by the Society of Urologic Oncology, 53% of providers reported routine use of urine cytology in patients with low-risk NMIBC, further corroborating overuse in this patient population[75].

ImmunoCyt/UCyt+ is a cytopathology-based biomarker with improved sensitivity for detection of low-grade tumours. Using immunofluorescent technology, ImmunoCyt/UCyt+ detects three cell antigens (M344, LDQ10 and I9A221). Notably, M344 and I9A211 are not found in MIBC, improving specificity for NMIBC[76,77]. In an analysis of 7,422 specimens, overall sensitivity of ImmunoCyt/UCyt + was 68.1% and specificity was 72.3%[77]. ImmunoCyt/UCyt+ also improved detection of low-grade NMIBC compared with cytology, with a sensitivity of 57% for G1 tumours[77]. This finding was corroborated in a subsequent series, in which the sensitivity of ImmunoCyt/UCyt+ was 47% for low-grade disease[74].

Another class of biomarkers detects tumour-specific proteins from the voided urine rather than relying on cell morphology. One example is Oncuria, a quantitative multiplex immunoassay based on ten distinct bladder-cancer-associated proteins (angiogenin (ANG), apolipoprotein E (apoE), α1 antitrypsin (A1AT), carbonic anhydrase 9 (CA9), IL-8, matrix metalloproteinase 9 (MMP9), MMP10, plasminogen activator inhibitor 1 (PAI1), stearoyl-CoA desaturase 1 (SCD1) and vascular endothelial growth factor (VEGF))[78]. In an analysis of 724 urine samples from patients with bladder cancer, Oncuria achieved an impressive overall sensitivity and specificity of 93%, with sensitivity remaining high in patients with low-grade disease (89%)[78]. Other tests in this class include nuclear matrix protein 22 (NMP22), which detects a family of nuclear matrix proteins involved in mitosis that are shed into the urine by apoptotic cancer cells[79,80], and bladder tumour-associated antigen (BTA), which detects human complement factor H-related protein (hCFHrp)[81,82]. Both tests outperformed urine cytology for the detection of low-grade disease (sensitivities 25% and 35%, respectively), but were inferior to Oncuria[74]. An important limitation of these latter two urine protein-based assays is their inability to distinguish between cellular content released from tumours and benign inflammatory cells. For example, NMP22 can be elevated in any condition that results in increased cellular turnover, such as infection or inflammation in the urinary system[80]. Similarly, because hCFHrp and complement activation are not specific to cancer, BTA could also yield false positives owing to benign inflammatory conditions[80,82].

Advances in gene-expression profiling have led to the development of mRNA-based urinary biomarkers. CxBladder Monitor measures the expression of five key genomic markers associated with bladder cancer (*IGF*, *HOXA*, *MDK*, *CDC* and *IL8R*)[83]. In a comparative analysis of 1,035 urine samples, CxBladder outperformed urine cytology, with an overall sensitivity of 91% and specificity of 61%[84]. CxBladder also demonstrated improved detection of low-grade NMIBC, with a sensitivity of 86%[85]. Xpert Bladder is another mRNA gene expression assay that detects a different set of bladder-cancer-related genes (*CRH*, *IGF2*, *UPK1B*, *ANXA10* and *ABL1*)[86]. A pooled analysis of 11 prospective studies of Xpert Bladder found an overall sensitivity of 73% and specificity of 77%, albeit with inferior performance characteristics in low-grade disease (58% sensitivity)[87].

Leveraging the frequently altered epigenomic profile unique to bladder cancer, urine-based DNA methylation signatures have also been employed for the detection of disease. Bladder Epicheck uses 15 proprietary DNA methylation markers with an overall sensitivity of 68% and specificity of 88%[88]. However, in a prospective, blinded study, Bladder Epicheck was more sensitive for high-grade disease (85% versus 40% for low-grade disease), like many other urine-based tumour

markers[88]. Assure MDx combines gene methylations (*OTX1*, *ONECUT2* and *TWIST1*) and mutations (*FGFR3*, *TERT* and *HRAS*) specific for bladder cancer[89]. Like Bladder Epicheck, this test was also more sensitive for the detection of high-grade disease (72%) than low-grade disease (57%)[89].

UroVysion fluorescence in situ hybridization (FISH) is a urine-based assay that applies fluorescent DNA probes to simultaneously detect aneuploidy in chromosomes 3, 7 and 17, as well as the loss of 9p21 locus[90]. The application of FISH to detect chromosomal changes has been demonstrated to reduce false-positive readings attributed to benign inflammatory conditions. This characteristic is particularly useful following intravesical BCG, which promotes inflammation and alters the bladder tumour microenvironment[91]. UroVysion has higher sensitivity (39%) but lower specificity (89%) than urine cytology[90]. However, when used in conjunction with cystoscopy, UroVysion can achieve near 100% sensitivity[92]. Unfortunately, the accuracy of UroVysion is still inadequate in the setting of low-grade NMIBC. In an analysis of 113 voided urine samples collected from patients with bladder cancer on surveillance, UroVysion demonstrated a sensitivity of only 22% in the detection of G1 tumours[92].

Improvements in high-throughput next-generation sequencing (NGS) technologies have led to several whole-genome-based assays. Using Cancer Personalized Profiling by Deep Sequencing, high overall sensitivity of 83–93% and specificity of 96–100% were acheived[93]. Notably, urinary tumour DNA (utDNA) was found in 100% of patients with bladder cancer with positive urine cytology, as well as in 82% of patients whose disease was missed by cytology alone. In this cohort, the sensitivity for low-grade NMIBC was 72%[93]. Urinary comprehensive genomic profiling (UroAmp) is another panelled NGS assay of cell-free urinary DNA that detects single-nucleotide variants, insertion–deletions, loss of heterozygosity, copy-number variants and aneuploidy[94]. In a multicentre, case-controlled study including 581 patients, UroAmp demonstrated an overall sensitivity of 95% and specificity of 90%[94]. UroAmp also showed improved detection of low-grade disease, with a sensitivity of 87%[94].

utDNA mutation analysis by NGS could have great clinical potential, as many gene alterations commonly found in various forms of bladder cancer can be analysed simultaneously with high analytical sensitivity and specificity[93]. Referenced against the compendium

Table 3 | Summary of low-grade non-muscle-invasive bladder cancer urine-based biomarkers

Type	Test	Technology: biomarker	Performance		Refs.
			Low-grade	Overall NMIBC	
Urine cell	Cytology	Cell morphology	Sensitivity 16%	Sensitivity 37%	74
				Specificity 95%	
Urine protein	Oncuria	Multiplex immunoassay: ANG, apoE, A1AT, CA9, IL-8, MMP9, MMP10, PAI1, SCD1, VEGF	Sensitivity 89%	Sensitivity 93%	78
			Specificity 93%	Specificity 93%	
	Immunocyt/uCyt+	Immunofluorescence: M344, LDQ10, I9A11	Sensitivity 47%	Sensitivity 62%	74
				Specificity 79%	
	BTA Stat	POC or ELISA: complement factor H-related protein	Sensitivity 36%	Sensitivity 61%	74
				Specificity 78%	
	NMP22	POC or ELISA: NMP22	Sensitivity 25%	Sensitivity 58%	74
				Specificity 85%	
Urine mRNA	CxBladder	RT-qPCR: *IGF*, *HOXA*, *MDK*, *CDC* and *IL8R*	Sensitivity 86%	Sensitivity 91%	84,85
				Specificity 61%	
	Xpert Bladder	RT-qPCR: *CRH*, *IGF2*, *UPK1B*, *ANXA10*, *ABL1*	Sensitivity 58%	Sensitivity 73%	87
				Specificity 77%	
Urine DNA	Assure MDx	MSP qPCR: DNA methylation in *OTX1*, *ONECUT2*, *TWIST1*. DNA mutation in *FGFR3*, *TERT*, *HRAS*	Sensitivity 59%	Sensitivity 97%	89
				Specificity 83%	
	Epicheck	qPCR: 15 DNA methylation biomarkers (proprietary)	Sensitivity 40%	Sensitivity 68%	88
				Specificity 88%	
	UroVysion	FISH: alteration in chromosome 3, 7, 17; deletion of 9p21	Sensitivity 22%	Sensitivity 39%	90
				Specificity 89%	
Next-generation sequencing of cell-free DNA	uCAPP-Seq	High-throughput sequencing of cell-free DNA in urine	Sensitivity 72%	Sensitivity 83–93%	93
				Specificity 96–100%	
	UroAmp	Comprehensive genomic profiling of urine DNA	Sensitivity 87%	Sensitivity 95%	94
				Specificity 90%	

A1AT, α1 antitrypsin; ANG, angiogenin; apoE, apolipoprotein E; BTA, bladder tumour-associated antigen; CA9, carbonic anhydrase 9; ELISA, enzymelinked immunosorbent assay; FISH, fluorescence in situ hybridization; MMP, matrix metalloproteinase; MSP, methylation-specific; NMIBC, non-muscleinvasive bladder cancer; NMP22, nuclear matrix protein 22; PAI1, plasminogen activator inhibitor 1; POC, point of care; RT-qPCR, reverse transcription quantitative polymerase chain reaction; SCD1, stearoyl-CoA desaturase 1; VEGF, vascular endothelial growth factor.

of bladder-cancer-specific genomic data from published datasets such as TCGA[95] and UROMOL[96] or the whole-genome sequencing data derived specifically from the host, utDNA testing has the potential to tailor surveillance with exquisite molecular specificity. Understanding how to use such information in the various stages of bladder-cancer management will be crucially important. Moreover, this promising comprehensive molecular test can potentially unlock early detection of minimal residual disease in urothelial carcinoma[97,98]. Real-time detection of tumour- and patient-specific mutations through urine-based, non-invasive monitoring during treatment may provide valuable insights into both response and resistance to therapy.

Finally, artificial intelligence (AI) algorithms trained on clinical, pathological, radiographical and genomic markers have been deployed to improve on current diagnostic and prognostic tools to aid the management of low-grade NMIBC. Cystoscopic images from 142 tumours (42 of which were low grade) were used to train a learning algorithm called CystoNet, which subsequently demonstrated sensitivity and specificity of 90.9% and 98.6% for tumour detection[99]. Furthermore, investigators have incorporated AI into the histological evaluation of tumour specimens to reduce inter-observer variability[100]. For example, 328 NMIBC samples independently reviewed by three uropathologists were used to train and subsequently validate a model used to segment layers of the urothelium and to assign tumour grading[101]. The resulting automatic classification correctly graded 76% of the low-grade and 71% of the high-grade tumours[101]. A preliminary study presented at ASCO GU 2023 leveraged a deep-learning algorithm to predict likelihood of recurrence in 30 low-grade NMIBCs based on various features of the tumour, including differentially expressed genes, myogenesis and expression of epithelial mesenchymal transition signatures[102]. The AI-derived signature was used to stratify patients into groups with significantly different risks of recurrence (86.5% versus 28.5%, $P < 0.01$)[102].

The rapid development of AI technology in oncology remains in its early stages, with most training and validation performed on small, retrospective cohorts — raising concerns about overfitting and limited generalizability. Beyond the need for well-designed prospective validation studies, AI-based tools face several unique challenges. Deep-learning models rely on complex mathematical processes that are often opaque to both clinicians and patients, which can lead to resistance in adopting these tools for high-stakes decisions such as cancer diagnosis and management. Ethical and legal ramifications exist in cases of misdiagnosis, attributable to potential over-reliance on AI. Ultimately, AI is best positioned as a complement to, rather than a replacement for, existing clinical decision-making tools.

Wide adoption of the novel biomarkers in diagnosis and surveillance of low-grade NMIBC has been limited by several factors, including the lack of large-scale validation and regulatory approval leading to refusal of payer reimbursement. Specific to low-grade NMIBC, careful consideration must be given to the cost-effectiveness of the proposed markers in the clinical context of escalating costs without corresponding improvement in clinical outcomes[10]. A randomized clinical trial is underway to evaluate the diagnostic utility of CxBladder compared with cystoscopy (STRATA Study, NCT03988309)[103]. The eventual adoption of novel technologies in the coming decades will lead to advances in NMIBC risk stratification, enabling improved identification of patients with low-grade disease most appropriate for de-escalation of surveillance and treatment when appropriate, while isolating those at the highest risk of progression to aggressive disease.

Clinical management of low-grade non-muscle invasive bladder cancer

Several options are available for managing patients with low-grade NMIBC including single-dose post-operative intravesical chemotherapy, adjuvant intravesical therapy, active surveillance and chemoablative therapy.

Single-dose post-operative intravesical chemotherapy

For newly diagnosed patients with low-grade NMIBC, as well as those with suspected low-grade recurrence, the AUA and EAU guidelines recommend single-dose chemotherapy immediately following TURBT[8,9]. The rationale for administering chemotherapy in this setting is to destroy the free-floating tumour cells in the bladder following surgical resection; to ablate residual tumour cells at the site of the resection; and to ablate any small, incipient tumours missed at the time of the resection. Several agents have been tested historically[104], but mitomycin C (MMC) and gemcitabine are the two most frequently used drugs in this setting.

MMC is an alkylating agent that inhibits DNA synthesis and causes single-strand DNA breaks along with chromosomal breaks[105]. Gemcitabine is a pyrimidine nucleoside antimetabolite that terminates DNA replication and initiates apoptosis[106]. Results of a 2004 meta-analysis of seven trials showed that single instillation of post-operative intravesical chemotherapy significantly reduced the risk of recurrence with OR 0.61 (95% CI 0.49 to 0.75, $P < 0.0001$), and a number needed to treat of 8.5 (ref. 107). An updated meta-analysis performed by the EAU NMIBC guidelines committee in 2016 included 13 trials (5 using epirubicin, 4 using MMC and 1 each using pirarubicin and thiotepa) with individual patient data collected from 2,278 eligible patients[108]. Long-term recurrence rate in patients treated with single perioperative chemotherapy instillation was 42.5% versus 56.2% in the control arm, yielding an HR of 0.65 (95% CI 0.58 to 0.74, $P < 0.001$). Landmark 5-year recurrence rates were 44.8% (95% CI 41.6 to 48.0) versus 58.8% (95% CI 55.7 to 61.9), with a number needed to treat of 7 (ref. 108). Of the agents used, only thiotepa was not found to be efficacious on subset analysis. Patients with >1 recurrence per year or those with European Organisation For Research And Treatment Of Cancer recurrence scores ≥5 were found not to have benefited from therapy. Unsurprisingly, single-dose postoperative instillation did not reduce the rate of progression to higher stage disease[108]. Conflicting subsequent trials have demonstrated perioperative chemotherapy to be ineffective in patients with recurrent disease or multiple tumours[109]. Additional data emerged subsequently comparing the optimal timing of intravesical MMC (within 24 h versus 2 weeks post-surgery), revealing a reduced risk of recurrence in the immediate MMC cohort (31% versus 41% in low-risk NMIBC), albeit with a minimal difference in RFS[110].

The SWOG initiated a randomized phase III trial in 2008 (S0337) investigating the efficacy of intravesical gemcitabine versus saline in patients with suspected low-grade NMIBC without a previous history of high-grade disease or frequent recurrence (>2 episodes within 18 months)[6]. In the intention-to-treat population ($n = 383$), the estimated 4-year recurrence rate was reduced in gemcitabine-treated patients (35% versus 47%, HR 0.53, 95% CI 0.35 to 0.81, $P = 0.001$). Only 2.4% of the gemcitabine-treated patients experienced grade 3 serious adverse events. A post hoc analysis in patients with high-grade disease revealed no benefit with treatment[6].

In summary, both compelling evidence and guideline recommendations support the use of single perioperative chemotherapy

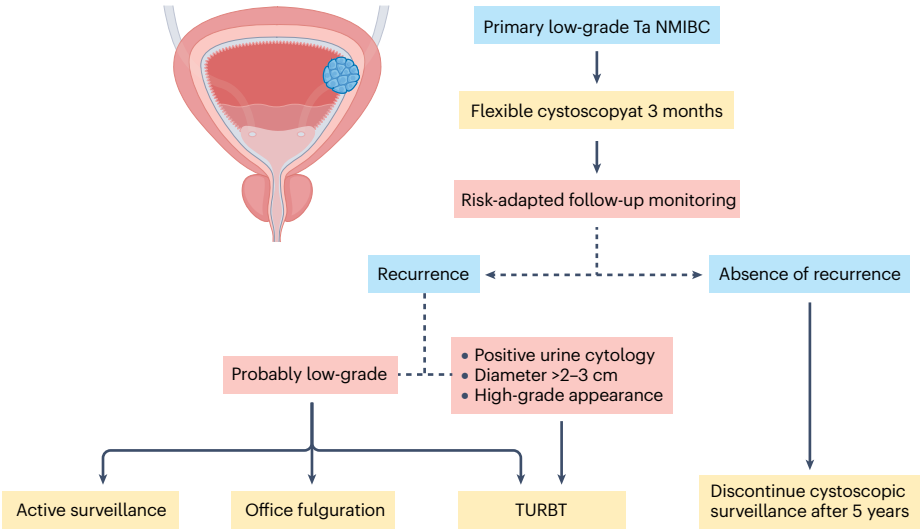

Fig. 2 | Clinical de-escalation pathway in low-grade non-muscle-invasive bladder cancer. Proposed risk-adapted algorithm for the management of low-grade non-muscle-invasive bladder cancer (NMIBC). TURBT, transurethral resection of bladder tumour. Adapted with permission from ref. 123, Elsevier.

instillation to reduce cancer recurrence in patients with low- to intermediate-risk NMIBC.

Adjuvant intravesical therapy

For patients with increased risk within the range of immediate-risk NMIBC (≥3 risk factors), current guidelines recommend induction and maintenance intravesical therapy with either BCG or chemotherapy[111]. Multiple trials and meta-analyses have interrogated recurrence rates following various regimens of BCG versus chemotherapy[106,112–119]. In a randomized phase III trial published in 2001, patients who received an optimized 40-mg dose of MMC in decreased volume and alkalinization experienced longer median time to recurrence than those who received standard 20-mg dosing without optimization (44.2 months versus 29.1 months), which has been the standard of care since then[120]. Drawing definitive conclusions is difficult owing to the heterogeneity present amongst the study populations and treatments. However, most studies have shown superior cancer control with BCG to chemotherapy in randomized controlled trials. In a meta-analysis of 11 clinical trials involving 1,421 patients with intermediate-risk or high-risk NMIBC, recurrence was 38.6% in patients treated with intravesical BCG, compared with 46.4% following MMC, yielding an OR of 0.56 (95% CI 0.38 to 0.84, $P = 0.005$)[113]. In particular, patients receiving BCG maintenance demonstrated additive therapeutic benefit, achieving OR of 0.43 compared with MMC[113]. Several subsequent clinical trials have corroborated the long-term recurrence rate following induction BCG with or without maintenance (36.0 to 40.1%), as well as its superiority to induction chemotherapy (recurrence rates 38.9 to 72%, OR 0.41 to 0.59)[117–119]. A Cochrane Review involving 12 randomized controlled trials encompassing 2,932 participants demonstrated that BCG might reduce the risk of recurrence over time from 45.0% to 40.9% (OR 0.88, 95% CI 0.71 to 1.09)[121]. Subgroup analyses in this review suggested positive effects associated with certain BCG strains including the Pasteur, Connaught and Tice strains, whereas the RIVM strain might not be as effective[121].

Trials evaluating BCG maintenance demonstrated the clear advantage of its use, reducing the risk of tumour recurrence from 45.8% to 36.1% (OR 0.79, 95% CI 0.70 to 0.89, $P < 0.0001$) and prolonging RFS by 33%[114]. In a landmark randomized trial in which reduced-dose BCG was compared with full-dose BCG, the patients with intermediate-risk NMIBC who received a reduced one-third dose of BCG for 1 year ($n = 192$) were noted to be statistically more likely to experience recurrence than those receiving a one-third dose for 3 years ($n = 218$, HR 1.35, 95% CI 1.03 to 1.79, $P = 0.03$). Conversely, no difference in RFS was observed when comparing 1 year ($n = 191$) versus 3 years ($n = 188$) of full-dose BCG with 3-year (HR 0.88, 95% CI 0.64 to 1.21, $P = 0.44$)[112]. Given the totality of the evidence, the IBCG recommends the use of induction and maintenance BCG for patients with intermediate-risk NMIBC with ≥3 risk factors[111]. For those with one to two IBCG risk factors, intravesical induction with maintenance chemotherapy should be considered because of improved tolerability and reduced risk of adverse events compared with BCG, and especially if BCG is in short supply[111]. Comparison of the efficacy and toxic effects of MMC versus gemcitabine in 109 patients with G1–3 NMIBC showed that recurrence (28% versus 39%) and toxic effects were reduced in patients treated with gemcitabine[106]. Based on a favourable benefit-to-risk profile and relatively low cost, gemcitabine has been widely adopted by urologists for the treatment of low-grade NMIBC in the USA. Additionally, the doublet intravesical chemotherapy combination of gemcitabine and docetaxel (gem/doce) has also been tested in intermediate-risk NMIBC. Results of a multi-institutional review demonstrated equivocal efficacy in reducing cancer recurrence to BCG, adjusted for IBCG risk subgrouping (47% BCG, 52% gem/doce, HR 1.06, 95% CI 0.65 to 1.73, $P = 0.8$)[122]. In the era of BCG shortage, doublet intravesical gem/doce remains the de facto treatment of choice for unfavourable intermediate-risk NMIBC or single-agent chemotherapy-recurring tumours.

Active surveillance

Active surveillance strategies for small low-grade tumours have been adopted by several groups owing to the low risk of progression associated with low-grade NMIBC, with the goal of minimizing interval surgical resection of small lesions while closely monitoring for clinical-disease progression. These aspects have been detailed in a dedicated IBCG publication focused on de-intensifying treatment for low-grade NMIBC[123] (Fig. 2). In 2003, the outcomes of a small cohort

of patients with low-grade NMIBC placed on active surveillance were reported[124]. Out of the 32 patients included, only 9% experienced disease progression over an average of 38 months[124]. Similarly, in a cohort of 64 patients with Ta or T1 NMIBC, grade PFS was 83.8% and stage PFS was 93.5% at 10.3 months' follow-up duration[125]. Results of a subsequent update to this series, now with 186 patients with a median follow-up duration of 6 years, showed that grade PFS was 79.3% and stage PFS was 86.4%[28]. Only 4 patients experienced stage progression to MIBC, all of whom had G2T1 at enrolment for active surveillance. Thus, the group has since modified their protocol to exclude patients with T1 disease. Importantly, none of the patients with G1–2 Ta disease on active surveillance progressed to MIBC, supporting the concept that active surveillance is a safe management strategy in well-selected patients.

This strategy was then tested by the Bladder Cancer Italian Active Surveillance (BIAS) project including 214 patients with low-grade NMIBC[126]. Use was restricted to those with ≤5 suspicious lesions, ≤1-cm lesions, absence of gross haematuria and negative cytology[126]. Patients were monitored with cystoscopy quarterly for the first year, and then semi-annually, with surgical resection offered to anyone upon request. The median time on active surveillance was 13 months (IQR 7–24 months), with TURBT required in 130 patients primarily owing to increases in tumour size (39.2%), number of tumours (26.1%) or a combination thereof (22.3%)[126]. At 24 months following protocol initiation, 46.3% of the patients had not yet required surgical resection. On examination of the terminal salvage TURBT specimens, <10% of patients were found to have grade and/or stage progression, with MIBC developing in a single patient[126]. Strict enrolment and predefined active surveillance termination criteria were used in this study, supporting its feasibility and safety for well-selected patients with low-grade NMIBC. Subsequently, the ability of the IBCG intermediate-risk scoring system to help predict the risk of receipt of TURBT in patients managed by active surveillance was demonstrated[127]. Conversely, acknowledging that, although rare, patients who experience progression to muscle-invasive disease while on active surveillance can have considerable challenges is important. Beyond potentially 'missing' the therapeutic window, evidence suggests that patients who develop secondary MIBC have worse outcomes than those diagnosed with de novo MIBC[128]. In the absence of precise molecular or clinical risk-stratification tools, and given the ambiguity in current guideline recommendations, both clinicians and patients might be hesitant to adopt active surveillance. Additionally, implementing active surveillance requires rigorous adherence to surveillance protocols, which might not be feasible in all health care settings owing to logistical, financial or patient compliance barriers. Taken together, current evidence supports the oncological safety of active surveillance for carefully selected patients with low-grade NMIBC. However, clearer guideline recommendations and continued efforts to refine patient selection — through improved risk stratification and biomarker development — are essential to facilitate broader adoption.

Chemoablative therapy

Traditionally, the efficacy of chemoablative strategies for visible marker lesions intentionally left untreated within the bladder in patients with intermediate-risk NMIBC has been evaluated in clinical trials. Assuming that elimination of a macroscopic tumour marker can translate to the eradication of microscopic, subclinical disease, results of such trials can enable rapid selection of efficacious agents to be moved to late-phase comparative trials[129]. Both chemoablative and immunomodulatory agents have been tested in marker lesion studies, yielding complete response (CR) rates of 30–50%[129]. With increasing appreciation of the risks associated with TURBT[130], evaluating the chemoablative approach as primary treatment for patients with low-grade NMIBC has received increased interest.

Most of the early chemoablative studies were single-arm studies[131] or randomized patients to different treatment doses and/or protocols of the same drug[132,133]. A CR rate of 56% was demonstrated using intravesical gemcitabine in 22 out of 39 patients with intermediate-risk NMIBC with a single marker lesion following a 6-weekly induction course[131]. The tolerability of an intensive MMC course, given three times weekly for 2 weeks in two studies in which impressive CR rates between 70.4% and 72.3% were reported[132,133]. The intensive treatment schedule provided enhanced efficacy compared with the traditional weekly for 6 weeks induction schedule (CR 44%) and approached that achieved with TURBT and adjuvant infusion for 8 weeks (CR 78.7%)[133]. Moreover, at the intermediate-term follow-up point at 39 months following the intensive induction course, 61.7% of the patients had a durable response[133]. Of the 27 patients included, 2 could not complete the treatment owing to intolerable lower urinary track symptoms; otherwise, local toxic effects were well tolerated[132].

In the subsequent DaBlaCa trial, this intensive MMC regimen was compared with the traditional TURBT plus weekly for 6 weeks induction schedule in 120 patients with low-grade or high-grade recurrent NMIBC to understand whether chemoablative therapy can reduce the number of surgical interventions[134]. Chemoablation led to significantly fewer TURBTs in the intervention group (71%, 95% CI 57–81) than in the non-intervention group (100%, 95% CI 94–100), $P < 0.001$), with a 12-month RFS of 36% and few toxic effects. The investigators attributed the lower than expected RFS rates to the inclusion of patients with high-grade NMIBC in the trial[134]. Notably, the majority of tumours were <1 cm, and biopsy of the index tumour was not performed before chemoablation, which might have affected accurate tumour staging and grading before treatment. In a separate phase II study, CR to a weekly for 4 weeks induction course of MMC was found to be 37%, with 84% of those patients continuing to have a durable response at 12 months[135]. Unfortunately, the study was terminated prematurely as it did not reach the prespecified 45% CR rate.

UGN-102 is a MMC-based reverse hydrogel that turns from liquid to a semi-solid state upon equilibration at body temperature, enabling the sustained release of the medication over a period of 6–8 h within the bladder[136]. In a phase II, single-arm trial, 63 patients with low-grade Ta NMIBC with visible tumours left in situ received six instillations of UGN-102 and were observed to have a CR rate of 65% at 3 months, with 61% remaining disease-free at 12 months (OPTIMA, NCT03558503)[136]. In a phase III, randomized controlled trial, UGN-102 with or without subsequent TURBT was compared with standard-of-care TURBT for 282 patients with low-grade Ta NMIBC. CR at 3 months was 65% in the UGN-102 arm and 64% in the TURBT arm (ATLAS, NCT04688931)[137]. Disease-free survival (DFS) at 15 months was 82% in the UGN-102 arm compared with 40% in the TURBT arm. However, interpretation is hindered, as residual low-grade disease at the 3-month assessment in the UGN-102 arm was not counted as a DFS event as these patients then went on to receive TURBT. Additionally, patients in the TURBT monotherapy group did not receive standard-of-care adjuvant intravesical therapy, which might have affected long-term DFS.

The first outcomes of the prospective, single-arm, phase III trial of primary chemoablation in 240 patients with recurrent, low-grade, intermediate-risk NMIBC (ENVISION, NCT05243550) have been reported[138]. The 3-month CR rate was reported to be 79.6%, with 82.3% of

Table 4 | Novel therapeutics for low-grade non-muscle-invasive bladder cancer

Agent	Study design	Inclusion criteria	Mechanism	Primary outcome	Results	Ref.
EMDA-MMC (NCT02202044)	RCT	Intermediate-risk or high-risk NMIBC	Electrical current improves uptake of MMC	RFS, PFS	97.5% PFS (EMDA-MMC) 95.8% PFS (BCG) (*n*=216)	160
CHT (HIVEC-II) (NCT06768346)	RCT	Intermediate-risk NMIBC	Hyperthermia+MMC increases uptake of MMC	DFS	61% 24-month DFS (CHT) 60% 24-month DFS (control) (*n*=259)	161
BC-819 (NCT00595088)	Phase II	Intermediate-risk NMIBC	DNA plasmid with diphtheria toxin	CR	33% CR at 3 months (*n*=47)	162
UGN-102 (NCT05243550)	Phase III RCT	Low-grade intermediate-risk NMIBC	Increases MMC dwell time	DFS	80% CR at 3 months (*n*=240)	163
TAR-200 (NCT02720367)	Phase I	Intermediate-risk NMIBC	Sustained release of intravesical gemcitabine	Safety	42% CR (*n*=12)	164
TAR-210 (NCT05316155)	Phase I	Intermediate-risk low-grade NMIBC with FGFR alteration	Sustained release of intravesical erdafitinib (FGFRi)	safety	87% CR (*n*=27) Recruiting	165
Pemigatinib (NCT03914794)	Single-arm phase II trial	Low-risk or intermediate-risk NMIBC	FGFR inhibitor 4–6 weeks before TURBT	CR at TURBT	Recruiting	166
Intravesical pembrolizumab (NCT03167151)	Phase I	Intermediate-risk or high-risk NMIBC	Anti-PD1 inhibitor	Safety	Failed to recruit within the permitted time frame	167

CHT, chemohyperthermia; CR, complete response; DFS, disease-free survival; EMDA, electromotive drug administration; FGFR, fibroblast growth factor receptor; MMC, mitomycin C; NA, not applicable; NMIBC, non-muscle-invasive bladder cancer; PD1, programmed cell death 1; PFS, progression-free survival; RCT, randomized controlled trial; RFS, recurrence-free survival; TURBT, transurethral resection of bladder tumour.

the responders remaining disease-free at 12 months. Patient-reported outcomes were assessed as the exploratory end point of ENVISION, demonstrating UGN-102 to be less invasive, less painful and less disruptive to daily routines and responsibilities[139].

Advances in the field have positioned primary chemoablation as an attractive option for selected patients with low-grade NMIBC who seek definitive treatment of their tumours but are either unwilling or unable to undergo TURBT. The FDA Oncologic Drugs Advisory Committee initially voted 5 to 4 against the approval of UGN-102, but the therapy was ultimately approved by the FDA in June 2025 for the treatment of recurrent intermediate-risk low-grade NMIBC. Critics of the supporting study have noted the absence of a control arm and questioned the risk–benefit trade-off, particularly given the relatively indolent natural history of the disease. Nonetheless, the approval of UGN-102 provides the first non-surgical alternative for managing this disease, underscoring the unmet need in this patient population. Additional validation and long-term durability studies will be essential before UGN-102 can be fully integrated into clinical practice guidelines.

Novel intravesical therapeutics

Intravesical chemotherapy has only demonstrated modest benefits in decreasing recurrence rates in intermediate-risk NMIBC. BCG is efficacious but its availability has been limited by the ongoing global production shortage, with use mainly confined to patients with high-risk NMIBC[140]. Thus, novel therapies to reduce disease recurrence in intermediate-risk NMIBC are urgently needed. Myriad agents had been or are undergoing clinical investigations that can be grouped into strategies to enhance drug delivery, to increase drug contact time, to activate immunosurveillance and to target altered molecular pathways specific to intermediate-risk NMIBC (Table 4).

Enhancing drug delivery

Electromotive drug administration (EMDA) and chemohyperthermia are two strategies employed to boost drug absorption into tumour cells[141–143]. In EMDA, an electrical current is passed through the bladder wall to enhance uptake of MMC into the urothelium[141] In a randomized control trial, 216 patients with intermediate-risk or high-risk NMIBC were randomized to adjuvant EMDA–MMC or BCG[144]. The risk of recurrence was lower in the EMDA–MMC-treated cohort than in the BCG cohort ($P = 0.025$) with no statistical difference in progression risk ($P = 0.7$)[144]. EMDA is currently available only in Europe under experimental status and has not been approved for use in the USA owing to a paucity of supporting evidence. This, global clinical adoption has remained limited to date.

Chemotherapy heated to a temperature of 40–44°C has previously been shown to enhance the cytotoxic activity against cancer cells through decreased cell proliferation[145,146]. Follow-up data for 10 years from 83 patients undergoing MMC administered with radiofrequency chemohyperthermia versus standard MMC suggest significantly reduced recurrence rates with chemohyperthermia (10-year DFS of 53% with chemohyperthermia–MMC versus 15% in MMC group ($P < 0.001$))[147]. However, a subsequent prospective phase II randomized clinical trial (HIVEC-II) in which conductive chemohyperthermia was compared with standard MMC in patients with intermediate-risk NMIBC showed no difference in 24-month DFS (61% versus 60%, $P = 0.8$)[148]. Thus, evidence for the use of chemohyperthermia over standard MMC in intermediate-risk NMIBC remains inconclusive. However, chemohyperthermia might be a viable alternative to BCG during BCG shortages based on findings suggesting similar recurrence (24–36-month recurrence: chemohyperthermia, 29.5%; BCG, 37.4%; 95% CI 0.61 to 1.13) and progression rates (24–36-month progression: chemohyperthermia, 4.4%; BCG, 7.6%; 95% CI 0.26 to 1.49) with similar safety profiles[149].

Innovative techniques such as EMDA and chemohyperthermia have been explored to enhance drug penetration into the urothelium and improve the efficacy of intravesical chemotherapy, with small studies demonstrating promising efficacy and safety. However, routine use remains limited owing to the lack of high-level evidence and regulatory approval.

Increasing drug contact time with the urothelium

A key limitation of intravesical drug delivery is the limited dwell time. Thus, several novel therapeutics have been introduced with the aim of prolonging drug delivery and contact time with the urothelium while reducing the treatment burden on patients. One example is UGN-102 (ref. 138); another is the TARIS intravesical drug-delivery system, comprising a specialized drug-eluting semipermeable tube that is inserted into the bladder cystoscopically in the office and left to dwell for up to 3 months[150]. This system provides sustained release of medication within the bladder during this time, increasing contact time as well as patient convenience. Results of a phase I study involving 12 patients with intermediate-risk NMIBC receiving two 1-week gemcitabine-eluting TAR-200 devices over a 4–6-week period demonstrated good tolerability with minimal adverse effects and a CR of 42%[151]. Currently, clinical trials investigating TAR-200 in low-risk or intermediate-risk NMIBC are being conducted. A clinical trial testing the utility of TAR-210, a different iteration of the TARIS device embedded with erdafitinib, is underway in intermediate-risk NMIBC[20].

Immunomodulation

Viral vector-based gene therapy has been widely adopted in the treatment of numerous cancers. Specifically, adenovirus is an attractive vector as therapeutic genes are expressed episomally and, therefore, have no risk of integrating into the patient genome[152]. Once delivered, the virus stimulates immunomodulatory effects through up-regulation of surface tumour-associated antigens and also increases the immunogenicity of tumour cells[152]. Nadofaragene firadenovec is the first FDA-approved therapeutic non-replicating adenovirus used for the treatment of NMIBC[152]. In a phase III multi-institutional study involving 151 patients with BCG-unresponsive NMIBC, 3-month CR was 45.5% with a relatively favourable adverse effects profile[153]. The proposed phase III ABLE-32 study will compare nadofaragene versus observation in patients with intermediate-risk NMIBC (NCT06510374)[154].

Cretostimogene grenadenorepvec is an oncolytic adenovirus that selectively replicates and kills bladder-cancer cells with alterations in the Rb protein and stimulates production of granulocyte macrophage-colony-stimulating factor resulting in stimulation of the immune system[155]. PIVOT-006 is a currently enrolling randomized phase III clinical trial studying adjuvant cretostimogene after complete TURBT in patients with immediate-risk NMIBC with a primary end point of RFS (NCT06111235)[156].

The above examples highlight the emerging role of immunomodulation in the management of NMIBC. Therapeutic approaches such as adenovirus-based gene therapy and oncolytic viral vectors could soon expand treatment options beyond traditional intravesical agents. As with other novel therapies, integration into clinical practice will depend on the outcomes of ongoing randomized trials. Cost and accessibility will also be important factors influencing adoption.

Targeted therapies

FGFR3 is a promising therapeutic target for low-grade tumours owing to its high prevalence and functional role as an oncogenic driver in low-grade NMIBC[157]. Pemigatinib is an oral FGFR1–FGFR3 inhibitor currently being studied in a phase II study in patients with low-risk or intermediate-risk NMIBC as a neoadjuvant therapy 4–6 weeks before TURBT with a primary end point of CR (NCT03914794)[158]. Erdafitinib, a FGFR1–FGFR4 inhibitor has been approved by the FDA for patients with locally advanced or metastatic bladder cancer with FGFR mutations who have progressed on previous platinum-containing chemotherapy, resulting in an increased overall survival (12.1 months versus 7.8 months) and PFS (5.6 months versus 2.7 months) compared with chemotherapy[159]. Enthusiasm for erdafitinib has extended to NMIBC and MIBC, with the introduction of the latest TARIS device, TAR-210, which elutes erdafitinib. This device is proposed to reduce systemic toxic effects by limiting drug exposure to the bladder lining[150]. Phase I application of TAR-210 for chemoablation in NMIBC with FGFR alterations demonstrated CR of 87% at 3 months while greatly minimizing the systemic toxic effects of erdafitnib[150]. Several clinical trials are underway with TAR-210 in intermediate-risk and high-risk NMIBC as well as MIBC. Notably, MoonRISe-1 is a phase III randomized study in intermediate-risk NMIBC comparing the effects and safety of TAR0210 erdafitinib versus traditional single-agent intravesical therapy (NCT06319820)[20]. Pending results of the study, TAR-210 is poised to become a feasible alternative treatment option for intermediate-risk, recurrent, low-grade NMIBC.

Targeting FGFR3 is a promising precision-medicine approach in NMIBC, with ongoing trials evaluating systemic and localized delivery of FGFR inhibitors. These therapies are aimed at leveraging the high prevalence of FGFR3 alterations in low-grade NMIBC while minimizing systemic toxic effects. Their success could mark a shift towards biomarker-driven treatment strategies in this traditionally uniform treatment landscape.

Future directions

The low-grade NMIBC space is rapidly evolving, with growing recognition of the need for nuanced, risk-adapted management strategies that emphasize de-escalation and the reduction of overtreatment. However, broad adoption of these approaches remains limited by the absence of well-defined, evidence-based guidelines tailored specifically to this disease subset. Clear best-practice recommendations are needed, particularly with respect to surveillance frequency, duration and criteria for de-intensified care. These recommendations will probably require consensus building across international cooperative groups, supported by robust prospective data.

A major priority for future research is the refinement of risk stratification. Improved delineation of patients at an increased risk of progression compared with those with indolent disease will enable personalized care, including the appropriate use of active surveillance and reduced surveillance intensity. Advances in molecular profiling and AI-assisted pathology are already showing promise in identifying relevant biomarkers and histological patterns that could support such stratification.

Additionally, the integration of AI into clinical workflows holds great potential for improving diagnostic accuracy, predicting recurrence or progression, and supporting clinical decision-making. AI models trained on multimodal data could one day provide real-time risk assessment and treatment guidance. However, challenges remain, including the need for large, diverse training datasets, transparent algorithm design and clear frameworks for ethical use and clinical accountability.

Ultimately, progress in this field will depend on prospective validation of emerging tools and therapies through well-designed randomized trials. As these technologies mature, their thoughtful integration into guidelines and clinical practice might substantially improve outcomes while reducing treatment burden for patients with low-grade NMIBC.

Conclusions

Low-grade NMIBC has a relatively favourable prognosis, but its management is challenging. The high risk of recurrence, along with

heretofore undefined best-practice guidelines for surveillance frequency and duration, underscore the need to refine the current approach. The continued reliance on invasive cystoscopy and outdated biomarkers has led to inconsistencies in clinical practice and increased burdens on patients and society. Fortunately, advances in our understanding of the molecular underpinnings of low-grade NMIBC have resulted in the development of both promising diagnostic tools and potential therapies to address these problems.

Despite the promise of urine-based, minimally invasive biomarkers for cancer detection, well-designed prospective studies are necessary to demonstrate clinical feasibility and utility. Until these tests have been rigorously validated, treatment and surveillance strategies for patients with low-grade NMIBC will continue to rely on the well-established clinicopathological risk parameters, such as the IBCG risk stratification system, which is strongly evidence based. In this scoring system, patients with multiple (≥3) risk factors warrant treatment, whereas other patients, particularly those with no risk factors, might be suitable candidates for active surveillance. The reality of the ongoing BCG shortage and clinical risk stratification need to be considered when selecting an intravesical therapeutic agent. Furthermore, novel drug development will undoubtedly enhance treatment efficacy, and perhaps reduce the surveillance burden in the future. However, deployment of novel agents should be considered against their negative effects on clinical and financial toxicity given the overall favourable prognosis of patients with low-grade NMIBC.

Only by considering all of these complex, counteracting factors will we be able to meaningfully advance the management of this disease.

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Competing interests

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