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High-risk nonmuscle invasive bladder cancer

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High-risk nonmuscle invasive bladder cancer: definition and epidemiology

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Purpose of review
Nonmuscle invasive bladder cancer represents a large majority of patients diagnosed with this disease. Precise definition and risk stratification are paramount in this group as high-risk patients have higher rates of progression and mortality and may benefit from early identification and aggressive treatment.

Recent findings
The mainstay definitions of high-risk nonmuscle invasive bladder cancer are based on grade and stage. Recently, efforts have been made to incorporate other clinical variables into multivariate risk assessment tools and nomograms to predict disease behavior and guide management. Variant histology and molecular biomarkers are being explored as tools to refine risk stratification; however, results are still preliminary and need validation.

Summary
Future research should concentrate on ways to better risk-stratify patients and identify early those that are most likely to recur and progress quickly. Topics of focus should be on better multivariate risk assessment tools and nomograms providing continuous scales and incorporating molecular markers with validation in large multi-institutional cohorts.

Keywords
bladder cancer, nonmuscle invasive, risk assessment

INTRODUCTION

Bladder cancer is the fifth leading new cancer diagnosis in the USA and has one of the highest treatment costs [1,2]. Most patients (>75%) newly diagnosed have nonmuscle invasive disease (i.e., restricted to bladder mucosa or lamina propria). Within this group, there is a subset of high-risk patients who progress to invasive, and possibly to metastatic stages, among whom early identification and aggressive treatment could reduce the morbidity and mortality associated with this malignancy. Indeed, recent studies suggest that progression of nonmuscle invasive bladder cancer (NMIBC) to muscle invasive disease is associated with a worse prognosis [cancer-specific survival (CSS) of 37% at 3 years] compared with patients diagnosed initially with muscle invasive disease (CSS 67%), which emphasizes a great need for substantially improved risk stratification and earlier definitive treatment for high-risk cases [3▪▪,4].

DEFINING HIGH RISK: GRADE AND STAGE

High-risk NMIBC can be defined in many ways. Historically, this definition has been based mostly on grade and stage of tumor which are consistently related to tumor progression, recurrence, and subsequently mortality [5]. Rates of progression in high-risk patients can be as high as 45% and rates of recurrence up to 80% within 5 years [6]. Four large organizations [European Association of Urology (EAU), First International Consultation on Bladder Tumors (FICBT), National Comprehensive Cancer Network (NCCN), and American Urologic Association (AUA)] have proposed criteria for risk stratification; these vary somewhat, but in general, high-risk NMIBC are those cancers which are T1 (invading the lamina propria), and high grade (Ta - confined to bladder mucosa - or T1), and associated with carcinoma *in situ* (CIS). The four sets of criteria are summarized in Table 1.

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KEY POINTS

- High-risk nonmuscle invasive bladder cancer has a high rate of recurrence and progression.
- Defining high-risk patients is currently based largely on basic grading and staging paradigms.
- New insight into the molecular pathways and variant histology has provided further opportunities to better risk stratify newly diagnosed patients and warrants further research.
- Dissemination of guidelines and risk assessment tools will be essential in the early identification of high-risk patients.

On the basis of these definitions, approximately 50% of patients with NMIBC have one or more high-risk features that correlate to progression and subsequent mortality. In those with high-grade Ta disease (20%), 15–40% will show progression and 10–25% will eventually succumb to their disease. Patients with T1 disease (20%) have a higher rate of progression (30–50%) and mortality (33%). CIS (which is primary disease in 10% of NMIBC) has the highest rate of progression (>50%) and a lower rate of mortality (21%) [5].

REFINED DEFINITION: MULTIVARIABLE RISK ASSESSMENT

The European Organization for Research and Treatment of Cancer (EORTC) recently incorporated standard clinical and pathologic criteria (in addition to grade and stage) in a multivariable risk analysis to develop a scoring system intended to predict recurrence and progression in individual patients. Risk factors were identified from a database of over 2500 patients with NMIBC from seven clinical trials (enrollment 1979–1989), and six predictors were determined: tumor grade, clinical T stage, presence of concomitant CIS, number of tumors, tumor diameters, and prior recurrence rate [6,7]. Table 2 and the relevant part of Table 1 are adapted from these results and demonstrate how recurrence or progression scores based on these risk factors affect the probability of both outcomes. These definitions likely offer more precise risk classification than the other consensus definitions; however, the results and scoring system will still need to be validated in other cohorts.

VARIANT PATHOLOGY AND HIGH-RISK CLASSIFICATION

Aside from general grade and stage as determinants of divergent biology of NMIBC, variant histology

Table 1. Definitions for risk stratification and rates of recurrence and progression by association

	Low risk			Intermediate risk			High risk		
	Definition	Recurrence (%, 95% CI)	Progression (%, 95% CI)	Definition	Recurrence (%, 95% CI)	Progression (%, 95% CI)	Definition	Recurrence (%, 95% CI)	Progression (%, 95% CI)
EAU	EORTC Score 0 for recurrence/ progression	1 year: 15 (10–19)	1 year: 0.2 (0–0.7)	EORTC Score >0 for recurrence, 2–6 for progression	1 year: 38 (35–41)	1 year: 1 (0.4–1.6)	EORTC score 7–23 for progression	1 year: 61 (55–67)	1 year: 17 (10–24)
		5 year: 31 (24–37)	5 year: 0.8 (0–1.7)		5 year: 62 (58–65)	5 year: 6 (5–8)		5 year: 78 (73–84)	5 year: 45 (35–55)
FICBT	Low-grade Ta (G1–G2)	–	–	Low-grade Ta multifocal/ recurrent tumors	–	–	High-grade Ta, all T1, CIS	–	–
NCCN	Low-grade Ta (G1)	5 year: 50%	Minimal	High-grade Ta (G2–3)	5 year: 60%	Moderate	All T1, CIS	50–90%	High
AUA	Small volume, low-grade Ta	–	–	Multifocal/large volume low-grade Ta	–	–	High-grade Ta, all T1, CIS	5 year: 32 (21–44)	5 year: 14 (8–22)

Recurrence and progression rates were only shown for high-risk group in AUA guidelines (2010) and not reported for FICBT guidelines in summary format.
Grading is based on the World Health Organization International Histological Classification of Tumors, 1973. Most pathologists would classify a grade 2 tumor as high grade.
EORTC scoring system: see Table 2.

Table 2. EORTC recurrence and progression scores

Predictive factor	Recurrence	Progression
No. of tumors		
1	0	0
2–7	3	3
8 or more	6	3
Tumor diameter		
<3 cm	0	0
3 or more cm	3	3
Recurrence rate		
First tumor	0	0
1 Recurrence per year	2	2
>1 Recurrence per year	4	2
Stage		
Ta	0	0
T1	1	4
Presence of CIS		
No	0	0
Yes	1	6
Grade (1973 WHO)		
1	0	0
2	1	0
3	2	5
Total score	0–17	0–23
Low risk	0	0
Intermediate risk	1–9	2–6
High risk	10–17	7–23

Overall risk: low = low risk recurrence score (0) and progression score (0). Intermediate = intermediate (1–9) or high (10–17) risk recurrence score and intermediate risk (2–6) progression score. High = high-risk progression score (7–23).
Adapted with permission from [7].
CIS, carcinoma *in situ*; EORTC, European Organization for Research and Treatment of Cancer.
Electronic Calculator available at http://www.eortc.be/tools/bladdercalculator.

may identify patients with poor prognosis. Histologic variants (micropapillary, glandular, nested, sarcomatoid, and squamous) have been associated with poor prognosis and respond poorly to conventional treatments [8]. Many variant tumors invade muscle early and a majority of the literature on this group addresses prognosis after cystectomy, but a subset of tumors are limited to the lamina propria and therefore considered NMIBC.

A few studies have highlighted that patients with NMIBC and variant histology should be defined as high risk, as their chance of progression is approximately 40%. Some researchers argue that early aggressive therapy is essential in this group of patients as usual treatments with intravesical therapy are ineffective (17% disease-free survival at 2 years with intravesical BCG therapy), whereas others state that intravesical therapy can be used safely in most of these patients with intensive follow-up and equivalent mortality rates [9–12]. Ultimately, it remains unclear at this point whether variant histology predicts poor outcomes independent of grade and stage or rather simply tends to associate with these standard adverse tumor characteristics. In future studies, variant histology may add valuable information to risk assessment tools and nomograms and help better define true high-risk NMIBC and identify patients for early treatment.

RISK STRATIFICATION: NOMOGRAMS

Multivariate risk classification, such as the EORTC classification, described above is invaluable in appropriately stratifying patients to specific groups followed by subsequent appropriate evidence based treatment. However, the predictive capability of risk groups for individual counseling is limited to an extent by their categorical nature and does not fully account for heterogeneity of tumor biology. Nomograms and related tools can classify individual risk more precisely, and therefore may be more useful in guiding individual treatment. A recent review of bladder cancer prediction tools revealed five nomograms in clinical practice [13]. By comparison, over 110 nomograms and related instruments for prostate cancer were published as of the same year [14]. Only one of the bladder nomograms is applicable to NMIBC, and, critically, none of the bladder nomograms has undergone external validation [13].

Shariat *et al.* [15] published the first nomogram for NMIBC to estimate the risk of recurrence and progression in these patients using a contemporary cohort of over 2500 patients from 10 institutions. Accuracy for predicting any cancer recurrence was 84%, and the model was able to distinguish more aggressive features in 87% of patients. However, the area under the curve (AUC) was improved by incorporating the institution into the model with AUC approaching 0.95, raising the concern for external validity. Interestingly, unlike other predictive tools which rely heavily on pathologic tumor characteristics, in this nomogram patient's age, sex, urinary cytology, and urinary biomarker levels (NMP22) provided the best predictive accuracy.

MOLECULAR BIOMARKERS: RISK STRATIFICATION OF THE FUTURE?

Many investigators have attempted to further define high-risk NMIBC patients with the use of molecular biomarkers with mixed results regarding clinically

relevant prognostic information in addition to grade and stage [16,17]. It is believed that superficial low-grade cancers and invasive or high-grade cancers progress via different molecular pathways [18,19]. Chromosome 9 losses occur early during tumorigenesis, whereas alterations to p53 and retinoblastoma tumor suppressor genes as well as loss of heterozygosity at chromosome 17 are more frequent in high-risk disease (CIS, high-grade NMIBC, and muscle invasive cancer) [20,21]. Other downstream pathways and interactions that contribute to progression and recurrence are not as well defined, but many studies suggest that cell cycle regulators may play an integral role in high-risk disease and subsequent progression. Combinations of cell cycle markers (p53, p21, p27, and pRB) were recently found to be more effective in stratifying patients into high-risk groups. The more markers with altered expression, the higher the risk ratio for progression, recurrence, and death (9 to 56, $P < 0.05$) [22]. Therefore, those with two or more alterations of cell cycle would be defined as high risk and may benefit from early aggressive treatment.

Conversely, investigators have found that fibroblast growth factor receptor 3 mutations (FGFR3) are associated with favorable prognosis and help identify a subgroup of lower risk NMIBC with 84% of Ta low-grade tumors having this mutation compared with only 7% of high-risk tumors [23]. Recently, investigators have attempted to combine information from molecular markers with other risk assessment tools. van Rhijn *et al.* [8] substituted histological grade in the EORTC calculator discussed above with a molecular grade based on FGFR3 and cell cycle marker mutations to denote lower and higher grade disease, respectively. They found an equivalent predictive value of defining low, intermediate, and high-risk disease with better reproducibility between institutions as compared with histological grade alone. Additionally, when molecular grade was combined with the original EORTC score predictive accuracy for progression increased by 7%, particularly in the intermediate-risk and high-risk groups.

By incorporating molecular markers into clinical decision tools, true high-risk patients could be defined early and treated aggressively, hopefully with the desired results of prolonged survival and decreased morbidity. Molecular biomarkers may play a key role in future risk stratification strategies; however, the details remain to be elucidated, as further studies will need to be completed to validate early results.

As discussed above, only one urinary biomarker (NMP22) has been incorporated into a risk stratification nomogram for NMIBC. Shariat *et al.* [24] assessed the ability of NMP22 individually to predict bladder cancer recurrence and progression in a multicenter cohort and found that there was a significant heterogeneity in diagnostic performance. Additionally, there was not a clearly defined cutoff point that denotes higher risk disease, but here is a continuum of risk for recurrence and progression. Other FDA approved urinary biomarkers that are mainly used in bladder cancer detection (e.g., BTA Trak and UroVysion) have not been studied in the context of defining high-risk patients with nonmuscle invasive disease.

TRENDS IN THE MANAGEMENT OF HIGH-RISK NONMUSCLE INVASIVE BLADDER CANCER

As described above, high-risk bladder cancer inherently has a high rate of recurrence and progression. Guidelines by the same entities described above were established to minimize the morbidity and mortality associated with disease progression, and include somewhat costly and invasive follow-up and treatments. Chamie *et al.* [25,26▪] recently published two articles highlighting the under-use of care in patients with high-risk bladder cancer. Out of 4545 patients analyzed using Surveillance, Epidemiology, and End Results (SEER)-Medicare linked dataset, only 5% of patients with high-risk disease had all appropriate cystoscopy and cytology performed, and 50% had proper imaging follow-up. Patients who had four or more cystoscopies, cytology, and early use of intravesical immunotherapy had a lower risk (59%) or mortality than those who had less intensive follow-up. However, only 14% of the SEER-Medicare cohort had this level of care that was associated with increased survival.

The guidelines discussed above for NMIBC also endorse early cystectomy as an option for selected patients with high-risk disease. There is conflicting evidence with some institutions finding improved cancer-specific mortality and others reporting equivalent outcomes between patients managed with early cystectomy and conservative management [27–30]. Unfortunately, the majority of these studies are single institutions and retrospective with likely selection bias explaining differences in conclusions. Kutikov *et al.* recently analyzed a SEER cohort of 8467 men to evaluate trends and outcomes in the use of early cystectomy in high-risk NMIBC defined as high-grade T1 disease. Only 4.7% underwent immediate radical cystectomy, suggesting an under-use in this population. They found that cystectomy patients were younger and had significantly improved overall survival than noncystectomy patients. Interestingly, however, cancer-specific mortality was not

statistically significant between patients managed with cystectomy and those managed more conservatively at 3 years [31▪]. The reason for this difference is unclear, but may be a result of selection bias, and further studies are needed to validate these findings.

CONCLUSION

Future research should concentrate on the ways to better risk-stratify patients and identify early those that are most likely to recur and progress quickly. Topics of focus should include better multivariate risk assessment tools and nomograms providing continuous scales and incorporating molecular markers. These tools will need to be validated on large cohorts of patients highlighting another deficiency in bladder cancer research: the lack of large, multi-institutional registries with prospective enrollment and long-term follow-up. Additionally, we will have to ensure that early treatment and quality-of-care follow suit with progress in risk assessment. The dissemination of – and adherence to – current and future guidelines that affect morbidity and mortality will be of critical importance, if we hope to make progress toward decreasing bladder cancer-specific mortality.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 436).

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