Title: A Multi-Modal Approach for Decision Making in Bladder Cancer

Author(s): Hasan Al-Sattar[1], Hao Ding[2], Oluchi Okoli[3], Somto Okoli[4], Aruni Ghose[5], Giuseppe Luigi Banna[6,7], Simon Wan[8], Athar Haroon[5], Jonathan Wong[9], Jeremy Teoh[10], Nikhil Vasdev[11,12], Eleni Efstathiou[13,14], Stergios Boussios[15,16] & Sola Adeleke[17]

Affiliations:

[1]School of Medicine and Biomedical Sciences, University of Oxford, Oxford, UK
[2]Faculty of Medicine, Imperial College London, London, UK
[3]School of Clinical Medicine, University of Cambridge, Cambridge, UK
[4]University of Bristol Medical School, Bristol, UK
[5]Department of Medical Oncology, Bartholomew's Hospital, Barts Health NHS Trust, London, UK
[6]Portsmouth Hospitals University NHS Trust, Portsmouth, UK
[7]Faculty of Science and Health, School of Pharmacy and Biomedical Sciences, University of Portsmouth, Portsmouth, UK
[8]Institute of Nuclear Medicine, University College London, London, UK
[9]London School of Hygiene & Tropical Medicine, London, UK
[10]Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong
[11]Department of Urology, Lister Hospital, ENHT Teaching NHS Trust, Stevenage, UK
[12]Hertfordshire Medical School, University of Hertfordshire, Hatfield, UK
[13]Department of Genitourinary Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, Texas, USA
[14]Houston Methodist Cancer Center, Houston, Texas, USA.
[15]Department of Medical Oncology, Medway NHS Foundation Trust, Gillingham, UK
[16]Faculty of Life Sciences and Medicine, School of Cancer & Pharmaceutical Sciences, King's College London, London, UK
[17]School of Biomedical Engineering and Imaging Sciences, Kings College London, London, UK

Corresponding author: Sola Adeleke

s.adeleke@kcl.ac.uk

Abstract

Bladder cancer remains a major global health challenge, characterised by diagnostic uncertainty, significant treatment costs, and high recurrence rates. Current diagnostic and treatment modalities, including cystoscopy, transurethral resection (TURBT), and standard histopathology, are not without limitations, highlighting a critical need for improved approaches. Recent advancements in artificial intelligence (AI), blue-light cystoscopy, narrow-band imaging, cytology, and urinary markers show promise in enhancing early detection and diagnosis. Developments in multiparametric MRI, radiomics, genomics and AI-driven algorithms for histopathological analyses have demonstrated significant improvements in staging and risk stratification of bladder tumours, enabling personalised therapy selection and prognostication. Incorporating these technologies, this review proposes a novel multimodal decision-making framework integrating these advancements for both non-muscle invasive

bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC), and extending to metastatic disease. Despite these promising developments, challenges remain regarding standardisation, external validation, cost-effectiveness, and ethical considerations in clinical implementation. Future research should prioritise addressing these barriers through collaborative, multi-institutional studies and robust validation frameworks. Ultimately, adopting a comprehensive multimodal strategy promises to significantly advance precision oncology in bladder cancer, improving patient outcomes and reducing healthcare burdens.

Introduction

Bladder cancer is the 9th most common cancer globally and the 4th most common cancer in men[1,2]. Major risk factors include smoking[3], occupational exposure to aromatic amines[4], and exposure to arsenic in drinking water[5]. The increased prevalence of these risk factors in high-income countries explains the higher incidence rates of bladder cancer in Europe and North America[6]. Urothelial carcinoma is the most common form of bladder cancer, found in around 95% of cases[7], with other types including squamous cell carcinoma, adenocarcinoma and small cell carcinoma[8–10]. Bladder cancer is often first suspected when a patient presents with painless gross haematuria and is subsequently diagnosed through cystoscopy, which continues to be the gold standard diagnostic procedure[11]. Transurethral resection of the bladder tumour (TURBT) can then stage and sometimes even resect the tumour. Tumours confined to the urothelium (stage Ta) or the lamina propria (stage T1) are classified as non–muscle-invasive bladder cancer (NMIBC) and are managed differently from tumours that invade the muscle (stage T2) or extend further (stages T3 and T4), which are categorised as muscle-invasive bladder cancer (MIBC)[12]. Carcinoma in situ (CIS) represents about 10% of NMIBC[8,13].

Bladder cancer also continues to be the most expensive cancer to treat, costing the US $7.93 billion in 2015 and projected to increase to $11.6 billion by 2030, largely driven by the need for lifelong surveillance and frequent interventions due to high recurrence rates[9,14,15]. This is exacerbated by patients with high-grade NMIBC or MIBC facing considerable risks of recurrence and progression[16]. 31-78% of NMIBC cases recur within 5 years, often requiring frequent and repeat TURBT, while 40% of patients do not respond to BCG intravesical therapy[7,8,17,18]. For MIBC, neoadjuvant chemotherapy followed by radical cystectomy means that patients are faced with significant morbidity and long recovery periods[18–21]. Furthermore, approximately 30% of those undergoing cystectomy experience recurrence at a median of 12 months[22,23].

Current bladder cancer management follows guidelines published by the American Urological Association (AUA), the European Association of Urology (EAU), and the National Comprehensive Cancer Network (NCCN)[8,24,25]. NMIBC comprises approximately 70-75% of bladder cancer cases and is typically managed with TURBT[16]. Additional intravesical therapies, such as chemotherapy or Bacillus Calmette-Guérin (BCG) immunotherapy, are recommended for high-risk cases. In contrast, MIBC, which accounts for 20-25% of cases, is often treated with radical cystectomy. For patients eligible for cisplatin, neoadjuvant cisplatin-based chemotherapy is offered, based on the SWOG 8710 trial[26–28]. For unresectable locally advanced or metastatic urothelial carcinoma, current EAU guidelines recommend first-line enfortumab vedotin plus pembrolizumab, with platinum-based chemotherapy followed by maintenance avelumab in patients without progression, and gemcitabine-cisplatin plus nivolumab as another approved first-line option[27,29–33]. Pembrolizumab monotherapy may be considered for platinum-ineligible patients regardless of PD-L1 status.

Despite advancements in diagnostic and treatment strategies, bladder cancer management remains challenging due to its heterogeneity, limitations in diagnostic tools, and the absence of precise risk stratification systems. Current standards such as white-light cystoscopy, while widely used, lack sensitivity and specificity, often leading to missed diagnoses or over-treatment[34–36]. Similarly, risk stratification systems remain suboptimal, as they rely primarily on clinical and pathological features, failing to incorporate the wealth of information available from genomic, radiologic, and molecular data[13]. There is an urgent need to develop better selection criteria to identify bladder cancer patients most likely to benefit from a specific treatment[16]. These deficiencies highlight the pressing need for improved decision-making frameworks that integrate more sophisticated diagnostic and therapeutic tools.

The emergence of artificial intelligence (AI) and related multi-modal technologies offers a transformative potential to address these persistent challenges. AI-driven models increasingly demonstrate their ability to enhance diagnostic precision, improve prognostic prediction, and therefore facilitate personalised treatment decisions[37–39]. In particular, AI-based models can analyse vast and complex datasets from imaging, genomics, and cytology, uncovering patterns and insights that traditional methodologies often miss[40,41]. Furthermore, advances in genomics and molecular profiling are shedding light on the heterogeneity of bladder cancer, allowing for stratification based on genetic and molecular subtypes[42–44]. These tools can guide clinicians in selecting personalised treatments such as immune checkpoint inhibitors or FGFR3-targeted treatments[42,45]. Radiomics, combined with machine learning, can aid urologists in both the diagnosis and prognosis of bladder cancer, such as by predicting tumour invasiveness or response to neoadjuvant chemotherapy[46–48].

This review will explore recent advancements in AI, genomics, radiomics and cytology and how they can be integrated into decision-making processes to improve the management of bladder cancer. By examining their potential to improve early detection, risk stratification, and personalised treatment planning, we aim to highlight the practical applications of these emerging technologies in clinical workflows and their implications for improving patient outcomes. Additionally, we will suggest novel multimodal approaches to the treatment of both NMIBC and MIBC by incorporating these advancements.

Early detection and diagnosis

Cystoscopy

Cystoscopy remains the gold standard for diagnosing and monitoring bladder cancer, providing direct visualisation of the bladder to identify lesions. In many cases, TURBT is used to confirm the diagnosis and remove tumours. However, traditional white-light cystoscopy (WLC) has several limitations, particularly in detecting subtle lesions such as carcinoma in situ (CIS). With a reported misdiagnosis rate of up to 30%[34,35], and a sensitivity and specificity of 60% and 70% respectively[36], there is scope for AI to improve its accuracy[49]. This variability highlights the need for better, more accurate diagnostic tools to improve detection and ensure optimal management of bladder cancer.

In recent years, many studies have shown the diagnostic potential of AI in cystoscopy, particularly convolutional neural networks (CNNs), a specialised deep learning (DL) architecture[40,41,49]. For instance, Shkolyar et al. developed “CystoNet”, a CNN-based platform using a training dataset consisting of 2335 frames of normal bladder mucosa and 417 frames of histologically-confirmed papillary urothelial carcinoma collected from a total of 95 patients[41].

Using a hold-out set of 65 patients, CystoNet achieved a per-frame sensitivity and specificity of 90.9% and 98.6%, respectively, in detecting bladder tumours during WLC and confirmed using histopathological analysis[50]. More recently, Wu et al. developed the Cystoscopy AI Diagnostic System (CAIDS) framework by employing a pyramid scene parsing network (PSPNet) trained on ImageNet and a training set consisting of 69,204 images of 10,729 patients[51]. Using a subgroup of 260 images of complex lesions for the test, CAIDS was shown to be quicker and more accurate when comparing to 20 expert urologists, with an accuracy and sensitivity of 93.3% and 96.4%, respectively. Many more AI-based models have been produced which have shown high specificities and sensitivities for tumour detection and localisation[52–58], but studies have also shown that AI can also be valuable for tumour segmentation. Segmentation is important in outlining tumour borders, therefore aiding in both diagnosis and treatment, enabling more accurate tumour resections during TURBT. For example, Mataguchi et al. used an augmented version of a U-net model (a DL model consisting of two CNNs), where cystoscopy images were flipped and randomly rotated to increase image variability[59,60]. The model was validated using a small cystoscopy imaging dataset of 120 patients, and presented a pixel-wise sensitivity and specificity of 84.9% and 88.5%, respectively. While the clinical utility of tumour segmentation is yet to be fully established, it shows potential for assessing resection quality and guiding surgery[61–63]. Additionally, other innovations in cystoscopy-based data collection, such as automatic video annotation[64,65] and 3D reconstructions[66–69], can improve diagnostic accuracy, streamline clinical workflows, and facilitate personalised treatment planning through seamless integration into medical records. Combining these AI techniques – including classification, detection, segmentation, and image enhancement – we propose a multi-stage cystoscopy workflow that improves diagnostic accuracy and personalised treatment planning (Figure 1).

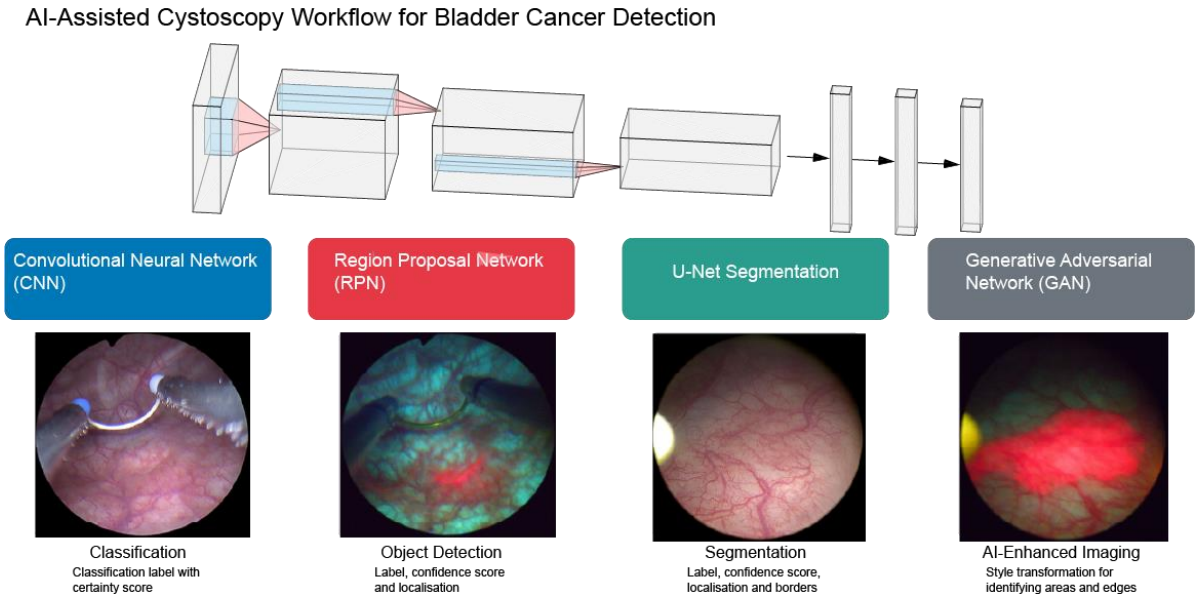

Figure 1: AI-Assisted Cystoscopy Workflow for Bladder Cancer Detection

This figure illustrates an AI-driven cystoscopy workflow for detecting bladder cancer. The process involves multiple deep learning models: a Convolutional Neural Network (CNN) for classification, a Region Proposal Network (RPN) for object detection, a U-Net model for segmentation, and a Generative Adversarial Network (GAN) for AI-enhanced imaging. Each stage progressively refines the analysis of cystoscopic images, providing classification labels, confidence scores, object localisation, and segmentation borders, while AI-enhanced imaging improves visual clarity for identifying lesions.

Although AI can help reduce interobserver variability and improve diagnostic precision, allowing clinicians to make better-informed decisions, its integration into clinical pathways remains a challenge. AI in cystoscopy faces barriers including limited data diversity, which affects model generalisability across institutions, the lack of specialised software and hardware, and the need for standardisation to assess the quality of studies[41]. Fortunately, the development of AI systems in other endoscopic fields, such as gastrointestinal endoscopy and colonoscopy, provides a valuable framework for the development of AI models in cystoscopy[70,71].

Blue light cystoscopy

Unlike the aforementioned AI models, blue light cystoscopy (BLC) and narrow-band imaging are enhanced cystoscopy options that are already approved for clinical use. BLC, sometimes referred to photodynamic diagnosis (PDD) uses hexaminolevulinate (HAL), a lipophilic derivative of 5-aminolevulinic acid[72]. Tumour cells of epithelial origin preferentially accumulate fluorescent porphyrins when exposed to HAL, which fluoresces red under blue light, enabling selective visualisation of malignant cells that white light cystoscopy (WLC) often misses[73]. This approach is particularly effective for detecting CIS and small papillary tumours[35,74,75].

Initial studies established the superiority of BLC over WLC. A pilot study in 1996 demonstrated significantly higher sensitivity for bladder cancer detection using BLC (96.9% vs. 72.7%, $P < 0.0001$)[76]. Subsequent trials refined its clinical application, confirming improved detection rates. A meta-analysis by Burget et al. revealed that BLC identified Ta or T1 tumours missed by WLC in 24.9% of cases and CIS in 26.7% of cases[35]. Large multicentre studies corroborated these findings, showing BLC improved detection rates for papillary lesions by 12% and CIS by 43%[74]. BLC has also proven beneficial for identifying recurrences after intravesical BCG therapy and for in-office surveillance, detecting recurrences missed by WLC in 20.6% of patients, including 5 cases of CIS[75,77].

Although BLC significantly improves detection and reduces recurrence rates, its impact on disease progression is less definitive[78,79]. Other systematic reviews have shown decreased recurrence rates with the use of BLC compared to WLC.[79–83]. However, evidence for reducing progression to MIBC is inconsistent[84]. The PHOTO trial, a randomised prospective trial, randomly assigned a group of 538 patients with an initial clinical diagnosis of intermediate-/high-risk NMIBC to undergo either white light or blue light resection at several UK centres[85]. Results did not find a difference in recurrence or progression rates over 44 months in intermediate- and high-risk NMIBC patients undergoing initial TURBT with BLC versus WLC. However, CIS was present in only 13% of the resection specimens of patients enrolled in the trial; which means the key group in which blue light detects the most “missed” tumours was under-represented in the study. Additionally, the trial was published before enrolling the full number of patients for adequate power to detect a significant difference between groups. Moreover, it's important to note that while no significant difference in recurrence was observed at 44 months, BLC demonstrated improved recurrence rates at 12 months—suggesting that beyond this period, the influence of tumour biology may outweigh the early benefits gained by BLC.

Guidelines acknowledge the utility of BLC but stop short of recommending it as the standard of care. The American Urological Association (AUA) advises its use during TURBT to enhance detection and reduce recurrence in non-muscle-invasive bladder cancer (NMIBC)[24]. Similarly, the European Association of Urology (EAU) recommends BLC for patients with positive cytology but negative WLC findings[25,86]. However, the lack of consistent evidence for progression

reduction and high initial costs has constrained its broader adoption[87–89]. Despite these upfront costs, studies have shown that the associated reduced recurrence rates lead to significant long-term cost savings by decreasing the need for repeat procedures and surveillance interventions[90,91]. The integration of BLC with AI has been proposed to address its limitations by enhancing its precision, improving cost-efficiency, and addressing challenges such as operator dependency and variability. For example, Ali et al. trained CNN models using 216 images and demonstrated their ability to classify malignancy, grade and stage of BLC images with high sensitivity (95.77%, 88% and 92.07%) and specificity (87.84%, 92.56% and 96.0%)[92], outperforming urologists by 15%, 50% and 40%, respectively. These results imply a great potential for the future of bladder cancer management, perhaps where AI could make BLC a more standard and essential diagnostic tool.

Narrow Band Imaging

Narrow band imaging (NBI), on the other hand, enhances vascular contrast by using specific light wavelengths absorbed by haemoglobin[93]. This highlights the hypervascularity associated with malignancy, aiding in the detection of flat and subtle bladder tumours without requiring an exogenous imaging agent. A meta-analysis by Li et al. consisting of 1,040 patients demonstrated that NBI identified additional cancers in 17% of patients and additional tumours in 24% of cases compared to WLC[94]. However, false positives were slightly higher with NBI, though not statistically significant in pooled analyses. A 2012 randomised prospective trial reported significantly lower recurrence with NBI (32.9% vs. 51.4%, P = 0.01), but a larger multicentre trial showed no significant difference (25.4% NBI vs. 27.1% WLC, P = 0.585)[95,96]. Sub-analyses suggested reduced recurrence for low-risk cancer patients only.

Owing to inconsistent data, both the AUA and EAU offer only conditional recommendations for NBI use[8,25]. The AUA suggests clinicians "may consider" NBI to improve detection and reduce recurrence, though its routine use is not widely endorsed[24]. As seen in BLC, AI could optimise NBI by improving image interpretation, reducing false positives, and standardising its application. For instance, Ikeda et al. used a dataset of 6,523 WLC and 1,636 NBI images to create a model based on the DL model ResNet50 pre-trained using ImageNet[97]. Defining accurate detection as a >50% overlap between the annotated lesion area and the AI estimated lesion are, results showed an average sensitivity, specificity and F1 scores were 83.7%, 82.3% and 0.637, respectively. As with BLC, AI could therefore allow NBI to become a more routine test for clinicians to use, allowing for more accurate diagnoses and therefore help improve decision-making in bladder cancer management. Next steps include validating these models for correct implementation into clinical workflows.

IMAGE1 S CHROMA

The IMAGE1 S CHROMA system enhances cystoscopic imaging by improving contrast and highlighting mucosal abnormalities, leading to better visualisation of bladder tumours[98]. Compared to WLC, CHROMA has demonstrated superior detection rates, particularly for subtle lesions that may otherwise go unnoticed, ultimately improving the completeness of TURBT. CHROMA enhances image contrast by analysing local colour differences, providing a sharper and clearer view of bladder lesions compared to conventional WLC. A prospective trial of 49 patients undergoing TURBT found that CHROMA detected an additional 25 tumours (15.2%) that were not visible under WLC, leading to an additional detection rate of 36% (95% CI: 21%–

53%)[99]. CHROMA was equally effective in detecting low-grade (43%) and high-grade (44%) tumours, demonstrating its utility across different tumour types. Furthermore, it was particularly effective at identifying lesions in challenging locations such as the bladder dome and anterior wall, where nearly a quarter of lesions were only seen with CHROMA.

By improving tumour detection, CHROMA helps reduce the likelihood of incomplete resections, a major factor in NMIBC recurrence. In a randomised clinical trial, the recurrence rate after TURBT with IMAGE1 S was 12.2%, compared to 25.9% with WLC alone[100]. Additionally, recurrence rates were significantly lower for patients in the low and intermediate-risk groups with CHROMA (7.7% vs. 30.8%, p = 0.003). These findings suggest that integrating CHROMA into routine bladder cancer management could significantly reduce the risk of early tumour recurrence and improve long-term patient outcomes. Unlike BLC, which requires preoperative intravesical dye instillation, or NBI, which requires dedicated hardware, CHROMA is seamlessly integrated into existing surgical workflows. Given its ability to improve detection rates, reduce recurrence, and optimise surgical outcomes without additional procedural complexity, CHROMA represents a cost-effective and practical enhancement to standard bladder cancer management (Table 1). These findings are based on preliminary evidence, and further research is needed to validate its efficacy and clinical utility.

Technology	Description	Key Findings	Limitations
Blue Light Cystoscopy (BLC)[35,77]	Uses hexaminolevulinate (HAL) to make tumour cells fluoresce red under blue light, enhancing lesion detection.	Improves detection of Ta/T1 tumours (24.9%) and CIS (26.7%) missed by WLC	High cost of HAL; logistical challenges with bladder instillation; mixed evidence on progression reduction.
Narrow Band Imaging (NBI)[93,94]	Enhances vascular contrast using specific light wavelengths to highlight hypervascularity in malignant tissue.	Detects additional cancers in 17% of patients and tumours in 24% of cases compared to WLC; reduced recurrence for low-risk tumours.	Increased false positives; mixed evidence for recurrence reduction in high-risk patients.
IMAGE1 S CHROMA[98]	Image-processing technology enhancing vascular lesion contrast without using an exogenous imaging agent.	Improved tumour detection and lower recurrence rates in early studies.	Preliminary evidence; further research needed to validate efficacy and clinical utility.

Table 1: Summary of enhanced cystoscopic imaging modalities for bladder cancer detection.

This table compares three advanced cystoscopy techniques—Blue Light Cystoscopy (BLC), Narrow Band Imaging (NBI), and IMAGE1 S CHROMA—highlighting their mechanisms of action, key diagnostic findings, and current limitations.

Cytology and urinary markers

An alternative and much more cost-effective first-line diagnostic tool to cystoscopy could be cytology. Urinary cytology analyses exfoliated urothelial cells in the urine to detect malignant changes[44]. Urine, being in continuous contact with bladder cancer tissues, is a valuable source of tumour-related information. Urinary cytology, the most widely used urinary marker, is recommended as an adjunct to cystoscopy in clinical practice, with a sensitivity of 48% and specificity of 86%[101]. While highly sensitive for high-grade tumours and carcinoma in situ (84%), it performs poorly for low-grade tumours (16%) and is affected by interobserver variability and confounding factors like infections or urolithiasis[101–103]. As a result, in 2016, the Paris Working Group published a standardised reporting system redefining diagnostic categories for cytology, which was subsequently validated in retrospective studies[104,105]. Cytology is still a long way from becoming a first-line diagnostic tool, but it may be helpful as a complimentary test for high-grade grade tumours. Furthermore, in experienced hands, the specificity exceeds 90%[106].

Driven by the low sensitivity of urine cytology, recent advancements in "liquid biopsy" technology have identified a range of potential urinary markers, including those based on proteins, exfoliated cells, RNA, DNA, and extracellular vesicles[44,107]. Despite FDA approval and commercial availability for some markers, the AUA and EAU guidelines describe a “limited role” for urinary biomarkers to replace cystoscopic surveillance but acknowledge that this field “holds promise” for the future[24,25]. The FDA has approved two protein-based markers, BTA (Bladder Tumor Antigen) and NMP22 (Nuclear Matrix Protein 22), and two cell-based markers, ImmunoCyt/uCyt+ and UroVysion, for clinical use. Although providing rapid results, the protein-based markers BTA and NMP22 suffer from limited sensitivity for low-grade bladder cancer, with 36% and 25%, respectively[101]. However, the two cell-based markers, ImmunoCyt/uCyt+ and UroVysion, show better sensitivities with 74% and 63%, respectively[108]. Unfortunately, their cost, time and reliance on expert interpretation limit their use to just supplementing diagnostic information.

Many emerging urinary markers are being developed which tackle the restrictions of the approved urinary markers, including protein-, cell-, DNA-, RNA-, and extracellular vesicle (EV)-based markers[107] (Table 2). Recent advancements in genomics and proteomics have allowed proteins, mRNA expressions, DNA mutations, methylation, and copy number alterations to be targets of analysis. This has shifted urinary marker assays toward multiplex genomic and transcriptomic approaches, improving diagnostic performance. Some markers are commercially available and undergoing prospective validation, with non-coding RNA and EVs emerging as promising targets for further research. One example are the Cxbladder assays, which are mRNA-based diagnostic urinary biomarker tests that can be used for risk stratification of patients presenting with haematuria (Cxbladder Detect and Cxbladder Triage) and the surveillance of patients with previously treated bladder cancer (Cxbladder Monitor)[109–112]. Cxbladder assays quantify the mRNA of 5 biomarkers (CDK1, MDK, IGFBP5, HOXA13, CXCR2), demonstrating moderate sensitivity (77%) and high specificity (94%) with Cxbladder Detect[109]. A recent multicentre randomised controlled trial evaluated the role of Cxbladder Triage in the initial work-up of patients presenting with microhaematuria[113]. In patients classified as lower-risk by pre-2020 AUA criteria, use of the assay reduced the proportion of patients undergoing cystoscopy to 27% (from 67% in the standard-of-care arm). Importantly, Cxbladder

Triage achieved a sensitivity of 90% and a negative predictive value of 99%, providing overwhelming support for its potential use in deferring invasive testing in carefully selected patients. However, it is worth noting that the study design did not require confirmatory cystoscopy in all participants, leaving the true-negative rate uncertain. Furthermore, specificity was low (56%), raising concerns about unnecessary downstream investigation in cases of false-positive results. The risk stratification applied also predates the 2020 AUA microhaematuria guidelines, meaning that a proportion of patients labelled as "low-risk" in the trial would now be considered intermediate or even high-risk. These limitations suggests that we cannot yet rely on this to replace cystoscopy as a first-line investigation; however, the evidence does indicate that with further refinement and validation, urinary markers may have a role in the initial investigation of bladder cancer.

Marker Name	Test Type	Sensitivity (%)	Specificity (%)	FDA-Approved	Target Marker(s)
BTA-Stat[114,115]	Protein-based	64	77	Yes	Human Complement Factor H-related Proteins (hCFHrp)
BTA-TRAK[115]	Protein-based	65	74	Yes	Human Complement Factor H-related Proteins (hCFHrp)
NMP22 BladderChek[114,115]	Protein-based	58	88	Yes	Nuclear Matrix Protein 22 (NMP22)
NMP22 Bladder Cancer ELISA-Test[115]	Protein-based	69	77	Yes	Nuclear Matrix Protein 22 (NMP22)
ImmunoCyt/uCyt+[115]	Exfoliated cell-based	78	78	Yes	Mucin Antigens (MAUB), carcinoembryonic antigen (CEA)
UroVysion[115,116]	Exfoliated cell-based	63	87	Yes	Chromosomal abnormalities (3, 7, 17, 9p21)
BLCA-4[117]	Protein-based	93	97	No	Bladder Cancer Antigen (BLCA-4)
ADXBLADDER[116]	Protein-based	61	67	No	Mini Chromosome Maintenance 5 (MCM5)
Oncuria[118]	Protein-based	93	93	No	10 Urinary Proteins (e.g., IL-8, vascular endothelial growth factor (VEGF), matrix metallopeptidase (MMP9))

Uro17[119,120]	Exfoliated cell-based	100	92.6	No	Keratin 17 (Cytokeratin 17)
CellDetect[121,122]	Exfoliated cell-based	84	70	No	Metabolic Activity in Cancer Cells
Xpert Bladder Cancer Monitor[123]	mRNA-based	60.3	76.5	No	5 mRNAs: ABL1, CRH, IGF2, UPK1B, ANXA10
Cxbladder Detect[109]	mRNA-based	77	94	No	5 mRNAs: CDK1 (CDC2), MDK, IGFBP5, HOXA13, CXCR2.
Bladder EpiCheck[124]	DNA methylation	68	88	No	15-locus methylation signature.
AssureMDx[125]	DNA methylation + mutations	93	86	No	Methylation**:** OTX1, ONECUT2, TWIST1. Mutations**:** FGFR3, TERT, HRAS.
UroSEEK[126,127]	DNA mutations + aneuploidy	95 (with cytology)	93 (with cytology)	No	TERT promoter + 10 genes (FGFR3, TP53, PIK3CA, ERBB2, HRAS, KRAS, CDKN2A, MET, VHL, MLL) + aneuploidy.
UroAmp[128]	Urine cfDNA NGS	95	90	No	Somatic SNVs/INDELs/CNVs/LOH + aneuploidy across recurrent UC genes.

Table 2: Diagnostic Performance of Urinary Biomarkers for Bladder Cancer Detection and Surveillance

The table summarises the diagnostic characteristics of various urinary biomarkers utilised in bladder cancer management, highlighting their test type, sensitivity, specificity, FDA approval status, and targeted biological markers. Sensitivity and specificity values reflect the performance of each marker based on clinical studies.

As with cystoscopy, there is hope for AI to improve the diagnostic accuracy of cytology and urinary markers[40]. Sanghvi et al. developed a computational pipeline for processing digitised liquid-based urine cytology slides using CNN models trained on 1,615 whole slide images (WSIs) and tested on 790 WSIs, achieving an AUC of 0.88[129]. Shao et al. trained a decision tree (DT) classifier using metabolomics data from mass spectrometry of urine samples, achieving a sensitivity of 0.72 and specificity of 0.87 with six metabolite markers[130]. In the French multicentre VISIOCYT1 trial, authors digitised urine cytology slides and applied a fully automated deep-learning pipeline to segment urothelial cells and quantify nuclear morphology

to generate a slide-level score[131]. In the validation phase, they reported an overall sensitivity of 80.9% (93.7% high-grade; 66.7% low-grade) with a specificity of 61.8%, whereas standard cytology achieved a 100% specificity in the study's preselected control cohort[132]. Although sensitivity gains are encouraging, spectrum and verification biases (controls defined by negative cytology, non-centralised histology, and allocation of cytology-positive cases to the cancer group) and the modest specificity argue for independent external validation and formal cost-effectiveness analyses before altering surveillance pathways. On the contrary, Sokolov et al. used atomic force microscopy (AFM) nano-resolution images of urine cells, achieving 94% accuracy with DT-based models analysing five cells per sample[133]. It should be noted, however, that AI models based on cystoscopy data generally outperform the urine-based AI models. This proves there is still a lot that remains in the progress of cytology in bladder cancer management.

Nevertheless, urinary cytology remains an invaluable tool in bladder cancer diagnostics, particularly for high-grade lesions. However, successful integration into clinical practice demands large-scale validation, regulatory approval, and clinician training. Future research should prioritise developing user-friendly, cost-effective tools that combine cytology, molecular diagnostics, and AI to create a cohesive and multi-modal diagnostic framework. By leveraging these advancements, cytology can transcend its traditional limitations and potentially replace invasive methods like cystoscopy, evolving into a cornerstone of precision oncology in bladder cancer management.

Staging and risk stratification

Advances in histopathological analysis

Once a tumour is suspected or detected, histopathological evaluation remains the gold standard for diagnosing and staging bladder cancer, providing valuable information regarding tumour grade and depth of invasion. However, traditional histopathological assessment is not without its limitations. Interobserver variability, particularly in borderline cases of NMIBC and MIBC, can lead to inconsistencies even for experienced pathologists[134]. Additionally, routine histopathological analyses can be time-intensive, and although effective, haematoxylin and eosin (H&E) staining provides limited molecular information. The growing demand for more efficient and accurate diagnostic methods has increased interest in AI-driven histopathology solutions. For instance, Chen et al. developed an ML-based pathomics model capable of diagnosing bladder cancer trained on 643 H&E-stained bladder cancer images[135]. Their study reported impressive diagnostic accuracy, with AUC values of 96.3%, 89.2%, and 94.1% in the training, test, and external validation cohorts, respectively. In addition, their model accurately distinguished bladder cancer from glandular cystitis (AUC = 93.4%), as well as predicted overall survival (AUC values of 77.7%, 83.8%, and 81.3% for 1-, 3-, and 5-year survival predictions).

Next, determining whether a tumour has invaded the muscle layer of the bladder is a critical step in staging and treatment planning. Misclassification can lead to suboptimal treatment—understaging can result in delayed radical treatment for MIBC, while overstaging can lead to unnecessary cystectomy in NMIBC patients. AI-based models have demonstrated promising accuracy in distinguishing NMIBC from MIBC. Pan et al. applied the DL model ScanNet to histopathological images to classify tumours based on invasion depth[136]. In distinguishing non-

invasive (Ta/T1) from muscle-invasive (T2+) disease, their AI-driven approach performed better than junior pathologists but slightly worse than senior pathologists. Similarly, Yin et al. developed a feature-centred ML model that effectively differentiated NMIBC from MIBC using WSIs[137]. Their models were able to differentiate between Ta and T1 tumours (accuracy of 91-96%), which can look very similar under a microscope, by identifying subtle histological features associated with muscle invasion. By providing a consistent and standardised approach to muscle invasion detection, AI models can improve staging accuracy, ensuring that MIBC patients are promptly referred for radical treatment while minimising overtreatment of NMIBC cases.

Beyond staging, accurate tumour grading is essential for risk stratification in bladder cancer, particularly in NMIBC, where higher-risk patients are offered more aggressive treatments[24]. Shalata et al. developed a multi-scale pyramidal CNN based on ShuffleNet, which showed 94.47% sensitivity and 94.03% specificity when grading NMIBC, outperforming traditional models like ResNet-18[138]. Such models can, therefore, allow for more reliability in grading tumours, providing a more objective assessment of tumour aggressiveness and reducing interobserver variability. Another way to tackle this is by applying AI to tumour segmentation. Niazi et al., for example, used a twelve layer U-net model to segment WSIs of T1 bladder biopsies, which aided pathologists by reducing the time needed to annotate slides[139]. This study exemplifies the idea that AI-based models should not be designed to replace human expertise—but to augment the expertise of clinicians[140]. Consequently, there is a need to foster collaboration between AI system creators and clinicians to co-design these models. Prospective clinical trials are still needed to validate AI pathomics models before full clinical adoption. Still, these studies highlight the potential of AI-powered histopathology to complement, rather than replace, traditional histopathological assessment.

Multi-parametric MRI and VI-RADS

Many tumours are under-staged by TURBT, and complications include bladder perforation, re-admission, reoperation and post-TURBT tumour dissemination[141–145]. This welcomes complimentary improvements in imaging such as ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI)[146,147]. Of these imaging techniques, only MRI provides the best tissue contract for differentiating NMIBC from MIBC[47,148]. However, using MRI in the diagnostic workup of bladder cancer has been limited, particularly due to non-standardised magnetic resonance image acquisition and reporting[149–151]. To unify these standards, the Vesical Imaging-Reporting and Data System (VI-RADS) was developed in 2018, which scores the likelihood of muscle invasion in bladder cancer from 1 to 5, based on multiparametric MRI (mpMRI)[48]. mpMRI combines T2-weighted (T2W), diffusion-weighted imaging (DWI), and dynamic contrast-enhanced (DCE) sequences to provide a more accurate visualisation of the bladder wall and surrounding tissues (Figure 2). The assessment of detrusor muscle invasion is critical for accurate staging, management and prognostication of bladder cancer[152]. A recent meta-analysis investigated the diagnostic accuracy of VI-RADS to predict pre-TURBT muscle-invasiveness, consisting of 20 studies and 2,477 participants. Pooled weighted sensitivity and specificity were 0.87 (95% CI 0.82–0.91) and 0.86 (95% CI 0.80–0.90) for cut-off ≥ 3 while 0.78 (95% CI 0.74–0.81) and 0.94 (95% CI 0.91–0.96) for cut-off ≥ 4. This demonstrated excellent worldwide diagnostic performance of VI-RADS in determining pre-TURBT staging. VI-RADS is now available in some centres of expertise but it is not yet recommended as a first-line test for bladder cancer due to the lack of high-quality evidence[153]. AUA guidelines acknowledge that VI-

RADS "may lead to a decrease in the burden of re-TURBT and improved selection of patients with MIBC for more appropriate therapy", but only if it proves to be "reproducible"[24]. This highlights the potential of VI-RADS to aid clinicians in decision-making, but further validation is still needed. Until further evidence from randomised controlled trials becomes available, consensus-based evidence could serve as a benchmark for formulating guidelines[153].

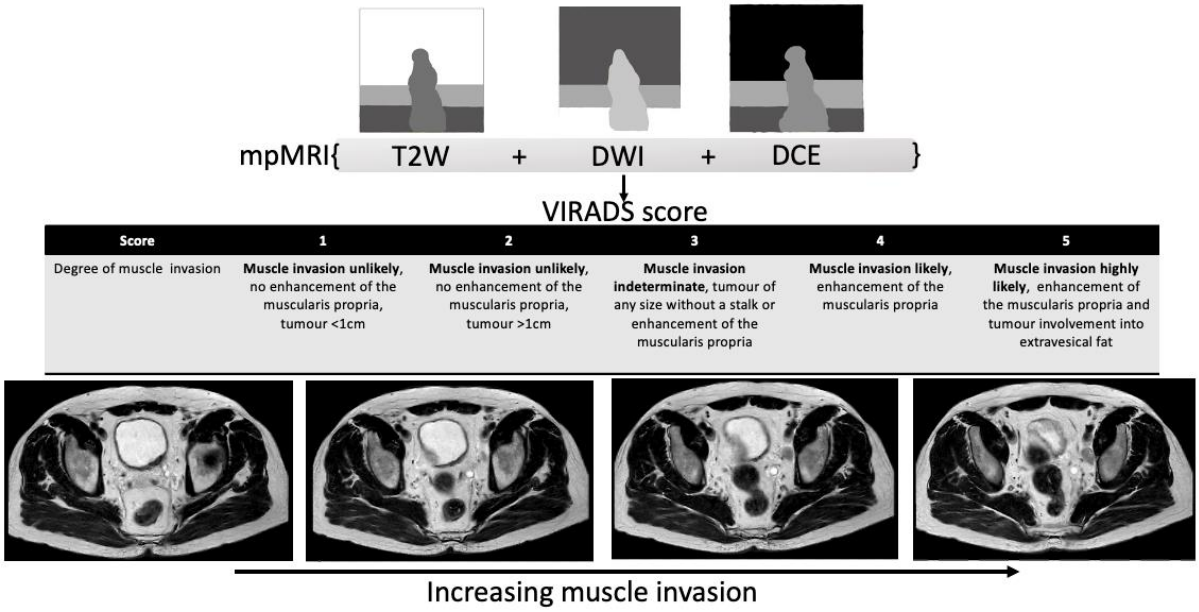

Figure 2: The Vesical Imaging-Reporting and Data System (VI-RADS) for Assessing Muscle Invasion in Bladder Cancer

The figure illustrates the Vesical Imaging-Reporting and Data System (VI-RADS), a multiparametric MRI-based scoring system used to predict muscle invasion in bladder cancer. VI-RADS integrates T2-weighted (T2W), diffusion-weighted imaging (DWI), and dynamic contrast-enhanced (DCE) sequences to assign a numerical score (1–5) indicating the likelihood of muscle invasion. A lower score (1–2) suggests that muscle invasion is unlikely, with minimal or no muscularis propria enhancement, while a higher score (4–5) indicates likely or highly likely muscle invasion, characterised by clear enhancement and possible extravesical extension. Score 3 indicates indeterminate cases, requiring additional investigation to confirm muscle invasion status. Examples of MRI images illustrating tumour characteristics at each VI-RADS score demonstrate increasing muscle invasion from left (VI-RADS 1) to right (VI-RADS 5), highlighting the utility of VI-RADS in improving preoperative staging and facilitating personalised treatment planning.

More recently, Bryan et al. proposed a novel pathway where patients with suspected MIBC can be treated sooner by staging the tumour using flexible cystoscopy followed by mpMRI, instead of TURBT[154]. Although TURBT is the first-line treatment for NMIBC, it is just a diagnostic procedure for MIBC. Alongside the previously mentioned complications, TURBT has also been shown to impede accurate staging by CT or MRI due to perivesical inflammation and reactive lymph nodes being mistaken for tumour extensions and metastases[155,156]. Given this, Bryan et al.'s randomised controlled trial conducted across 17 UK hospitals and 143 participants demonstrated that the mpMRI-directed pathway expedited treatment for MIBC by reducing the time to correct treatment (TTCT) by 45 days compared to the TURBT-first pathway. The trial emphasised that mpMRI is feasible, with 92% of eligible participants completing the mpMRI pathway, and showed no detriment to patients with NMIBC. Furthermore, mpMRI is approximately one-tenth the cost of TURBT, highlighting it as a more economical and efficient pathway while being less invasive[154]. Despite initial scepticism, the integration of mpMRI in the prostate cancer pathway has shown that there is now widespread recognition that more

accurate imaging improves clinical decision-making[157]. For bladder cancer, often managed by the same teams, the introduction of mpMRI is likely to be more straightforward, as clinicians are increasingly becoming more confident in using mpMRI to guide downstream decisions. However, even though the diagnostic performance of mpMRI and VI-RADS is encouraging, TURBT remains the standard for establishing histological confirmation of MIBC. This is particularly important given that radical cystectomy, often the treatment of choice for MIBC, is a highly morbid procedure. Reliance on imaging alone, therefore, carries a significant risk. For example, a VI-RADS 4 score has a positive predictive value of 79.5%, meaning that over one in five patients predicted to have MIBC on mpMRI would, in fact, have NMIBC[158]. In such cases, proceeding directly to cystectomy could lead to unnecessary overtreatment with significant consequences. As a result, despite promising data, it remains challenging to replace histology with mpMRI alone in making definitive management decisions.

Radiomics and AI

Alternatively, there is scope for AI and radiomics to enhance imaging in bladder cancer. Several AI-based models have been published that boast accurate staging of bladder cancer[159–165]. Xu et al., for example, employed a radiomics approach based on mpMRI[165]. They extracted 1,104 radiomics features from segmented tumour regions and used a support vector machine (SVM) with recursive feature elimination to build the model. The inclusion of synthetic minority oversampling techniques (SMOTE) helped address data imbalance between MIBC and NMBIC, resulting in an AUC of 0.99. This suggests that radiomics-based models could enhance preoperative decision-making by accurately distinguishing MIBC from NMIBC, reducing reliance on invasive procedures. More recently, Li et al. compared the ability of radiomics, single-task DL, and multi-task DL methods to predict muscle invasiveness on MRI data[163]. The multi-task model used the improved 3D-ResNet as the backbone network to design a multi-task segmentation and classification network similar to U-net. Although all three models exhibited good diagnostic performance in predicting MIBC preoperatively, the AUC of the multi-task model (0.932 and 0.932) significantly outperformed the radiomics (0.920 and 0.844) and single-task model (0.933 and 0.884) in both the training and test cohorts, respectively. Furthermore, the study highlighted that the multi-task model saved time and effort compared to the radiomics method, whilst it was more lesion-focused compared to the single-task DL method. This emphasises the clinical application of integrating multi-task frameworks for the accurate preoperative prediction of bladder cancer muscle invasiveness.

The application of AI and radiomics to more accurately stage bladder cancer is not limited to muscle invasion alone. Gresser et al. proposed a CT-based radiomics model using either manual or fully automated segmentation to detect lymph node metastases in bladder cancer patients[164]. The manual segmentation model outperformed automated segmentation, achieving an AUC of 0.80 compared to 0.70. This study therefore emphasises the potential of radiomics in non-invasive staging of bladder cancer, going as far as detecting lymph node metastases. However, there currently is limited research in this area, and more prospective multi-centre studies are needed to validate this approach.

Ultrasound is a non-invasive, cost-effective diagnostic tool with high sensitivity and specificity for bladder cancer, offering advantages over invasive cystoscopy in certain cases[166,167]. The integration of AI with ultrasound enhances diagnostic accuracy by analysing images in detail, identifying subtle early-stage lesions, reducing human subjectivity, and providing objective

diagnostic support[49]. Gao et al. developed a radiomics model using ultrasound images from 157 patients to predict tumour stage and pathological grade[168]. For tumour staging, the model achieved AUCs of 0.94 and 0.84 in the training and validation sets, respectively, while for grading, it achieved AUCs of 0.84 and 0.75. These models demonstrated strong predictive ability, offering a non-invasive, reliable and economical tool for preoperative staging and grading, allowing for effective risk stratification of patients. In general, radiomics holds promise in bladder cancer staging, grading and segmentation, offering a pathway to precision medicine. However, there is still a need for refining the standardisation of image preprocessing, feature extraction and external validation before applying radiomics models in the clinical setting[46].

Genomics

Malignant transformation of normal cells is a complex, multifactorial process involving numerous genomic alterations. Each stage of bladder cancer development is driven by distinct molecular mechanisms and epigenetic dysregulation. Decoding the human genome is pivotal for decision-making and personalising cancer management. In recent years, advancements in understanding the genetic basis of bladder cancer and its molecular landscape have accelerated exponentially.

In the 1990s, polymorphic DNA markers for bladder cancer were identified and analysed manually[169]. Today, advanced technologies such as whole-exome sequencing and transcriptomic analyses provide comprehensive insights into the genomic heterogeneity of bladder cancer, allowing classification into subgroups with distinct molecular profiles[170]. Genomics is not only critical for identifying potential pharmacological targets or estimating prognosis but also for reshaping every aspect of decision-making in managing bladder cancer patients.

The first and arguably most critical step in cancer management occurs even before malignancy is detected. Identifying high-risk patients for screening enables early detection and prevention. Yu et al. analysed genome-wide single nucleotide polymorphism (SNP) interactions using ML and identified 10 SNP-SNP interactions associated with bladder cancer risk[171]. They proposed a screening model incorporating an interaction-empowered polygenic risk score (iPRS) based on these newly identified interactions. This study represents a progression from earlier discoveries on SNPs associated with bladder cancer risk to exploring genomic interactions[172]. Recent studies identified additional SNP-SNP interactions, paving the way for future research that integrates larger datasets[173].

After identifying high-risk patients, an effective and non-invasive bladder cancer screening method is needed. Silva-Ferreira et al.'s meta-analysis highlighted urinary DNA methylation-based biomarkers as highly accurate for diagnosing bladder cancer[174]. Although these biomarkers still require clinical validation, they represent a promising step toward affordable and rapid bladder cancer screening. Additionally, De Jong et al.'s research demonstrated that genomic urine assays can detect urinary tract recurrences after treatment in patients with muscle-invasive bladder cancer (MIBC)[175]. This suggests that genomic urine assays could serve as a screening modality throughout a bladder cancer patient's treatment journey.

Most bladder cancers originate from precursor lesions in the urothelium but may develop into distinct histological and molecular subtypes, including micropapillary, plasmacytoid, small-cell carcinoma, and sarcomatoid. Microscopically, papillary tumours are often non-invasive but

have a high recurrence rate, whereas non-papillary carcinomas are more likely to be invasive, with poorer prognoses[176]. Identifying the histology of bladder cancer is crucial for ongoing treatment planning. As summarised by Guo et al. and Olislagers et al.'s reviews, recent genomic advancements have identified molecularly distinct bladder cancer subtypes with clinically significant prognostic implications[177,178]. Zhang et al. reported key genes in bladder cancer patients with more than 10 methylation sites as independent prognostic factors[179]. Future studies may incorporate epigenetic changes to construct molecular subtypes for bladder cancer.

Genomic studies, when integrated with proteogenomic and transcriptomic analyses, can provide a more comprehensive understanding of the molecular pathways leading to cancer development. Groeneveld et al. analysed proteomic, transcriptomic, and genomic data from 40 MIBC and 23 NMIBC samples[180]. They identified five proteomic groups and linked specific genomic variations to biological processes such as DNA repair and lipid metabolism. Additionally, FGFR3-mutated tumours showed a higher abundance of apoptosis proteins, suggesting the potential of TRAIL (tumour necrosis factor-related apoptosis-inducing ligand) for treating NMIBC. Dressler et al. analysed proteomic data from 434 samples, encompassing all stages of urothelial bladder cancer[181]. They identified five proteomic groups reflecting the tumour's biological spectrum, providing additional prognostic information. Future studies should focus on linking bladder cancer-associated genes to their biological implications and utilising clustering to refine prognosis and treatment strategies. Utilising genomic data, alongside radiomics, pathomics and imaging, is therefore important in fully understanding the clinical picture of bladder cancer patients, allowing for more personalised decision-making (Figure 3).

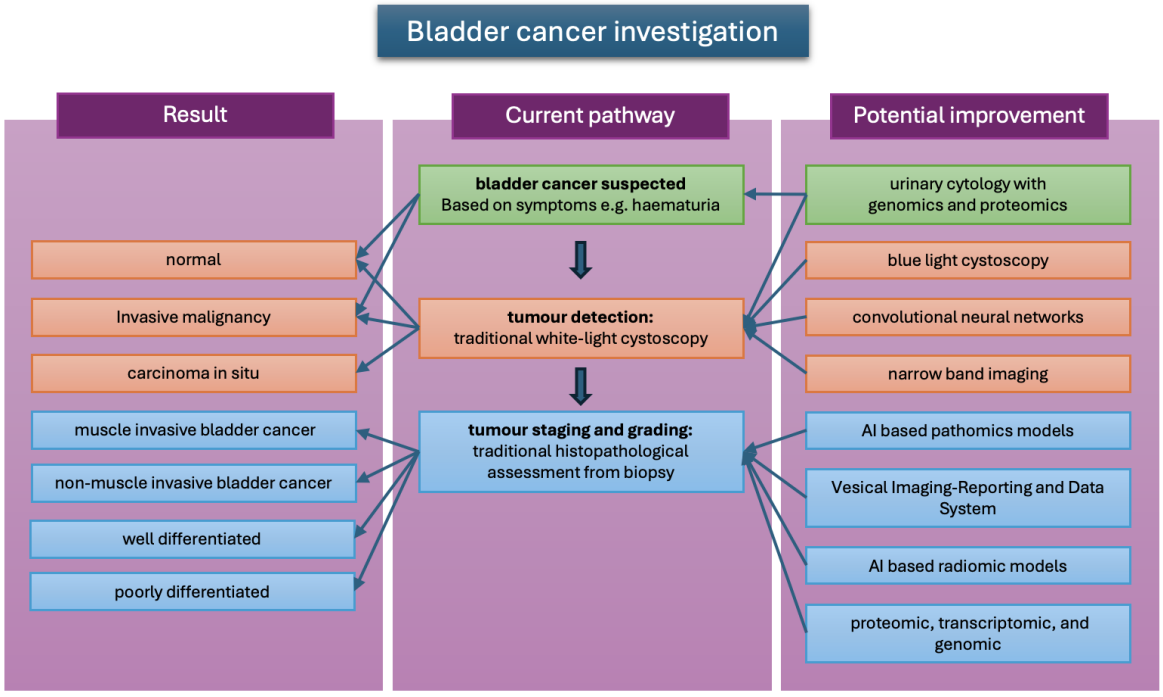

Figure 3: Clinical decision-making flowchart showing how emerging technology can be used at each stage of detecting and investigating bladder cancer.

This diagram outlines the diagnostic pathway for bladder cancer, beginning with initial suspicion based on symptoms (e.g., haematuria), followed by tumour detection using traditional white-light cystoscopy, and concluding with tumour staging and grading via histopathological assessment. Results can range from benign findings to invasive or non-

invasive malignancies, with differentiation status also noted. Potential improvements using emerging technologies are highlighted at each stage, including urinary cytology enhanced by genomics and proteomics, advanced imaging methods (e.g., blue light cystoscopy, narrow band imaging), and artificial intelligence applications such as convolutional neural networks and AI-based pathomics and radiomic models. These advancements aim to enhance diagnostic accuracy, streamline workflows, and improve personalised treatment strategies.

Advances in treatment planning and selection

Emerging advancements in risk stratification, treatment selection, and recurrence prediction of NMIBC

The high recurrence rates associated with NMIBC necessitate frequent surveillance, repeated intervention, and, in some cases, escalated treatment such as radical cystectomy. This means that accurate decision-making, planning and treatment selection are crucial to maximise patient outcomes. Current limitations include inconsistent risk stratification, reliance on tools that may miss subtle high-risk lesions, and challenges in tailoring treatment to the heterogeneity of disease presentations. Existing recurrence risk calculators, such as EORTC and CUETO scores, remain suboptimal, as they do not adequately capture tumour heterogeneity[182]. Emerging technologies, including AI and radiomics, have the potential to address these limitations and enable clinicians to refine decision-making at every stage of the workflow—risk stratification, treatment selection, and recurrence prediction. Now, clinicians have additional foresight into the prognostic implications of various treatments and can personalise treatment selection in higher-risk patients to improve their outcomes.

Risk stratification is guided by clinical and pathological criteria outlined by organisations such as the AUA and the EAU, which categorise patients into low-, intermediate-, and high-risk groups based on factors such as tumour size, grade, recurrence, and presence of CIS[24,25]. Recent advancements in computational pathology have introduced weakly supervised deep-learning models to enhance histopathological grading, thereby improving risk stratification. The NMGrad model, as described by Fuster et al., utilises CNNs and attention-based learning to analyse WSIs of urothelial carcinoma[183]. By extracting features at different magnification levels and identifying high-risk regions within a slide, NMGrad demonstrated superior grading accuracy (F1 score: 0.85) compared to traditional methods. The model provides explainability through heatmaps, highlighting regions of interest contributing to malignancy classification. This approach reduces interobserver variability and enables more consistent and objective grading of NMIBC, ensuring that high-risk patients are appropriately identified and managed.

Traditional risk stratification relies on structured data from pathology reports, but unstructured electronic health records (EHRs) contain valuable, often underutilised information. Narayan et al. developed a Natural Language Processing (NLP) model to extract high-risk NMIBC features from EHRs, achieving a sensitivity of 83.7% and specificity of 91.1% in identifying high-risk cases[184]. The model successfully classified patients based on criteria such as T1 disease, tumour multifocality, and CIS, providing a real-world tool for large-scale patient screening and registry development. By automating the identification of high-risk patients, this approach improves the efficiency of clinical workflows and ensures timely intervention for patients at greatest risk of recurrence or progression.

Yang et al. developed a radiomics-clinical nomogram incorporating multi-sequence MRI to predict recurrence-free survival (RFS) in NMIBC patients[185]. The study extracted radiomic

features from T2W, DWI, ADC and DCE images, identifying imaging biomarkers that significantly correlated with recurrence risk. Their integrated radiomics-clinical model outperformed traditional recurrence risk calculators such as EORTC and CUETO scores, achieving a C-index of 0.853 in the training set and 0.832 in validation. This enhanced stratification allows clinicians to differentiate between high- and low-risk patients more effectively, guiding personalised surveillance intensity and adjuvant therapy selection. With this predictive capability, low-risk patients can avoid unnecessary interventions, while high-risk individuals receive timely and intensified treatment, reducing the likelihood of disease progression. Wang et al. took a different approach by developing a deep learning-based pathomics model to predict early NMIBC recurrence using WSIs[186]. Their model utilised a two-phase prediction system, first analysing images at the patch level and then aggregating predictions to a WSI-level recurrence probability score. The model, trained on a multi-institutional dataset, demonstrated an AUC of 0.860 in the test cohort, outperforming existing histopathology-based risk assessments. Notably, it provided explainable AI-based insights by highlighting key histopathological features most predictive of recurrence, offering an additional layer of interpretability to AI-assisted decision-making. This predictive accuracy can refine post-TURBT treatment plans by identifying high-risk patients who may require early radical cystectomy or adjuvant intravesical therapy, while avoiding overtreatment in low-risk individuals.

Perhaps the most important contribution to the surveillance setting comes from the DaBlaCa-15 randomised non-inferiority trial, which tested whether alternating cystoscopy with the Xpert Bladder Cancer Monitor (XBCM) could safely reduce surveillance intensity in patients with high-grade bladder cancer[187]. The trial demonstrated that recurrence-free survival at 24 months in the study arm was non-inferior to standard cystoscopy-only follow-up (risk difference 0.08%, 95% CI –7.3 to 7.4), while reducing the number of cystoscopies by more than half (455 vs 1,029 procedures). Interestingly, XBCM detected several recurrences earlier than cystoscopy, highlighting its potential anticipatory value. However, the trial design has attracted considerable criticism. The chosen non-inferiority margin of 30% was unacceptably wide, making it statistically easier for the biomarker arm to be deemed non-inferior. Moreover, three months after trial initiation, a new eligibility criterion was introduced requiring a recurrence within two years, a change that shifted the study population to a higher risk and raises questions of methodological rigour. While the results are encouraging and provide the first randomised evidence that urinary biomarkers may safely de-escalate surveillance, the limitations of the trial design must be noted. The UroFollow trial is a similar trial in which 214 patients with low- and intermediate-risk NMIBC were randomised to surveillance by standard cystoscopy or a marker-based algorithm combining UroVysion, cytology, NMP22, and ultrasound. Although this approach reduced cystoscopy use by 75%, the non-inferiority margin was set at 20% for sensitivity – again an overly generous threshold. Furthermore, per-protocol sensitivity was lower in the marker arm (81.5% vs 96.5%), with five low-grade recurrences missed compared to one in the control group. Although the authors concluded there was no meaningful difference, the Kaplan-Meier curves suggest a clear separation that likely would not reach significance due to the limited sample size. Given these limitations and the inclusion of ultrasound, this trial further supports the notion that we cannot yet rely on urinary markers.

Finally, a randomised clinical trial (NCT02298998) evaluated the impact of two different cystoscopy surveillance schedules in NMIBC patients, high frequency (HF) and low frequency (LF) surveillance[24,188]. Of 70 eligible patients, 64.3% agreed to participate, though over a third declined randomisation due to a preference for HF surveillance. Recurrence rates were similar between groups (14.3% in HF vs. 20.8% in LF, p=0.71), with no cases of high-grade recurrence or

progression, suggesting that less frequent surveillance may be safe in appropriately selected patients. Additionally, LF surveillance significantly reduced costs, with an annual per-patient saving of $383.80, supporting its potential economic benefits. However, patient reluctance to reduce surveillance and study withdrawals highlights challenges in changing clinical practice, emphasising the need for future studies incorporating patient education, urine biomarkers, or AI-driven monitoring to improve acceptance and personalise follow-up schedules.

Emerging advancements in risk stratification, treatment selection, and recurrence prediction of MIBC

MIBC is a more advanced stage of disease in bladder cancer and although there are an increasing number of bladder-sparing therapies such as TURBT, chemotherapy and external beam radiotherapy[189], survival outcomes in MIBC are usually poor and more aggressive management is often required[190]. Clinician decision-making heavily relies on TNM staging. However, novel technologies are now including prognostic factors such as lymphovascular invasion, the presence of residual tumour surgical margins and genetic information in decision-making[190,191].

Similarly to NMIBC, AI has similar applications in MIBC[191]. For example Wang et al. developed a ML-based autophagy-related prognostic signature (ARPS) to enhance risk stratification and predict treatment response in bladder cancer[192]. Their study found that patients with high-ARPS had significantly worse prognoses, with lower overall survival, more advanced tumour grades and stages, and a reduced efficacy to immunotherapy compared to the lower ARPS group. The study also identified four potential therapeutic targets and five candidate drugs specifically tailored for high-risk patients, offering a precision medicine approach that could be integrated into clinical decision-making. For example, Polo-like kinase 1 (PLK1) was identified as a potential therapeutic target for high-ARPS patients, with inhibitors such as RO3280 demonstrating promising antitumour activity in vitro and in vivo. This approach optimises treatment selection by tailoring interventions to patient-specific molecular profiles, complementing the current TNM staging system and improving personalised management of MIBC.

As previously mentioned, DL-CNN is used to segment and measure gross tumour volumes from CT images of bladder cancer. Although its performance is comparable to that of radiologists when evaluating response to neoadjuvant chemotherapy, it was found to be more extensive than existing WHO and RECIST criteria as it accounts for three-dimensional measurements and the complexity of tumour shape[193]. Additionally, DL has been able to differentiate risk in MIBC and has found that prognosis may not always be worse in patients with higher TNM stage in MIBC showing its enhanced prognostic abilities compared to the TNM[190,191]. Wei et al. expanded on this by developing a deep-learning radiomics nomogram (DLRN) that integrates DL-score, radiomics features, and clinicopathological factors to predict overall survival in MIBC patients undergoing radical cystectomy[191]. Their model demonstrated superior prognostic accuracy compared to traditional clinical models, achieving a C-index of 0.713 in internal validation. This allows for improved identification of high-risk patients who may benefit from intensified adjuvant therapy and closer postoperative surveillance, while potentially sparing low-risk

individuals from unnecessary interventions. This highlights the potential of AI-enhanced imaging to refine preoperative treatment planning and risk-adapted patient management. Despite these benefits, external validation of these models is required as the lack of standardised validation protocols for AI models currently undermines their applicability in MIBC.

Radiomics can improve the preoperative treatment planning in MIBC, particularly alongside VI-RADs. Studies have shown that junior radiologists often require at least 150 cases before attaining the independence and confidence to give an accurate diagnosis using VI-RADS[46,193]. Enhanced versions of radiomics now combine clinical factors to support its predictive abilities, providing additional information on the extent of muscle infiltration in MIBC[194]. Finally, radiomics can be applied to predict patients' need for neoadjuvant chemotherapy for stage T2 or greater based on CT findings, achieving an AUC of 0.88-0.97 in extracting additional morphological findings in MIBC compared to clinician analysis[159,195].

Integration of multimodal tools

Novel multimodal approaches for the treatment of NMIBC

NMIBC poses a unique clinical challenge due to its high recurrence rate despite a generally low risk of progression. This characteristic behaviour demands a nuanced approach to treatment planning, where clinicians must carefully weigh the likelihood of recurrence against the potential for progression. The EAU's risk stratification framework, the EORTC risk tables, estimate individual patient risk of recurrence and progression based on tumour characteristics such as size, number, stage, grade, and presence of carcinoma in situ[196]. This model supports more tailored management strategies in NMIBC care, allowing clinicians to adapt treatment intensity based on stratified risk profiles.

Understanding the mechanisms behind recurrence in NMIBC is essential for improving treatment strategies. Recurrence can arise from both surgical and oncological factors. Surgically, limitations in WLC may lead to missed lesions, while incomplete resection during TURBT can leave residual disease[197]. Furthermore, tumour fragmentation during the procedure raises the risk of reimplantation, potentially seeding new lesions. On the oncological side, phenomena such as the field change effect—where the entire urothelium is genetically predisposed to malignancy—and drop metastases also contribute to recurrence. TURBT, although a cornerstone of NMIBC management, is highly operator-dependent, which introduces variability and potential for incomplete resections[198]. As a result, repeat TURBT is often recommended to mitigate these limitations, particularly in high-risk cases[199].

In recent years, there has been a growing emphasis on enhancing the surgical quality of TURBT to reduce early recurrence, which is predominantly influenced by technical factors. One promising advancement is en-bloc resection of bladder tumour (ERBT), which aims to remove the tumour in one piece, thereby avoiding fragmentation and improving margin assessment. Evidence from studies such as the EB-STAR trial has shown that ERBT can reduce recurrence rates from 38% to 28%, especially in patients with single, low- or intermediate-risk Ta tumours[198]. While these results are encouraging, their impact in high-risk patients appears limited, suggesting that biological factors become increasingly influential over time. Indeed, Kaplan-Meier analyses indicate that while improved surgical techniques may delay recurrence within the first few months for these high-risk patients, recurrence rates begin to climb again by

12 months, underscoring the need for robust adjuvant therapies. For high-risk NMIBC, combining effective surgery with adjuvant intravesical therapy is therefore critical. Perhaps combining ERBT with BCG therapy could address both short- and long-term challenges: ERBT reduces recurrence driven by surgical shortcomings of TURBT in the early postoperative period, while BCG offers sustained immunological protection against biologically driven recurrence over time. These findings support a multimodal approach, where improved surgical techniques addresses the immediate tumour burden, and BCG provides ongoing immunological surveillance to prevent regrowth.

The management of BCG-unresponsive NMIBC presents a more complex challenge, however. Recurrence within six months of adequate BCG treatment typically reflects aggressive disease biology, warranting consideration of more intensive interventions[200]. Traditionally, this scenario has led to early cystectomy; however, advances in systemic and local therapies have opened the door to bladder-sparing options[201]. Immunotherapeutic agents such as PD-1/PD-L1 inhibitors target the tumour microenvironment and modulate immune responses, offering hope for more durable control[202]. Hyperthermic intravesical chemotherapy, which enhances cytotoxicity through heat, has shown differential efficacy depending on tumour subtype, with particular benefit in high-grade disease lacking CIS[203]. Conversely, its effectiveness diminishes in CIS-positive cases, where immunotherapy may be more appropriate. Genomic profiling is also emerging as a tool for guiding therapy selection, potentially enabling a more personalised approach to treatment[204]. Adstiladrin (Nadofaragene firadenovec), the first FDA-approved intravesical gene therapy for BCG-unresponsive NMIBC, delivers interferon- α2b via an adenoviral vector with Syn3 to enhance urothelial transduction[205,206]. In the Pivotal phase 3 study by Boorjian et al., patients with BCG-unresponsive CIS disease showed a 53.4% complete response rate at 3 months and 45.5% at 12 months, with a median duration of 9 months[207]. However, long-term data show that only a subset maintains durable disease control, which prompts attempts to potentially integrate biomarker-guided patient selection and combinational strategies to optimise outcomes[208]. Recently, the FDA also approved the gemcitabine intravesical delivery system (Inflexzo; formerly TAR-200) for adults with BCG-unresponsive NMIBC with CIS, supported by the SunRISe-1 cohort study in which TAR-200 monotherapy demonstrated a complete response rate of ~82% with about half of responders maintaining complete response for ≥12 months[209,210]. While the approval of TAR-200 represents another important step and option toward bladder-sparing therapy in BCG-unresponsive NMIBC, its rapid approval has raised concerns about unproven long-term outcomes, frequent relapse within 2 years, and urinary toxicities, emphasising the need for longer follow-up and comparative trials before it can be considered a true alternative to cystectomy. With multiple agents now approved, enthusiasm for bladder-sparing strategies in BCG-unresponsive NMIBC is high; however, most data come from single-arm studies with relatively short follow-up (Table 3). As such, it is not yet clear which option or combination is most effective among the available treatments, and longer-term, comparative trials will be essential to define their true role.

Treatment	Mechanism	Pivotal Trial (type)	FDA Approval (year)	CIS cohort (n)	Reinduction allowed?	CR at 12 mo	Grade 3/4 AEs
Pembrolizumab	Systemic PD-1 inhibitor	Balar et al., 2021 (KEYNOTE-057 Cohort A, Phase 2, single-arm)[202]	2020	96	No	19%	13%
Nadofaragene firadenovec (Adstiladrin)	Non-replicating adenovirus delivering IFN-α2b (with Syn3)	Boorjian et al., 2021 (Phase 3, single-arm)[207]	2022	103	No	24%	4%
N-803 (Nogapendekin alfa inbakicept) + BCG	IL-15 superagonist + intravesical BCG	Chamie et al., 2023 (QUILT-3.032, Phase 2/3, single-arm)[211]	2024	82	Yes	45%	3%
TAR-200 (Inlexzo)	Gemcitabine-eluting intravesical device	Daneshmand et al., 2025 (SunRISe-1 Cohort 2, Phase 2b, single-arm)[209]	2025	85	No	46%	13%
Cretostimogene grenadenorepvec (CG0070)	Replicating adenovirus with GM-CSF transgene	Tyson et al., 2025 (BOND-003, Phase 3, single-arm)[212]	Not approved	112	Yes	46%	0%

Table 3: Regulatory landscape and efficacy outcomes of emerging bladder-sparing therapies for BCG-unresponsive NMIBC

Summary of FDA-approved and late-phase investigational treatments for BCG-unresponsive non-muscle-invasive bladder cancer with carcinoma in situ (CIS), including trial design, year of approval, and efficacy outcomes.

Taken together, current evidence supports the notion that early recurrence is often related to surgical inadequacy, while late recurrence is more reflective of tumour biology. As such, achieving a high-quality initial resection followed by appropriate adjuvant therapy offers the best chance of long-term disease control (Figure 4). In the future, incorporating advanced imaging modalities such as MRI to confirm complete tumour clearance, alongside genomic and molecular profiling to tailor adjuvant strategies, may help to further refine and personalise care for patients with NMIBC. This integrated approach holds the promise of shifting the management paradigm from recurrence control to potential cure, particularly in those with high-risk disease.

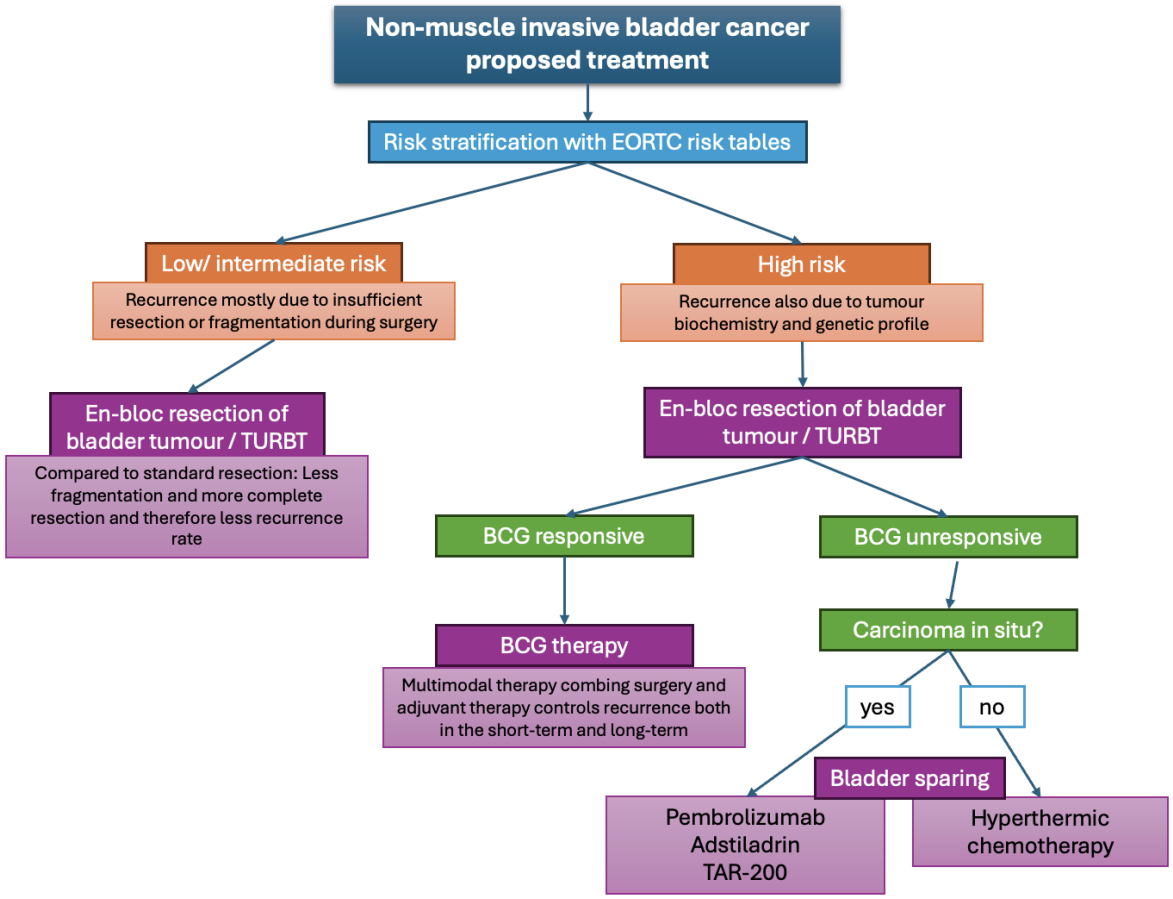

Figure 4: Clinical decision-making flowchart explaining how emerging technology can be integrated into each stage of treatment planning and staging for NMIBC.

This flowchart depicts the recommended treatment pathway for NMIBC, beginning with risk stratification using the EORTC risk tables to estimate recurrence and progression risk based on tumour characteristics. Patients are categorised into low/intermediate or high-risk groups, with both pathways initially involving en-bloc resection of the bladder tumour (ERBT)—a surgical technique that minimises tumour fragmentation and improves resection quality. ERBT has shown potential in reducing early recurrence, particularly in low- and intermediate-risk cases. For high-risk patients, adjuvant intravesical BCG therapy is recommended to prevent long-term recurrence. For those who are BCG-unresponsive, management depends on the presence of carcinoma in situ (CIS). Immunotherapy (e.g., immune checkpoint inhibitors) is indicated for CIS-positive disease or hyperthermic intravesical chemotherapy for CIS-negative, high-grade tumours. This multimodal approach, combining surgical precision with tailored adjuvant therapies, reflects an evolving paradigm in NMIBC management—one that seeks to address both technical and biological causes of recurrence, while preserving bladder function where possible.

Novel multimodal approaches for the treatment of MIBC

MIBC represents a biologically and clinically distinct subset of bladder cancer that necessitates a more aggressive and multimodal treatment approach compared to NMIBC. Traditionally, the standard of care has involved a diagnostic or staging TURBT, followed by neoadjuvant chemotherapy (NACT) and radical cystectomy. However, emerging evidence and innovative surgical strategies are reshaping our understanding of what is possible in terms of local tumour control and bladder preservation. Historically, TURBT in MIBC was not performed with curative intent, particularly in patients with T2 or greater disease. The rationale was that resecting the

tumour completely would not be feasible due to the depth of muscle invasion. As such, TURBT served as a staging tool rather than a therapeutic one. Standard data suggest that pathological complete response (pT0) post-cystectomy in patients who did not receive NACT is 15%[28,213]. This rate improves to 31-38% with the addition of neoadjuvant chemotherapy, supporting its role in improving local tumour control.

A potential alternative treatment lies in the emerging role of maximal TURBT, particularly using a modified ERBT technique, in carefully selected patients with muscle-invasive disease. This more aggressive surgical approach may offer enhanced local control, even in cases of substantial T2 tumours. The rationale is that complete endoscopic resection could theoretically eliminate visible disease and delay or potentially even avoid the need for cystectomy in selected patients, thus preserving the bladder. Although robust data are still awaited, this strategy warrants further investigation as a possible curative modality in highly selected cases where anatomical and tumour characteristics are favourable[198].

Parallel to surgical innovations, immunotherapy is gaining ground as a powerful systemic modality in MIBC. The PURE-01 trial evaluated neoadjuvant pembrolizumab (a PD-1 inhibitor) prior to cystectomy in patients with cT2–T4aN0M0 MIBC. The updated results reported a pT0 rate of 37% and a pT ≤1 rate of 55% in the overall population[214]. Importantly, higher response rates were observed in biomarker-defined subgroups: patients with high PD-L1 expression (CPS ≥10) and high tumour mutational burden (TMB) demonstrated an increased likelihood of pathological response, with multivariable analysis confirming both as independent predictors of pT0 response[215]. Not all trials, however, have validated the predictive value of PD-L1. The AMBASSADOR trial (NCT03244384), a phase 3 study comparing adjuvant pembrolizumab to observation, showed a significant improvement in disease-free survival (median DFS: 29.6 vs. 14.2 months; HR 0.73, 95% CI 0.59–0.90; p=0.003), but failed to show a consistent predictive role of PD-L1 status[216].

In contrast, the CheckMate 274 trial (NCT02632409) demonstrated a clear benefit of adjuvant nivolumab over placebo in high-risk MIBC[217]. After a median follow-up of 36.1 months, disease-free survival in the intent-to-treat population was significantly longer in the nivolumab group (HR 0.71, 95% CI 0.58–0.86). In patients with PD-L1 ≥1%, the benefit was even greater (HR 0.52, 95% CI 0.37–0.72). Interim overall survival data also suggested a trend favouring nivolumab, with HRs of 0.76 (ITT) and 0.56 (PD-L1 positive). These results led to regulatory approval of adjuvant nivolumab.

The utility of ctDNA is also gaining traction as a dynamic biomarker. Data from the IMvigor011 study demonstrated that patients with persistently ctDNA-negative status after cystectomy had excellent outcomes, with 12-month DFS rates of 92% and OS rates of 100%[218]. These findings support the potential of serial ctDNA testing to identify patients who may safely avoid adjuvant treatment and, conversely, to guide its use in ctDNA-positive patients. Additionally, DNA damage response (DDR) gene alterations, such as mutations in ERCC2, have been associated with increased sensitivity to neoadjuvant cisplatin-based chemotherapy in MIBC[219]. The SWOG1314 trial demonstrated that deleterious DDR alterations significantly correlate with improved pathologic response rates following neoadjuvant cisplatin-based chemotherapy, suggesting their potential as predictive biomarkers to guide therapy[220]. This highlights the notion that response to therapy in MIBC is multifactorial, and thus, treatment planning must reflect that complexity.

This evolving evidence base supports a multiparametric approach to MIBC treatment planning. Pre-operative MRI provides anatomical clarity and helps assess the feasibility of maximal TURBT. Post-operative imaging helps confirm the completeness of resection. Biomarkers such as PD-L1 and DDR mutation status, together with ctDNA surveillance, refine systemic therapy decisions and allow for individualised treatment. Based on this integrated assessment, patients may be broadly classified into two categories. First, those with excellent local control, favourable biomarker profile, and negative ctDNA are ideal candidates for bladder-sparing strategies. Second, those with residual bulky tumours, unfavourable biomarkers, or positive ctDNA may benefit from more radical interventions such as cystectomy or intensified systemic therapy. There remains a grey zone—for instance, patients with ambiguous imaging findings or discordant biomarker results. In such cases, ctDNA may provide additional clarity, potentially guiding adjuvant therapy duration and intensity.

In conclusion, MIBC management is shifting toward an era of personalised, multimodal therapy. Maximal TURBT, immunotherapy, imaging, and molecular biomarkers, including ctDNA, are converging to inform clinical decision-making. Integrating these elements holds the promise of not only improving outcomes but also expanding opportunities for bladder preservation in carefully selected patients (Figure 5).

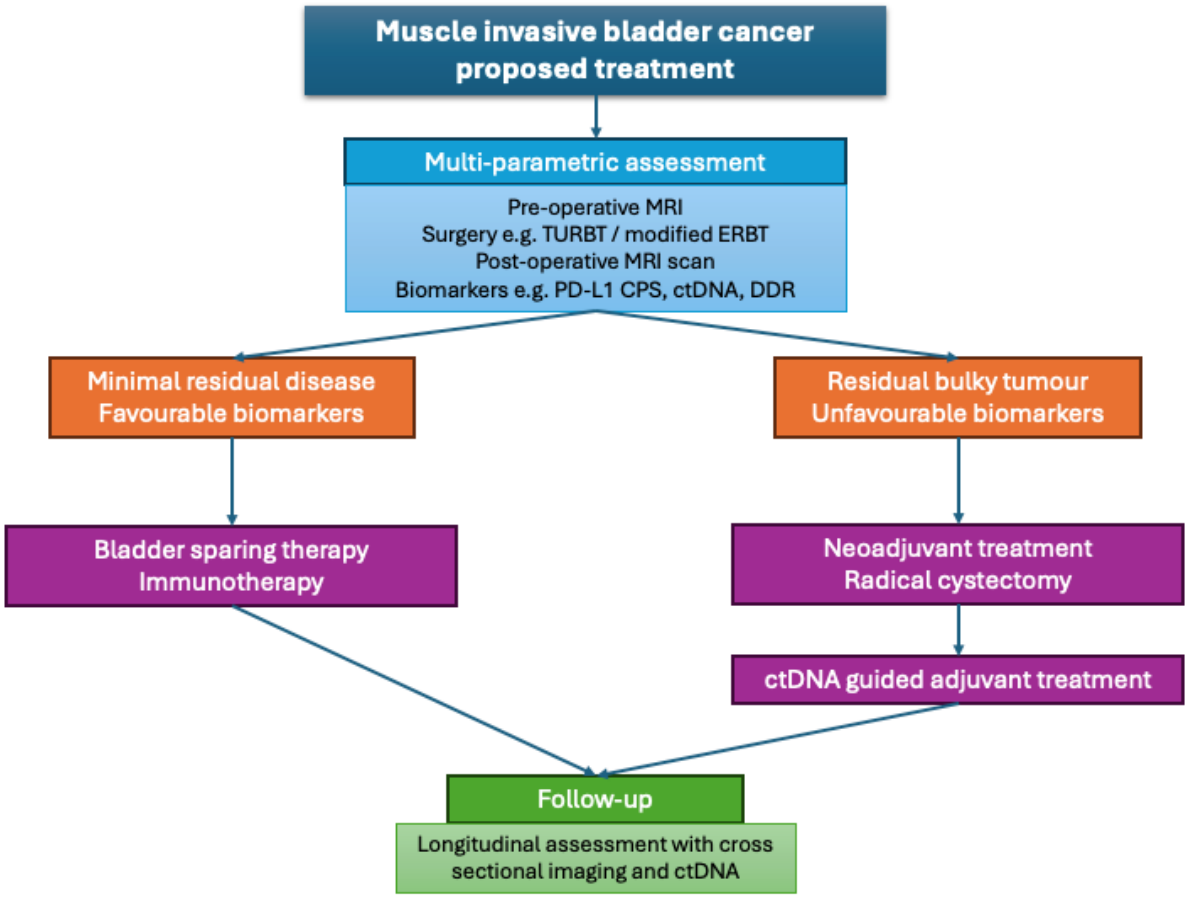

Figure 5: Clinical decision-making flowchart explaining how emerging technology can be integrated into each stage of treatment planning and staging for MIBC.

This diagram outlines a multiparametric approach to MIBC management, incorporating advanced imaging, surgical techniques, and biomarker analysis to guide personalised treatment. Initial assessment includes pre- and post-operative MRI and modified resection strategies such as enhanced TURBT or en-bloc resection, alongside biomarker

profiling (e.g., PD-L1 CPS, ctDNA, DDR mutations). Patients with minimal residual disease and favourable biomarker profiles may be candidates for bladder-sparing therapy with immunotherapy. In contrast, those with residual bulky tumours or unfavourable markers typically proceed to neoadjuvant chemotherapy followed by radical cystectomy, with ctDNA used to guide subsequent adjuvant therapy. Longitudinal follow-up with cross-sectional imaging and ctDNA surveillance supports ongoing risk assessment and timely intervention. This personalised, multimodal strategy aims to improve outcomes while expanding opportunities for bladder preservation in select patients.

Novel multimodal approaches in the treatment of metastatic urothelial carcinoma

Metastatic urothelial carcinoma (mUC) has historically been associated with a poor prognosis, with platinum-based chemotherapy as the mainstay of treatment yielding only modest survival benefits[1,2]. In recent years, however, the therapeutic landscape has shifted dramatically from a one-size-fits-all chemotherapy approach to a biomarker-driven paradigm that integrates clinical, genomic, and molecular data to guide personalised therapy. This evolution reflects the urgent need to tailor treatment strategies to distinct tumour biology and patient characteristics, particularly in the metastatic setting where treatment selection can have a critical impact on outcomes[1–3].

The EV-302 Phase 3 trial established the combination of enfortumab vedotin, an antibody-drug conjugate (ADC) targeting Nectin-4, with the immune checkpoint inhibitor (ICI) pembrolizumab as a new frontline standard, demonstrating superior overall survival compared to chemotherapy alone[1]. Nectin-4 is highly expressed in most urothelial carcinomas, although expression may differ between primary and metastatic sites[1,2]. This regimen is now widely considered the preferred first-line option for eligible patients.

Chemotherapy-immunotherapy combinations remain essential. The CheckMate 901 trial demonstrated that gemcitabine-cisplatin, combined with nivolumab, improves survival outcomes, offering a valuable option for patients eligible for cisplatin[1]. For patients unfit for first-line cisplatin or chemoimmunotherapy, maintenance avelumab following carboplatin-gemcitabine represents a standard alternative[1], whereas pembrolizumab or atezolizumab monotherapy remains appropriate for those ineligible for any platinum-based regimen[1,2].

A comprehensive decision-making framework should consider: (1) eligibility for enfortumab vedotin, contraindicated in uncontrolled diabetes or significant peripheral neuropathy; (2) cisplatin fitness, based on renal function, performance status, and comorbidities; and (3) emerging biomarkers.

Among the biomarkers with predictive or therapeutic relevance, Nectin-4 represents the most established, being highly expressed in the majority of urothelial carcinomas and serving as the target for enfortumab vedotin, now a frontline standard of care[1,2]. Trop-2 is another relevant marker, frequently overexpressed across basal, luminal, and stroma-rich molecular subtypes; its role is under investigation as a predictor of response to anti–Trop-2 ADCs, such as sacituzumab govitecan and datopotamab deruxtecan[1–3]. HER2 overexpression, observed in approximately 12% of urothelial cancers and more commonly within luminal subtypes, has paved the way for therapeutic targeting with HER2-directed ADCs, such as disitamab vedotin and trastuzumab deruxtecan (T-DXd)[1,2].

The broader framework of molecular classification also carries therapeutic implications: Ba/Sq and LumNS tumours appear more sensitive to neoadjuvant chemotherapy, whereas stroma-rich tumours may derive limited benefit[1]. Beyond these established markers, several exploratory targets - including SLITRK6, EGFR, Integrin β6, B7-H1, and CD25 - are variably expressed and remain under clinical investigation as potential avenues for future therapeutic strategies[1].

In addition to single biomarker assessments, composite tools have been developed to support clinical decision-making. The ITACA score, for example, integrates clinical and pathological parameters to provide prognostic and predictive guidance, while more recent approaches based on integrative biomarker-driven stratification combine molecular, genomic, and immune features to further refine treatment selection and individualise therapy[1,2].

Genomic profiling increasingly informs treatment personalisation. FGFR3 alterations predict response to erdafitinib in patients ineligible for platinum and enfortumab vedotin[1,2]; liquid biopsy facilitates rapid mutation detection[1]. DNA damage response (DDR) pathway mutations, particularly homologous recombination repair (HRR) defects, may guide PARP inhibitor maintenance after platinum-based therapy[1].Serial ctDNA monitoring must also be considered as it enables real-time tracking of response, early detection of molecular progression, and identification of emerging actionable mutations, allowing dynamic adaptation of therapy[1,2].

Following progression, sacituzumab govitecan (a Trop-2–targeting ADC) has been withdrawn from the U.S. market due to safety concerns and lack of overall survival benefit in the TROPiCS-04 trial[1]. Nonetheless, other Trop-2 ADCs such as datopotamab deruxtecan remain under investigation[1]. HER2-targeting ADCs (disitamab vedotin, T-DXd) are being evaluated in HER2+ or HER3+ urothelial carcinoma[1,2]. Nectin-4 remains a validated biomarker, with ongoing research into resistance mechanisms and ADC optimisation[1,2].

Selection of subsequent therapies should integrate tumour biomarker expression, prior treatments, and patient characteristics. Management should therefore combine the following: Clinical assessment, including performance status and comorbidity; Pathology and imaging, such as histologic subtype and metastatic burden; Static biomarkers, including genomic, proteomic, and immunohistochemical profiles (Nectin-4, Trop-2, HER2, DDR, and FGFR3); and Dynamic biomarkers, including serial ctDNA for adaptive therapy.

Optimal management of metastatic urothelial carcinoma requires the integration of multiple dimensions of patient and disease assessment. A careful clinical evaluation, including performance status and comorbidities, remains the cornerstone of treatment choice. This should be complemented by detailed pathological and radiological characterisation, taking into account the histological subtype and metastatic burden. On the molecular level, static biomarkers—such as genomic, proteomic, and immunohistochemical profiles encompassing Nectin-4, Trop-2, HER2, DDR alterations, and FGFR3 mutations—provide predictive and prognostic information that can guide the selection of targeted agents and ADCs. Finally, the incorporation of dynamic biomarkers, particularly serial ctDNA analysis, offers a real-time window into treatment response and tumour evolution, supporting adaptive therapeutic strategies that go beyond static baseline information.

The proposed decision-making flowchart outlines a sequential, biomarker-driven decision framework. The first step is to determine eligibility for enfortumab vedotin, which is contraindicated in patients with poorly controlled diabetes or significant peripheral neuropathy, followed by an assessment of cisplatin fitness, based on renal function and performance status. Once clinical suitability has been established, biomarker profiling becomes central to treatment allocation. High PD-L1 expression or elevated tumour mutational burden (TMB) tends to favour immunotherapy-based regimens, whereas strong expression of targets such as Nectin-4, HER2, or Trop-2 may support the use of ADCs in the frontline setting. Beyond this, FGFR3 alterations guide the use of erdafitinib, while DDR mutations provide a rationale for PARP inhibitor maintenance after platinum therapy. Dynamic monitoring with ctDNA adds a further

adaptive layer, enabling early assessment of treatment response, detection of molecular progression, and identification of emerging actionable mutations. In the second-line setting, sacituzumab govitecan is no longer an option following its withdrawal, but investigational Trop-2–targeting ADCs such as datopotamab deruxtecan, as well as HER2-directed agents including disitamab vedotin and trastuzumab deruxtecan (T-DXd), are under evaluation. These therapeutic choices must ultimately be contextualised within each patient's prior treatment history, tumour molecular profile, and clinical characteristics, reinforcing the principle of multi-modal, personalised decision-making in metastatic urothelial carcinoma.

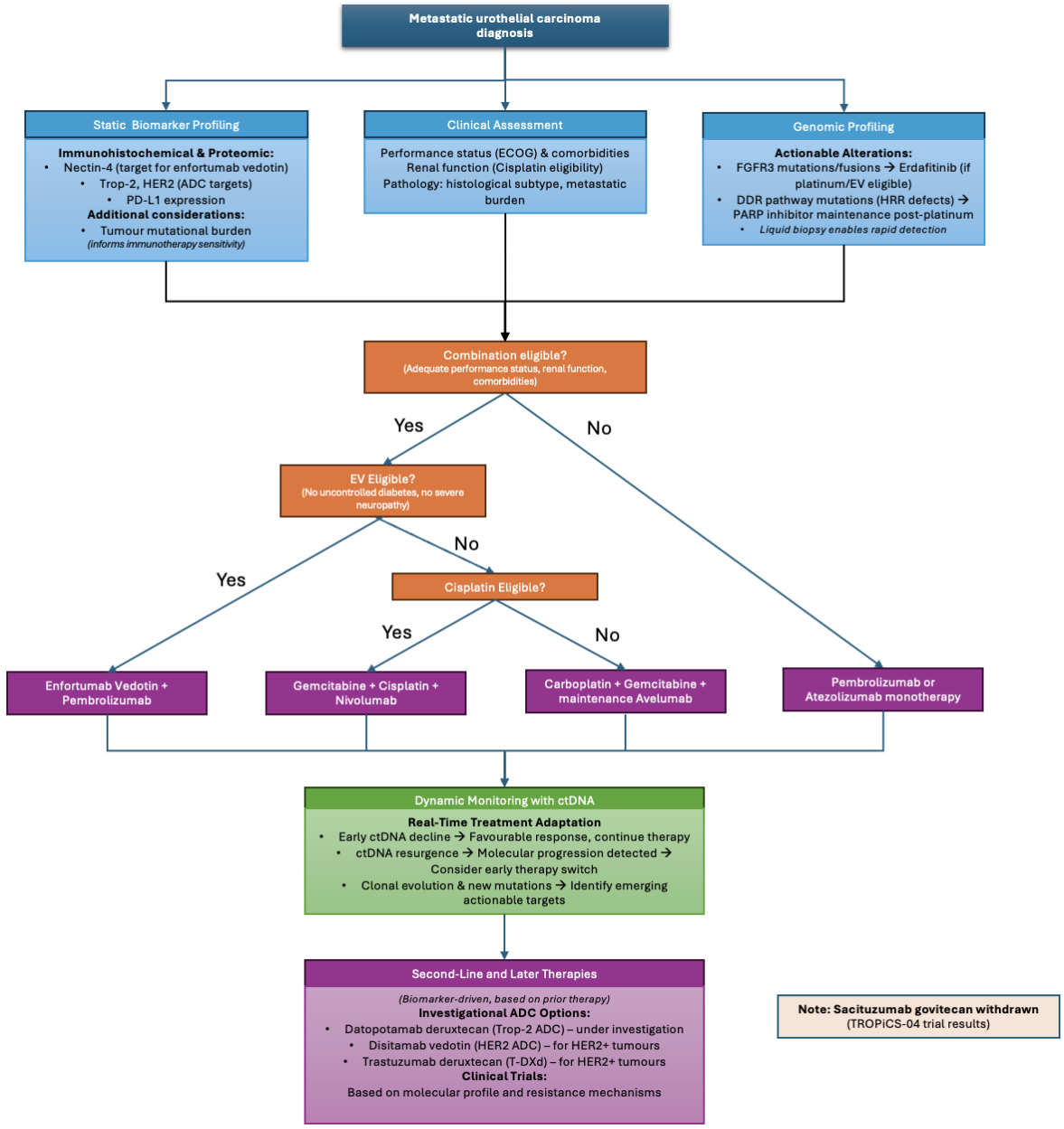

Figure 6: Clinical decision-making flowchart for personalised management of metastatic urothelial carcinoma

This diagram illustrates a biomarker-driven approach to treatment selection in metastatic urothelial carcinoma. Initial evaluation integrates clinical fitness, static biomarker profiling, and genomic profiling to assess eligibility for first-line therapies. Patients suitable for combination therapy receive enfortumab vedotin (EV) plus pembrolizumab if eligible for EV. Patients not eligible for EV will receive gemcitabine, cisplatin and nivolumab, with those not cisplatin eligible

receiving carboplatin, gemcitabine and maintenance avelumab instead. Dynamic monitoring with ctDNA allows real-time adaptation, and second-line therapy incorporates investigational ADCs or clinical trials based on molecular evolution and prior treatment.

Current limitations and future directions

The potential of AI to address clinical needs—from diagnosis and treatment planning to outcome prediction—is undeniable[40,49,53,55,61,66,159,193,195,231,240,241]. However, emerging ideas will never achieve clinical implementation without integration, standardisation, and rigorous evaluation. AI studies in bladder cancer often have limitations such as small sample sizes, retrospective designs, and a lack of external validation[40,46,193,195,240]. The APPRAISE-AI framework (A Reporting Checklist for the Evaluation of Artificial Intelligence Studies in Medical Imaging) is a structured tool designed to assess the methodological and reporting quality of AI research, promoting transparency, reproducibility, and clinical relevance in AI development and evaluation[242]. Although the APPRAISE-AI guidelines have shown strong interrater and intrarater reliability, correlating well with expert ratings and citation rates, their initial evaluation included only 28 studies—a relatively small sample[242]. Nonetheless, as APPRAISE-AI is increasingly utilised, its validity continues to strengthen. For instance, a systematic review conducted by Kwong et al. using the APPRAISE-AI framework found that, out of 15 studies on NMIBC, only one met high-quality standards, and only four used data from multiple institutions[240]. This limits generalisability and puts the models susceptible to instability, where over-reliance on training data can lead to volatility in predictions[40,46,231,240]. Similarly, He et al.'s systematic review highlighted poor quality in AI models predicting MIBC outcomes, using tools such as CLAIM, RQS, and PROBAST[243]. Thus, familiarity with multiple evaluation tools remains essential for researchers and reviewers.

Currently, ML applications in this area depend on supervised learning, where human guidance is still essential[40]. For example, bladder segmentation—a key step in diagnosing and treating bladder cancer—typically relies on manual or semi-automatic methods, which are expensive and not widely accessible. DL, a more advanced subset of ML, offers the potential to automate this process by extracting features directly from raw data without human input. However, inconsistent imaging techniques across hospitals limit DL's full effectiveness, often requiring semi-supervised approaches[193]. To fully leverage AI in bladder cancer research, standardising scanning methods across institutions will be essential[49,231].

Concerns over accountability, transparency, data privacy, and high costs hinder clinical AI adoption[49]. The "black box" issue complicates understanding AI decision-making processes, highlighting the trade-off between transparency and model accuracy[40,46,195]. While rigorous validation may manage this trade-off, practical solutions remain unclear[231]. Patient confidentiality versus the need for extensive datasets is another significant challenge[49]. Distributed learning techniques like federated learning provide promising solutions, enabling collaborative model training without compromising sensitive information. Truhn et al. successfully applied somewhat-Homomorphically-Encrypted Federated Learning (SHEFL) to cancer imaging, achieving secure, collaborative model training across multiple institutions[244]. Further development and validation of such methods could enhance predictive model accuracy and accelerate clinical adoption while maintaining patient confidentiality. Addressing these

limitations through rigorous methodological standards, enhanced data-sharing, and innovative integration will be critical to realising AI's full potential in bladder cancer decision-making.

Advanced imaging modalities such as mpMRI and molecular profiling techniques, including ctDNA, remain underutilised despite their demonstrated clinical utility. Current barriers such as limited availability, high costs, and the absence of routine integration into clinical workflows hinder widespread adoption[245]. To overcome these limitations, future research should focus on cost-effectiveness analyses, standardising imaging protocols, and robust validation studies to establish molecular profiling as part of standard practice[246]. Even when advanced diagnostic methods are implemented, frequent cystoscopic surveillance for NMIBC continues to impose significant economic and psychological burdens on patients. Although reduced-frequency surveillance schedules have demonstrated safety in selected low-risk groups, clinical adoption remains low due to hesitation among clinicians and patients[188]. Future efforts should prioritise the incorporation of validated non-invasive biomarkers and advanced imaging technologies into surveillance protocols, aiming to reduce patient discomfort and costs while maintaining clinical effectiveness and compliance[247]. Further compounding the challenge of effective management in NMIBC is the significant variability in surgical outcomes associated with TURBT. Residual tumours are frequently observed following TURBT due to variability in surgical techniques and differences in surgeon experience. To address this issue, future strategies should focus on the development and standardisation of advanced resection techniques, such as en-bloc resection, complemented by rigorous training programmes and validation studies to enhance surgical consistency and patient outcomes[25,198]

Managing patients with BCG-unresponsive NMIBC remains particularly problematic, given the limited effective alternatives beyond radical cystectomy. The lack of clear criteria for patient selection and response prediction significantly hampers the use of promising bladder-sparing therapies[202,203]. Future directions in this field should emphasise identifying robust predictive biomarkers and expanding molecular profiling capabilities to tailor personalised treatments, thereby enhancing clinical outcomes and patient quality of life.

Lastly, despite emerging alternatives, radical cystectomy remains the standard approach for MIBC, primarily due to a lack of clear patient selection criteria for bladder-sparing treatments. Future clinical trials and comprehensive longitudinal studies should aim to establish clear criteria and assess the long-term safety and efficacy of bladder-sparing approaches, ultimately promoting more personalised and less invasive therapeutic options for patients with MIBC[214]. The scarcity of publicly accessible data highlights the need for increased collaboration and transparency. Boca et al. noted limited open data practices in their systematic review of MRI-based radiomics in bladder cancer[46]. Initiatives such as the Cancer Imaging Archive could help facilitate data sharing and transparency[46,49,240]. Integrative approaches combining genomic, radiomic, and pathomic features have potential, exemplified by Brancato et al.'s concept of a "biobank" that can facilitate comprehensive analysis of tumours[248]. However, this approach currently faces ethical, legal, operational, and maintenance challenges that must be addressed for large-scale validation and cross-comparisons.

Conclusions

In conclusion, bladder cancer management is rapidly evolving through advancements in artificial intelligence, imaging modalities, genomics, and biomarker detection. Incorporating these advancements into a unified multimodal framework allows us to propose novel approaches to both NMIBC and MIBC, enabling more accurate diagnosis, personalised risk

stratification, and tailored treatments. Future research should focus on validating these in clinical practice and addressing current barriers to widespread implementation.

References

Automatic citation updates are disabled. To see the bibliography, click Refresh in the Zotero tab.