REVIEW

Advances in risk stratification of bladder cancer to guide personalized medicine [version 1; referees: 4 approved]

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Abstract

Bladder cancer is a heterogeneous disease that poses unique challenges to the treating clinician. It can be limited to a relatively indolent papillary tumor with low potential for progression beyond this stage to muscle-invasive disease prone to distant metastasis. The former is best treated as conservatively as possible, whereas the latter requires aggressive surgical intervention with adjuvant therapies in order to provide the best clinical outcomes. Risk stratification traditionally uses clinicopathologic features of the disease to provide prognostic information that assists in choosing the best therapy for each individual patient. For bladder cancer, this informs decisions regarding the type of intravesical therapy that is most appropriate for non-muscle-invasive disease or whether or not to administer neoadjuvant chemotherapy prior to radical cystectomy. More recently, tumor genetic sequencing data have been married to clinical outcomes data to add further sophistication and personalization. In the next generation of risk classification, we are likely to see the inclusion of molecular subtyping with specific treatment considerations based on a tumor's mutational profile.

Keywords

Bladder cancer, bladder cancer genetics, personalized medicine, risk stratification, urothelial carcinoma

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Introduction

Bladder cancer ranks among the most common non-cutaneous malignancies in the United States (4th for men and 11th for women) and worldwide (6th for men and 16th for women)[1–3]. Though it is commonly referred to by the generic term "bladder cancer", urothelial neoplasms represent a broad spectrum of disease with vastly different treatment pathways from routine bladder surveillance to intravesical therapy to radical surgery with chemotherapy. Staging is broadly divided into two major categories—non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC)—which is perhaps the most important determining factor when choosing an initial therapy. Tumor stage is classified according to the Tumor-Node-Metastasis staging system developed by a collaboration of the American Joint Commission on Cancer and Union for International Cancer Control, now in its 8th edition which went into effect in January 2018[4]. Tumors categorized as NMIBC include carcinoma *in situ* (CIS), papillary (Ta), or invasive into or beyond the lamina propria (T1). Once the tumor invades the muscularis propria (T2) or beyond (T3 and T4), it is considered MIBC. Somewhat confusingly, these have been referred to as "superficial" and "invasive" disease, respectively, though that practice has been abandoned more recently for the sake of clarity. The tumor grade, describing the aggressiveness of tumor cells based on microscopic appearance, is also very important for the prognosis of bladder cancer. The 2016 World Health Organization classification system for urothelial carcinoma is divided into a binary system of high and low grade, though this is mainly applicable to Ta tumors, since nearly all (≥95%) disease ≥T1 is high grade and CIS is high grade by definition[5].

Diagnosis

A complete clinical assessment for bladder cancer includes history, physical exam, imaging of the upper urinary tracts, and cystoscopy. Cystoscopy is the cornerstone in the diagnosis and treatment of bladder cancer, being used in virtually all patients at some point throughout the course of their disease. Traditionally, this is carried out using a standard light source ("white light") to illuminate an endoscopic lens with the subsequent image transmitted via a camera head to a monitor. Directly visualized tumors are then biopsied, fulgurated, and/or resected to provide staging information that forms the basis for widely different treatments (i.e. surveillance versus radical cystectomy). Low-grade, papillary tumors not invading into the lamina propria (Ta) are reliably eradicated in a single setting; however, more advanced disease (high-grade and/or T1) is often incompletely resected. Studies have found residual disease to be present in 40–78% of re-transurethral resection (TUR) specimens after original diagnosis of high-grade Ta or any T1, with an upgrading rate to muscle invasion of 2% and 14%, respectively[6–9]. This fact has led to the recommendation by leading urologic organizations that all patients with T1 tumors should undergo a repeat resection within 6 weeks of the original procedure to confirm tumor stage and ensure maximal removal of any residual disease, as this improves response to intravesical therapy[10,11]. Recent technological advances, referred to as photodynamic aids (i.e. Blue Light® cystoscopy and narrow band imaging), promise improved detection over traditional white light cystoscopy alone, theoretically allowing for a more complete endoscopic tumor removal and more accurate risk assessment[12–19].

The urothelium is not limited to the bladder and urethra; it also extends into the ureters and renal collecting system. The main purpose of imaging in the diagnostic evaluation of bladder cancer is to assess the upper urinary tracts for malignancy and for staging local and distant extent of disease. Computed tomographic urography, which uses intravenous contrast with delayed image acquisition (10–15 minutes) to allow for urinary excretion, has the highest diagnostic value for the detection of upper tract malignancy with a sensitivity of 67–100% and a specificity of 93–99%[20–23]. Magnetic resonance imaging is a viable alternative in patients with iodinated contrast allergy with a diagnostic accuracy of 84–92%, though it is more time intensive and still requires a contrast agent (gadolinium) and, therefore, is a poor choice in patients with significantly impaired renal function[24]. Ultrasonography plus retrograde pyelography at the time of cystoscopy can be used if cross-sectional imaging is otherwise contraindicated, but this is suboptimal for assessing disease extent and upper tract involvement, so it is reserved for special circumstances. Upper tract evaluation is recommended as part of initial diagnostic work-up by the American Urological Association (AUA) and European Association of Urology (EAU) despite the very low likelihood of finding synchronous upper tract tumor at the time of NMIBC diagnosis (1.5%); however, certain features like multifocality, trigonal location, and CIS increase the risk (7.5%)[10,11,25,26]. A more nuanced approach to long-term surveillance is favored over repeat imaging, being applied only to patients with high-risk tumors, and is our first example of a risk-adapted approach to bladder cancer.

Risk stratification in bladder cancer

Not all bladder cancers are created equal and, therefore, risk stratification is an important tool for achieving optimal patient outcomes while avoiding overtreatment. Formal classification systems exist for NMIBC given the wide variability in possible treatment options (surveillance to radical cystectomy), but a one-size-fits-all approach to MIBC is no longer appropriate either.

Non-muscle-invasive bladder cancer

The risk tables from the European Organization for Research and Treatment of Cancer (EORTC) and scoring system from the Spanish Urological Club for Oncological Treatment (CUETO) for NMIBC classify patients into low, intermediate, or high risk for recurrence and progression to muscle invasion based on factors including grade, stage, tumor size, multifocality, variant histology, lymphovascular invasion, and prior therapy[10,11,27,28]. Validation studies based on these tools have shown consistent overestimation of recurrence and progression rates among the high-risk group, likely owing to the suboptimal administration of intravesical therapy seen in the developmental cohorts[29–32]. Though there is now widespread acceptance of induction intravesical immunotherapy (bacillus Calmette-Guérin [BCG]) plus maintenance therapy for 1 to 3 years based on the results of the randomized Southwest Oncology Group (SWOG) protocol, patients from EORTC and CUETO were largely treated with intravesical chemotherapies (mitomycin C, epirubicin, thiotepa,

etc.) or a lack of appropriate maintenance BCG[33]. Despite the limitations of both aforementioned studies, they form the foundation for the risk stratification systems used by the EAU and AUA to help guide treatment decisions (Table 1)[10,11,34].

There is general agreement among urological organizations that a more-conservative approach to treatment (cystoscopic resection and single-dose intravesical chemotherapy) is warranted for low-risk tumors (solitary, low-grade, papillary), while the high-risk group (multifocal high-grade, CIS, or any T1) should be managed aggressively through the use of intravesical immunotherapy, and even radical cystectomy in some cases[10,11]. This leaves a broad middle ground for intermediate-risk disease, representing a spectrum ranging from a small, recurrent low-grade papillary tumor to large treatment-resistant low-grade tumors to small high-grade lesions. In order to more effectively tailor an appropriate treatment regimen for these patients, further substratification of intermediate-risk bladder cancer has been proposed by an international consortium of bladder cancer experts using a simple scoring system based on four main tumor features (Figure 1)[35].

Muscle-invasive bladder cancer

MIBC is often treated as a single disease entity with only one acceptable therapy in the form of neoadjuvant chemotherapy followed by radical cystectomy with urinary diversion and lymphadenectomy[36]. However, risk assessment can be applied before or after definitive therapy to identify which patients require the most aggressive approach, specifically those that include adjuvant treatments with significant added toxicity. For example, the decision to delay radical cystectomy so that neoadjuvant chemotherapy can be administered for a small—5% absolute improvement in overall survival at 5 years—but statistically significant benefit can be more precisely applied only to patients with the highest chance of seeing a benefit[37]. This topic will be re-addressed in more detail in a later section. Although lacking consensus recommendations for risk grouping from any major urological societies, the stratification and personalization of MIBC therapy is on the verge of a significant paradigm shift supported by a growing body of genomic data.

Pathologic subtypes

The most common histology of bladder cancer is urothelial carcinoma (~90%) followed by squamous, adenocarcinoma, micropapillary, small cell, and other rare tumors[38]. Not all urothelial carcinoma exists in pure form; instead divergent differentiation may occur within the tumor exhibiting different morphology and labeled as "variant histology"[5]. Of these variants, several are worth noting, as certain subtypes are known to be associated with a more aggressive clinical course. When taken as a group, variant histology is associated with more advanced stage at diagnosis and may not be amenable to standard treatment algorithms, even when adjusting for stage. For instance, plasmacytoid is particularly aggressive with up to 90% diagnosed with extension outside of the bladder (≥T3) and poor responsiveness to cisplatinum-based adjuvant chemotherapy

Table 1. Risk stratification of non-muscle-invasive bladder cancer[10,11].

Risk category	EAU definition[9]	EAU recommendations	AUA definition[10]	AUA recommendations
Low	• Primary, • Solitary (<3 cm), • Low-grade/G1, and • Ta	• Single immediate post-TUR instillation of chemotherapy	• Solitary <3 cm, • Low-grade, and • Ta	• Single immediate post-TUR instillation of chemotherapy
Intermediate	• Any disease not fitting low- or high-risk criteria	• Single immediate post-TUR instillation of chemotherapy, and either • Induction chemotherapy for 1 year, or • Induction BCG with 1 year of maintenance therapy	• Low-grade Ta recurrence <1 year • Solitary low-grade Ta >3 cm, • Multifocal low-grade Ta, • High-grade Ta ≤3 cm, or • Low-grade T1	• Single immediate post-TUR instillation of chemotherapy, and either • Induction chemotherapy with or without maintenance, or • Induction BCG with maintenance
High	• Any T1, or • High-grade/G3, or • CIS present, or • Multiple, recurrent, large (>3 cm), papillary (Ta), low-grade/G1 or G2 tumors	• Single immediate post-TUR instillation of chemotherapy, and either • Induction BCG with 1–3 years of maintenance therapy, or • Immediate radical cystectomy	• High-grade T1 • Recurrent high-grade Ta • High-grade Ta >3 cm • CIS • Any high-grade failing BCG • Variant histology • LVI • High-grade prostatic urethral involvement	• Induction BCG with maintenance therapy, or • Immediate radical cystectomy for highest risk features (with LVI, variant histology, T1 with CIS, persistent T1 on re-TUR)

AUA, American Urological Association; BCG, bacillus Calmette-Guérin; CIS, carcinoma *in situ*; EAU, European Association of Urology; LVI, lymphovascular invasion; TUR, transurethral resection

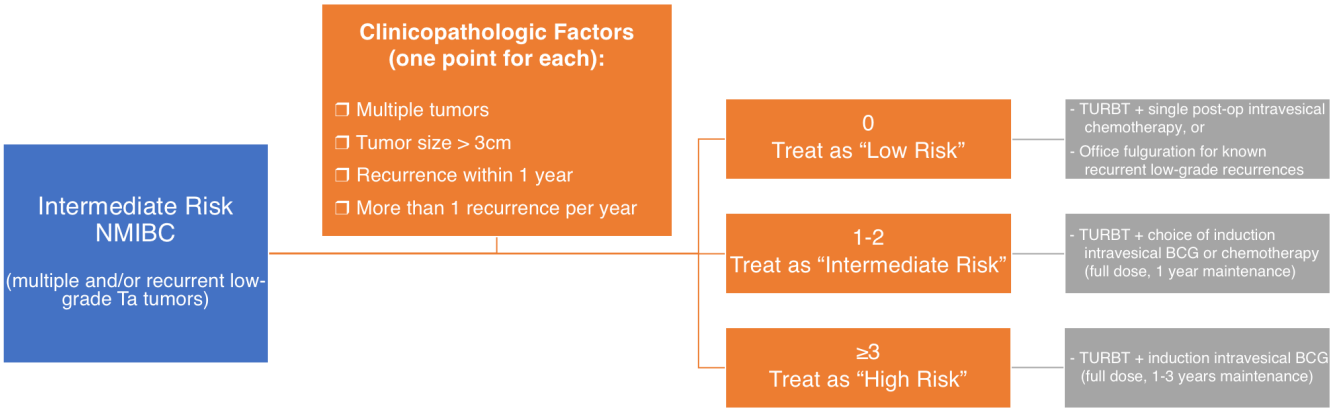

Figure 1. Proposed substratification of intermediate-risk non-muscle-invasive bladder cancer (NMIBC) based on the recommendations of the International Bladder Cancer Group[35]. BCG, bacillus Calmette-Guérin; TURBT, transurethral resection of bladder tumor.

following radical cystectomy[39–41]. Early cystectomy appears to offer survival advantage for micropapillary disease, even for clinical stage T1, because of a high rate of pathologic upstaging and node positivity[42–46]. Squamous differentiation, the most recognized subtype, and glandular are often reported on pathology reports; however, clinical outcomes are no different than those for conventional urothelial carcinoma[47,48]. These should also be recognized as very different to pure squamous cell carcinoma and adenocarcinoma of the bladder, which are distinct histologic entities lacking urothelial components[49,50]. Other less-common variants worth mentioning include nested, lymphoepithelioma-like, and small cell, the latter being morphologically similar to the lung cancer version and sharing the same aggressive clinical course[51,52].

Molecular subtyping

MIBC ranks among the most highly mutated cancers, with frequencies similar to non-small cell lung cancers and head and neck squamous cell carcinoma, resulting in a heterogeneous mutational profile involving numerous cellular pathways[53–56]. Investigators from around the world have taken on the task of genetically characterizing MIBC samples, resulting in the publication of several major molecular classification systems (the Cancer Genome Atlas [TCGA], Lund, University of North Carolina, MD Anderson, etc.)[55,57–59]. Each analysis yielded groups of tumors enriched with certain mutations that shared common features with other carcinomas, specifically the breast cancer "basal" and "luminal" subtypes, which led to similarities in the naming schemes. Broadly speaking, basal tumors tend to exhibit a more aggressive phenotype than do luminal tumors and are more prone to metastasis at the time of diagnosis[55–60]. The major publications on this topic have each included a classification system with more-or-less overlap in the mutational profile—i.e. basal-like (UNC), UroB (Lund), Cluster III (TCGA), etc.—that correlates with clinical outcomes. An effort to achieve consensus definitions for all subtypes is underway, thus far producing the Basal-Squamous-like group (BASQ) with elevated *KRT5/6* and *KRT14* expression but low *FOXA1* and *GATA3* expression[61]. By using the information from cohorts like TCGA, several researchers have sought to define the prognostic significance of these genetic mutations through the creation of molecular subtypes with correlation with clinical outcomes[56–58,62,63].

The association of molecular subtypes with response to bladder cancer therapy is certain to help guide treatment in the near future: for instance, which patients are most likely to benefit from neoadjuvant chemotherapy prior to surgery or response to immunotherapy over conventional chemotherapy[56,57,64]. Systemic therapy for bladder cancer can then be more carefully tailored to the individual patient using information obtained from genetic sequencing to select the best candidates for a given treatment regimen (Figure 2). For example, tumors exhibiting mutations in genes associated with DNA damage repair (i.e. *ERCC2*, *ERBB2*, *ATM*, and *RB1*) or those grouped into the basal/squamous subtype display a greater degree of cisplatinum sensitivity as demonstrated by more favorable clinical outcomes among these patients[56,57,65–68]. The luminal-papillary and luminal-infiltrated subtypes, on the other hand, show poor response to neoadjuvant chemotherapy; however, tumors with upregulation of the immune checkpoint markers (luminal-infiltrated and basal/squamous) may benefit from treatment with anti-PD-L1, PD-1, and/or CTLA-4 immunotherapy[56,69].

The clinical impact of NMIBC is just as significant as that of MIBC, though maybe not as immediate a threat to survival, especially when taking into account rates of progression reaching as high as 50–60%. A considerable amount of information is available on molecular subtyping for NMIBC that is helping researchers hone in on the most important mutations in the evolution of bladder cancer[59,70,71]. Low-grade bladder tumors would appear to be genetically distinct from high-grade and MIBC, demonstrating highly conserved genetic mutations of *FGFR3*, *PIK3CA*, *STAG2*, and/or the RTK/RAS/RAF pathway[72–75]. High-grade NMIBC, on the other hand, is more like muscle-invasive disease, exhibiting alteration of DNA damage repair genes (*ERBB2*), cell cycle regulators (*p53*, *RB1*, *MDM2*, and *CDKN2A*), and chromatin-modifying genes (*KDM6A* and *ARID1A*)[75].

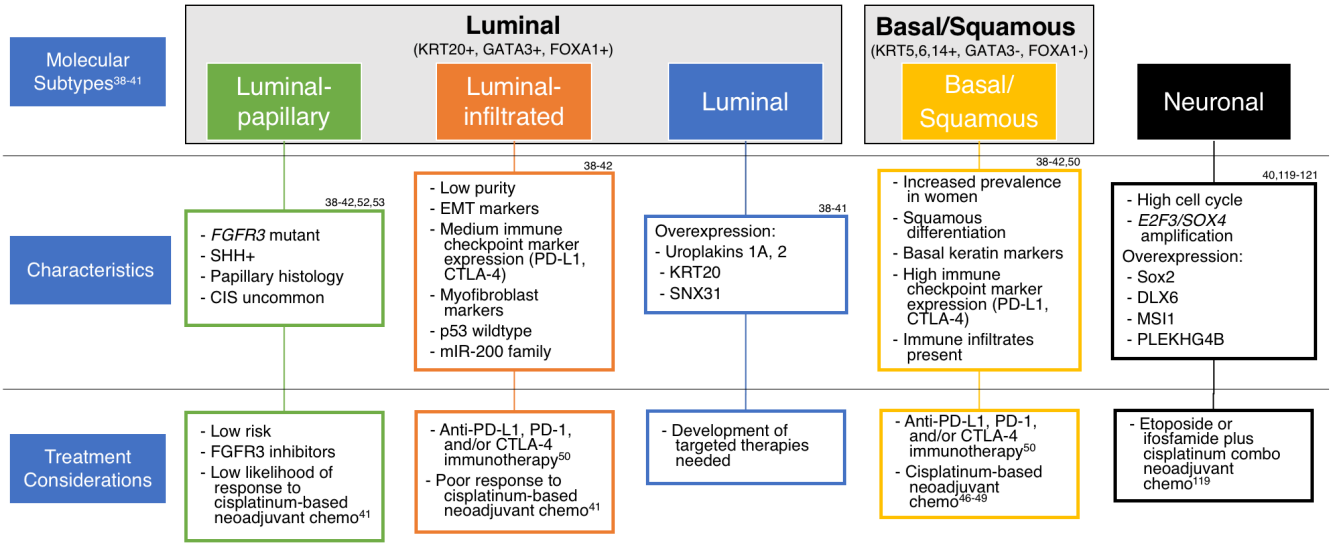

Figure 2. Molecular subtypes of muscle-invasive bladder cancer with associated clinicopathologic and genomic characteristics. Proposed treatment considerations are listed for each subtype based on available clinical data[53–57,63,64,66–69]. CIS, carcinoma *in situ*; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; DLX6, distal-less homeobox 6; E2F3, E2F transcription factor 3; EMT, epithelial to mesenchymal transition; FGFR3, fibroblast growth factor receptor 3; FOX, forkhead box; GATA, GATA-binding protein; KRT, keratin; miR-200, microRNA 200; msi1, Musashi homolog 1; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PLEKHG4B, pleckstrin homology and RhoGEF domain containing G4B; SHH, sonic hedgehog; SNX31, sorting nexin 31; SOX, SRY-box.

Molecular subtyping based on transcriptome analysis of 460 NMIBC and 16 MIBC samples by Hedegaard *et al.* identified three predominant classes of NMIBC, of which class two showed clustering of high-grade and CIS pathology with an increased risk of clinical progression, indicating that this may be a signature warranting more aggressive, definitive therapy upfront[71]. The *TERT* promoter is worth specific attention owing to similar frequency throughout all tumor stages and grades, regardless of tumor aggressiveness or molecular subtype, and likely represents an early event in the development of urothelial neoplasms[76–78].

Personalized approach to bladder cancer therapy

Intravesical therapies

Instillation of chemotherapy immediately (within 24 hours) following TUR has been proposed as a method of reducing bladder cancer recurrences, specifically for low- and intermediate-risk disease, and is recommended by both the AUA and the EAU guidelines for NMIBC[10,11]. It is hypothesized to work via two main methods: (1) residual tumor that has not been fully resected will be killed and (2) elimination of free-floating cancerous cells dislodged during resection that may adhere to the urothelium and proliferate in a region separate from the primary[79,80]. The most well-studied agents include mitomycin C, doxorubicin, and epirubicin, all of which have been found to reduce recurrences (HR 0.40–0.65) without impacting progression or survival outcomes[81–89]. This is probably because of the preponderance of low-risk tumors included in the study cohorts, which are already at very low risk of progression to begin with. According to a recent, large meta-analysis, immediate post-resection instillation would appear to be most effective for small (<3 cm), low-grade, papillary tumors with a baseline recurrence rate of >1 year[89]. Not all urologists support this mode of treatment owing to the small but catastrophic possibility of chemotherapy leaking into the perivesical space via missed bladder perforation, in some cases resulting in end-stage bladder fibrosis, for the minimal clinical benefit of prolonging time between recurrences of relatively indolent tumors[90,91]. Though the overwhelming majority of available literature may offer support for this viewpoint, Bosscheiter *et al.* published a prospective, randomized trial of immediate post-operative mitomycin C versus instillation 2 weeks later among more than 2,000 patients across all risk categories, finding an overall reduction in 3-year recurrence (27% versus 36%) and progression (2.7% versus 5.5%)[92]. Interestingly, on subgroup analysis, only the intermediate- and high-risk patients—who also received an adjuvant 6- to 12-week course of intravesical mitomycin C—were found to benefit from the immediate post-operative dose.

Induction intravesical therapy refers to a period of weekly instillations of chemotherapy (i.e. mitomycin C, epirubicin, gemcitabine, etc.) or immunotherapy (i.e. BCG) following a complete TUR for NMIBC. At this point, TUR followed by a 6-week course of BCG plus 1 to 3 years of appropriate (3-weekly instillations based on SWOG protocol) maintenance therapy is the first-line option for high-risk disease with a proven improvement in disease recurrence and progression[10,11,93–96]. Intermediate-risk bladder cancer, on the other hand, can be successfully treated with either chemotherapy or immunotherapy; however, BCG must be followed by at least 1 year of maintenance in order to maintain an advantage in recurrence over mitomycin C[94,97]. Furthermore, while only BCG has shown improvement in progression for these patients, the potential side effects should be considered when selecting a treatment strategy[97–99].

Patients who fail an adequate induction course of intravesical therapy, particularly those receiving BCG who are at highest risk for disease progression, pose a therapeutic dilemma: remove the bladder immediately to prevent muscle invasion and possible metastasis or continue local treatment with further instillations. It is preferable to avoid the morbidity and impact on quality of life associated with radical cystectomy; however, there are currently few alternatives in this setting. The lack of a standardized definition of BCG failure, recognizing that not all forms share the same prognosis, has hindered research into this area. To address these shortcomings, an international panel published guidance for clinicians and researchers to aid in creating more uniformity when designing trials and reporting on this group of patients, as well as to differentiate those with poorest prognosis (BCG unresponsive) who may not benefit from further BCG therapy (Table 2)[100]. The AUA recommends enrolment in clinical trials for patients who have demonstrated BCG unresponsiveness but are unwilling or unable to undergo a radical cystectomy[11]. Several such trials have offered promising results, with most reporting short-term reduction in recurrence of approximately 30–50%, but longer follow-up is associated with sharp declines in responsiveness, and, therefore, there is insufficient evidence to support any single approach, and radical cystectomy remains the gold standard in this population[94,101–107].

Early cystectomy for non-muscle-invasive bladder cancer

Immediate radical cystectomy may be the best treatment option for selected patients with certain adverse "very high-risk" factors found at the time of diagnosis of NMIBC (Figure 3). High-volume T1, persistent high-grade T1 on re-TUR, lymphovascular invasion, certain variant histologies (i.e. micropapillary, plasmacytoid, nested), or concomitant CIS have all been associated with increased risk of progression and are best managed with surgery[108–113]. A group from the United Kingdom has designed a prospective, randomized controlled trial, with end of accrual set for March 2018, comparing immediate cystectomy against BCG induction with maintenance therapy for a "very high-risk" population of NMIBC patients[114]. Notably excluded from their cohort are any patients with variant histology.

Radiotherapy

Trimodal bladder-preserving therapy involves complete endoscopic resection of all visible tumor followed by neoadjuvant chemotherapy and definitive whole-bladder external beam radiotherapy. The use of this strategy is not widespread in the United States, but prospective European cohorts have demonstrated comparable disease-specific outcomes when compared to contemporary radical cystectomy cohorts[115]. Limited evidence regarding optimal patient selection has identified increased expression of MRE11, a protein involved in the cellular response to radiation damage, as a potential prognostic marker for improved cancer-specific survival following radiotherapy[116,117].

Timing of chemotherapy for muscle-invasive bladder cancer

Muscle invasion at diagnosis of bladder cancer is a poor prognostic indicator best treated with neoadjuvant cisplatinum-based multiagent chemotherapy followed by radical cystectomy according to evidence from several phase III clinical trials[118–121]. Disease status on final pathology is strongly correlated with oncologic outcomes, and neoadjuvant therapy leads to significant downstaging, including rates of complete response in the range of 30–40% compared to only 15% with surgery alone[119]. However, this still leaves a large portion of patients who will not derive benefit, instead undergoing unnecessary toxic therapy while at the same time delaying surgery. Risk stratification can be useful in this setting by selecting those patients with the highest risk (pre-operative T3b–T4, hydroureteronephrosis, lymphovascular invasion, and specific histologic variants) for poor outcomes after cystectomy and only administering neoadjuvant chemotherapy to this subgroup (Figure 4)[122,123]. Likewise, post-operative chemotherapy (i.e. adjuvant) can be administered in patients with proven pathologic predictors of developing metastasis, though evidence to support its use is lacking. One study (EORTC 30994) was able to show an improvement in progression-free survival; however, there was no statistically significant impact on overall survival[124].

Conclusions

The appropriate management of bladder cancer patients relies heavily upon risk stratification to personalize the therapy for the patient. Currently, clinicopathologic features are the cornerstone of the most widely used risk assessment tools with ample room for improvement. Advances in genetic sequencing of tumors has led to classification systems based on the mutational profile of each individual, offering prognostic information. As these data expand, it is feasible that in the near future

Table 2. A classification system for bacillus Calmette-Guérin (BCG) failures[100].

Type of failure	Description
BCG refractory	Persistence of high-grade disease at 6 months (3 months for T1 high grade) following adequate BCG treatment
BCG relapsing	Recurrence of high-grade disease following adequate BCG treatment with a disease-free period of 6 months
BCG unresponsive	Includes BCG refractory and BCG relapses within 6 months (12 months for carcinoma *in situ* patients)
BCG intolerant	Persistence of high-grade disease in a patient who is unable to tolerate induction BCG secondary to toxicity

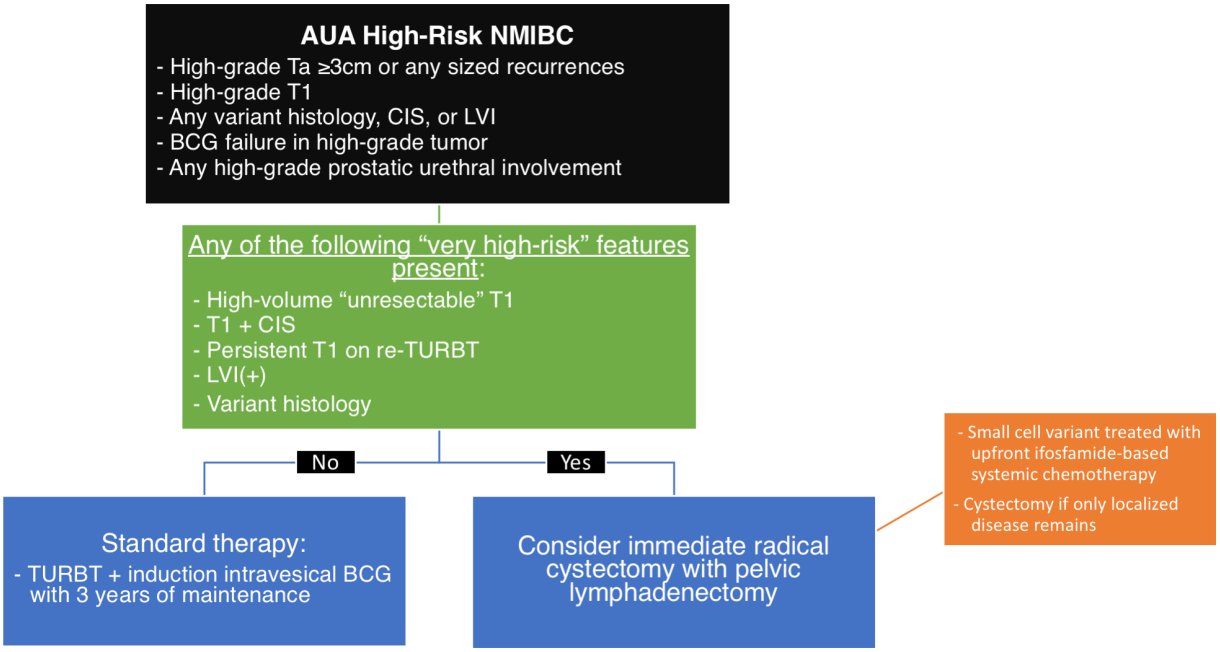

Figure 3. Proposed decision model for immediate radical cystectomy in patients with "very high-risk" non-muscle-invasive bladder cancer (NMIBC)[11,125–129]. AUA, American Urological Association; BCG, bacillus Calmette-Guérin; CIS, carcinoma *in situ*; LVI, lymphovascular invasion; TURBT, transurethral resection of bladder tumor.

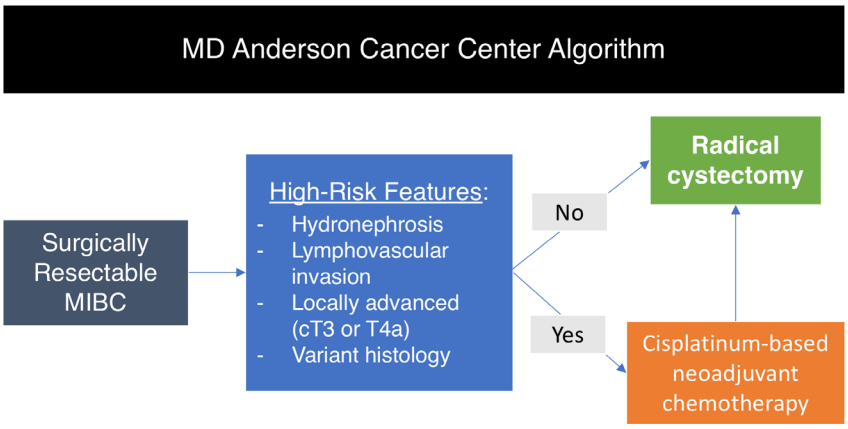

Figure 4. Current MD Anderson Cancer Center algorithm for determining which patients should receive neoadjuvant chemotherapy versus immediate radical cystectomy. Inclusion of molecular markers for further risk stratification is pending clinical validation[37]. MIBC, muscle-invasive bladder cancer.

this could be integrated to provide guidance that is truly "next generation".

Abbreviations

AUA, American Urological Association; BCG, bacillus Calmette-Guérin; CIS, carcinoma *in situ*; CUETO, Spanish Urological Club for Oncological Treatment; EAU, European Association of Urology; EORTC, European Organization for Research and Treatment of Cancer; MIBC, muscle-invasive bladder cancer; NMIBC, non-muscle-invasive bladder cancer; SWOG, Southwest Oncology Group; TCGA, the Cancer Genome Atlas; TUR, transurethral resection

Competing interests

AMK is a consultant to TMC Innovation, Merck, BMS, Arquer, MDxHealth, Photocure, Theralase, Cepheid, Medac, Asieris, Pfizer, and Astra Zeneca and has received research funding from FKD, Merck, Telesta, and Adolo. JTM has no competing interests to declare.

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The referees who approved this article are:

Version 1

1 **Michael O Koch** Department of Urology, Indiana University, Indianapolis, Indiana, USA
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1 **Francisco X Real** Epithelial Carcinogenesis Group, Cancer Cell Biology Programme, Spanish National Cancer Research Centre, Madrid, Spain
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