Review Article

Non-muscle invasive bladder cancer risk stratification

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ABSTRACT

Introduction: Non-muscle invasive bladder cancer (NMIBC) comprises about 70% of all newly diagnosed bladder cancer, and includes tumors with stage Ta, T1 and carcinoma in situ (CIS.) Since, NMIBC patients with progression to muscle-invasive disease tend to have worse prognosis than with patients with primary muscle-invasive disease, there is a need to significantly improve risk stratification and earlier definitive treatment for high-risk NMIBC.

Materials and Methods: A detailed Medline search was performed to identify all publications on the topic of prognostic factors and risk predictions for superficial bladder cancer/NMIBC. The manuscripts were reviewed to identify variables that could predict recurrence and progression.

Results: The most important prognostic factor for progression is grade of tumor. T category, tumor size, number of tumors, concurrent CIS, intravesical therapy, response to bacillus Calmette–Guerin at 3- or 6-month follow-up, prior recurrence rate, age, gender, lymphovascular invasion and depth of lamina propria invasion are other important clinical and pathological parameters to predict recurrence and progression in patients with NMIBC. The European Organization for Research and Treatment of Cancer (EORTC) and the Spanish Club UrológicoEspañol de Tratamiento Oncológico (CUETO) risk tables are the two best-established predictive models for recurrence and progression risk calculation, although they tend to overestimate risk and have poor discrimination for prognostic outcomes in external validation. Molecular biomarkers such as Ki-67, FGFR3 and p53 appear to be promising in predicting recurrence and progression but need further validation prior to using them in clinical practice.

Conclusion: EORTC and CUETO risk tables are the two best-established models to predict recurrence and progression in patients with NMIBC though they tend to overestimate risk and have poor discrimination for prognostic outcomes in external validation. Future research should focus on enhancing the predictive accuracy of risk assessment tools by incorporating additional prognostic factors such as depth of lamina propria invasion and molecular biomarkers after rigorous validation in multi-institutional cohorts.

Key words: Non-muscle invasive bladder cancer, superficial bladder cancer, outcome, prediction models, progression, recurrence, risk stratification

INTRODUCTION

Bladder cancer is the second most commonly diagnosed genitourinary malignancy in the USA, with an estimated 74,000 newly diagnosed cases and 16,000 deaths in 2015.[1] The incidence of bladder cancer rises with age, peaking between age 50 and 70 years, and is three times more common in men than in women.[1] Commonly accepted risk factors for bladder cancer include cigarette smoking, occupational exposure to aniline dyes, benzidene compounds, analgesic abuse (phenacetin) and chronic irritation, such as indwelling catheters.[2]

Of all newly diagnosed cases of bladder cancer, about 70% present as non-muscle invasive bladder cancer (NMIBC), also known as superficial bladder cancer.[3,4] It comprises a

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heterogeneous group of patients and includes pathological stage Ta (confinement to the epithelium or mucosa), T1 (invasion of the subepithelial connective tissue or lamina propria) and CIS (Tis: Flat, high-grade, non-papillary carcinomas confined to the urothelium). Of all newly diagnosed NMIBC, 70% present as stage Ta, 20% as T1 and 10% as CIS.[3,4] Approximately 50-70% of NMIBC will recur and roughly 10–20% will progress to muscle (i.e., muscularis propria) invasive disease.[3,4] In patients with low-grade Ta disease, the 15-year progression-free survival is 95% with no cancer-specific mortality.[5] Patients with high-grade Ta tumors had a progression-free survival of 61% and a disease-specific survival of 74%, whereas patients with T1 disease had a progression-free survival of 44% and a disease-specific survival of 62%, providing support to the view that grouping all patients with NMIBC as one disease is misleading as one patient's prognosis can be quite different from that of another patient.[5] When considering a patient's prognosis with NMIBC, it is necessary to consider not only clinical and pathological factors but also take into account the potential effect of the intravesical treatment received and molecular alterations present in the tumors.

RISK STRATIFICATION BASED ON CLINICAL AND PATHOLOGICAL PARAMETERS

Table 1 summarizes the available predictive models to predict recurrence and progression in patients with NMIBC. The most important risk factor for progression is grade, not stage, because patients with high-grade tumors progress with similar frequency regardless of whether they were invasive (T1) or non-invasive (Ta).[19] Millan-Rodriguez *et al.*[19] evaluated a cohort of 1529 primary NMIBC patients treated with transurethral resection (TUR) and random bladder biopsy and identified prognostic factors for recurrence, progression and disease-specific mortality (median follow-up: 40 months). Multivariate analysis demonstrated that the main prognostic factors of recurrence were multiplicity, tumor size >3 cm, presence of CIS and treatment with bacillus Calmette–Guerin (BCG). The prognostic factors for progression were grade 3 disease, multiplicity, tumor size >3 cm, CIS and treatment with BCG. Furthermore, the prognostic factors for mortality were presence of grade 3 disease and CIS.

In another study, Millan-Rodriguez *et al.*[9] stratified NMIBC into three risk groups based on previously identified risk factors.[19] Risk groups were classified as:

- Low risk (grade 1 stage Ta disease and a single grade 1 stage T1 tumor)
- Intermediate risk (multiple grade 1 stage T1 tumors, grade 2 stage Ta disease and a single grade 2 stage T1 tumor)
- High risk (multiple grade 2 stage T1 tumors, grade 3 stages Ta and T1 disease and any stage disease associated with CIS).

The rates of recurrence, progression and mortality were 37%, 0% and 0% in the low-risk group, 45%, 1.8% and 0.73% in the intermediate-risk group and 54%, 15% and 9.5% in the high-risk group. The relative risks of recurrence, progression and mortality in the low-risk versus intermediate-risk and high-risk groups were 1.37, 2.84 and 1, and 1.87, 24.76 and 14.69, respectively.

The European Organization for Research and Treatment of Cancer (EORTC) developed risk tables to predict recurrence and progression in patients with NMIBC using clinical and pathologic information from 2596 patients enrolled in seven clinical trials that utilized prophylactic treatments after TUR.[3] The median follow-up was 3.9 years and 78% of patients had received intravesical treatment, mostly with chemotherapy. In their study cohort, 80% of patients had a maximum tumor diameter < 3 cm and 56% of patients had pTa tumors. The EORTC risk tables [Tables 2 and 3] for recurrence and progression were based on the scoring system derived from the following six clinical and pathological factors:

- Number of tumors
- Tumor size
- T category
- Tumor grade (WHO 1973)
- Prior recurrence rate
- Presence of concurrent CIS.

Based on these EORTC risk tables (electronic calculator is available at http://www.eortc.be/tools/bladdercalculator/), the probability of recurrence varied from 15% to 61% at 1 year and from 31% to 78% at 5 years. The probability of progression varied from 0.2% to 17% at 1 year and from 0.8% to 45% at 5 years. For their recurrence and progression models, Harrell's concordance indices at 1 year were 0.66 and 0.74, respectively. Of note, only 6.6% (171 of 2596) patients received BCG for six induction instillations. In addition, patients with high-grade disease did not have a second TUR or receive maintenance BCG therapy.

BCG is currently the most effective intravesical therapy for NMIBC, especially in intermediate- and high-risk tumors. A meta-analysis of 24 randomized trials (n = 4863) showed that BCG significantly reduces the risk of progression to muscle-invasive disease after TUR in patients with NMIBC who receive maintenance BCG.[20] The patient's response to BCG at 3 or 6 months is an important prognostic factor to predict subsequent tumor recurrence and progression.[21,22] Because the EORTC risk tables were generated using NMIBC patient's clinical and pathological information, where majority of the patients did not receive BCG induction and/or BCG maintenance therapy, the EORTC risk tables tend to overestimate patient's risk for recurrence and progression after BCG therapy.[23]

The Spanish Club UrológicoEspañol de TratamientoOncológico (CUETO) group[4] developed a

Table 1: Prediction of disease recurrence and progression in patients with non-muscle invasive bladder cancer

Author	Year	No. of patients	Risk estimation method	Outcome	Variables	Accuracy	Validation
Parmar *et al.*[6]	1989	919	Risk groups	Recurrence	Cystoscopy at 3 months after initial transuretheral resection and number of tumors	Not reported	Not performed
Kiemeney *et al.*[7]	1993	1674	Risk groups	Recurrence	Tumor stage, number of tumors, tumor extent, intravesical therapy	57.60%	Internal
				Progression	Tumor stage, tumor grade, number of tumors, result of random biopsies	67.30%	
Mulders *et al.*[8]	1994	387	Risk groups	Recurrence	Location of tumor, number of tumors	Not reported	Not performed
Millan-Rodriguez *et al.*[9]	2000	1529	Risk groups	Recurrence	Number of tumors, tumor size, CIS association, intravesical therapy	Not reported	Not performed
				Progression	Number of tumors, tumor grade, tumor size, CIS association, intravesical therapy		
Quershi *et al.*[10]	2000	56 for recurrence, 105 for progression	Artifical neural network	Recurrence	Tumor stage, tumor grade, tumor size, number of tumors, gender, EGFR status, smoking status, histology of mucosal biopsies, CIS association, tumor metaplasia, tumor architecture, tumor site, c-erbB2 status, p53 status	75%	Internal
				Progression	Tumor stage, tumor grade, tumor size, number of tumors, gender, EGFR status	80%	
Catto *et al.*[11]	2003	109	Neuro-fuzzy modeling, artificial neural network	Recurrence	p53, mismatch repair proteins, stage, grade, age, smoking status, previous cancer	NFM: 88-92%, ANN: 90-95%	Internal
Fujikawa *et al.*[12]	2003	90	Artificial neural network	Recurrence	Tumor stage, tumor grade, number of tumors, age, gender, tumor architecture, estimates of mean nuclear volume	No prediction possible	Internal
				Progression	Tumor stage, tumor grade, number of tumors, age, gender, tumor architecture, estimates of mean nuclear volume	72.70%	
Shariat *et al.*[13]	2005	2542	Nomogram	Recurrence	Age, gender, urine cytology and NMP22	81.10%	Internal
				Progression	Age, gender, urine cytology and NMP22	77.40%	
Catto *et al.*[14]	2006	117	Neuro-fuzzy modeling, artificial neural network	Progression	Tumor stage, tumor grade, age, gender, smoking status, p53 expression, methylation status of 11 loci	NFM: 94-100% ANN: 89-90%	Internal
Sylvester *et al.*[3]	2006	2596	Risk tables	Recurrence	Number of tumors, tumor size, tumor grade, T category, prior recurrence rate, presence of concurrent CIS	61% at 1 year, 78% at 5 years	Internal and external
				Progression	Number of tumors, tumor size, tumor grade, T category, prior recurrence rate, presence of concurrent CIS	74% at 1 year, 75% at 5 years	
Hong *et al.*[15]	2008	1587	Nomogram	Recurrence	Age, number of tumors, tumor size, tumor grade, CIS association, intravesical therapy	60%	Internal
Fernandez-Gomez *et al.*[4]	2009	1062	Risk tables	Recurrence	Gender, age, recurrent tumor, number of tumors, CIS association, tumor grade	63.6% at 1 year, 64.4% at 5 years	Internal and external
				Progression	Age, recurrent tumor, number of tumors, T category, CIS association, tumor grade	68.7% at 1 year, 70% at 5 years	
Yamada *et al.*[16]	2010	800	Nomogram	Recurrence	Number of tumors, tumor size, tumor shape, tumor grade, BCG use, anthracyline use	61%	Internal and external
				Progression	Tumor shape, tumor grade, T category	71%	
Pan *et al.*[17]	2010	1366	Nomogram	Recurrence	Tumor grade, number of tumors, prior recurrence rate, intravesical therapy	66%	Internal
				Progression	Tumor grade, T stage, age, intravesical therapy	79%	
Ali-El-Dein *et al.*[18]	2013	1019	Nomogram	Recurrence	Intravesical therapy, T category, number of tumors, history of recurrence	64.9% at 1 year, 69.4% at 5 years	Internal
				Progression	Intravesical therapy, tumor grade, tumor size	70.2% at 1 year, 73.5% at 5 years	

CIS=Carcinoma *in situ*, EGFR=Epidermal growth factor receptor, NFM=Neuro-fuzzy modeling, ANN=Artifical neural network, BCG=Bacillus Calmette-Guerin

Table 2: Weights used to calculate EORTC risk tables' recurrence and progression scores

Factor	Recurrence	Progression
Number of tumors		
Single	0	0
2-7	3	3
≥8	6	3
Tumor size		
<3 cm	0	0
≥3 cm	3	3
Prior recurrence rate		
Primary	0	0
≤1 rec/year	2	2
>1 rec/year	4	2
T category		
Ta	0	0
T1	1	4
CIS		
No	0	0
Yes	1	6
Grade		
G1	0	0
G2	1	0
G3	2	5
Total score	0-17	0-23

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Table 3: Probability of recurrence and progression according to the EORTC risk tables total score

Recurrence score	Recurrence at 1 year (95% CI)	Recurrence at 5 years (95% CI)
0	15% (10-19%)	31% (24-37%)
1-4	24% (21-26%)	46% (42-49%)
5-9	38% (35-41%)	62% (58-65%)
10-17	61% (55-67%)	78% (73-84%)
Progression scores	**Progression at 1 year (95% CI)**	**Progression at 5 years (95% CI)**
0	0.2% (0-0.7%)	0.8% (0-1.7%)
2-6	1.0% (0.4-1.6%)	6% (5-8%)
7-13	5% (4-7%)	17% (14-20%)
14-23	17% (10-24%)	45% (35-55%)

Reproduced with permission: Sylvester *et al*. European Urology 49: 466-477, 2006. CI=Confidence interval, EORTC=European Organization for Research and Treatment of Cancer

scoring model using information from 1062 patients treated with intravesical adjuvant BCG therapy to predict risk of recurrence and progression. Patients had BCG induction as weekly instillations for 6 weeks and six additional instillations repeated at 2-week intervals as a maintenance therapy. By the end of the study, 4.2% of patients received fewer than six instillations, 22.5% of patients received six to nine instillations and 73.3% of patients received more than 10 instillations. The risk tables for recurrence and progression were based on the scoring systems derived from seven clinical and pathological factors:

- Age
- Gender
- Number of tumors
- Recurrent tumor
- T category
- Tumor grade (WHO 1973)
- Presence of concurrent CIS.

Based on the CUETO risk tables, the probability of recurrence varied from 8.24% to 41.79% at 1 year to 20.98% to 67.61% at 5 years. The probability of progression varied from 1.17% to 13.97% at 1 year to 3.76% to 33.57% at 5 years. For their recurrence and progression models, Harrell's concordance indices at 1 year were 0.636 and 0.687, respectively. Using the CUETO risk tables, the calculated risk of recurrence were lower than that obtained by the EORTC risk tables. For progression probabilities, the risk is lower only in high-risk patients. The lower risks in the CUETO tables is likely attributable to using BCG, which is a more effective intravesical therapy.

Although the EORTC and CUETO risk tables are the two best-established predictive multivariate models for recurrence and progression risk calculation in patients with NMIBC, limitations include retrospective analysis, use of the 1987 TNM classification and use of the WHO 1973 grading system. In addition, repeat TUR for high-grade cancer and immediate instillation of chemotherapy, such as mitomycin, was not routinely performed after TUR; hence, both models are prone to overestimate the risk of recurrence and progression in patients treated with current standard of care. A restaging TUR is routinely performed these days in patients with high-grade NMIBC, especially for high-grade T1, as the rate of residual tumor is high and 30% of tumors are upstaged when muscle is absent in the first obtained specimen.[24] Photodynamic diagnosis with blue light and narrow-band imaging have been shown to reduce residual tumor rates by roughly 20% and to improve recurrence-free survival of NMIBC patients compared with white light cystoscopy.[25] A meta-analysis of seven randomized trials ($n = 1476$) confirmed the effectiveness of single immediate intravesical instillation of chemotherapy in treated patients compared with TUR alone, reporting a 39% decrease in the odds of recurrence.[26] The efficacy of intravesical mitomycin C can be optimized by administering a dose of 40 mg at a concentration of 2 mg/mL in water, complete bladder emptying just before dose administration, fluid restriction and oral bicarbonate to alkalinize the urine.[27] This approach improved the recurrence-free rate at 5 years from 24.6% to 41% and increased the interval to tumor recurrence from 11.9 to 29 months.[27] Using a

multi-institutional cohort of 4689 patients with NMIBC, Xylinas *et al.*[28] showed that both the EORTC and CUETO risk tables exhibit a poor discrimination for disease recurrence and progression. These models overestimated the risk of disease recurrence and progression in high-risk patients.

Additional factors not included in the EORTC or the CUETO models could be added to new prognostic models to enhance their usefulness. Bladder neck involvement,[29] prostatic urethra involvement,[30] lymphovascular invasion[31] and depth of lamina propria invasion, i.e., whether the tumor is superficial to, into or beyond the muscularis mucosae (T1a, T1b, T1c),[32] have been identified as risk factors for progression in patients with NMIBC. In the prognostic factor meta-analysis of 33 studies of high-grade T1 bladder cancer patients (n = 8880), the highest impact risk factor for progression and cancer-specific survival was depth of invasion (T1b/c) into the lamina propria.[33] In this meta-analysis, several other previously proposed factors, i.e. lymphovascular invasion, associated CIS, non-use of BCG, tumor size >3 cm, gender, multiple tumors and older age, also predicted progression.[33] NMIBC patients with progression to muscle-invasive disease tend to have worse prognosis compared with patients with primary muscle-invasive disease, and it underscores the need to significantly improve risk stratification and earlier definitive treatment for high-risk NMIBC.[34]

Risk groupings and risk tables provide average predictions, which may or may not apply to the patient interested in knowing individualized risk. Nomograms have been proposed as a method that avoids the arbitrary division of patients into risk groups.[13] They provide individualized predictions based on the characteristics of individual patients. Shariat *et al.*[13] developed nomograms to estimate the risk of disease recurrence and progression in patients with NMIBC using a large international cohort. Nomograms based on age, gender, urine cytology and dichotomized NMP22 had accuracy of 0.811 for recurrence of any bladder cancer; 0.772 for recurrence of grade 3 Ta or T1 or CIS and 0.774 for recurrence of stage ≥T2 bladder cancer after bootstrap validation. However, this nomogram had several limitations, including failure to incorporate established predictors, such as pathologic grade and stage, number and pattern of previous recurrences, time since the original diagnosis and prior use of intravesical therapy. Furthermore, the performance of the nomograms varied significantly among the institutions, emphasizing the need for external validation prior to its clinical use.

Artificial neural networks (ANN) are algorithms that can be trained to identify complex patterns between input variables and outcomes in the data sets and then apply these patterns to new cases.[35] They have a theoretical advantage over conventional statistics as they are not limited by predefined mathematical relationships between input variables and outcomes; thus, they are able to model complex non-linear parameters. Qureshi *et al.*[10] used ANN to predict bladder cancer recurrence and progression within 6 months of diagnosis in a small cohort of about 100 patients with NMIBC. The accuracy of ANN in predicting stage progression and recurrence was 80% and 75%, respectively. However, there was no significant difference between the ANN and the clinicians' predictions of progression and recurrence in the patients with NMIBC. On restricting the validation subset to patients with T1G3 tumors in relation to stage progression, ANN accuracy was better than predictions of clinicians. Several investigators have compared ANN and other machine learning techniques with standard statistical approaches to predict outcomes and did not find improvement in predictive accuracy with ANN and other machine learning techniques over standard statistical approaches.[36,37]

Most of the currently available predictive tools assume that NMIBC is pure urothelial carcinoma and does not consider the impact of variant histology on prognosis prediction. Variant histology such as micropapillary, sarcomatoid and plasmacytoid has been shown to be associated with poor prognosis, and early cystectomy is generally advocated in such cases.[38,39] Small cell carcinoma of the bladder is considered a systemic disease and chemotherapy followed by tailored local therapy is recommended for patients with non-muscle invasive small cell carcinoma of the bladder.[39] However, Spaliviero *et al.*[40] reported not significantly worse outcomes in conservatively managed T1 micropapillary bladder cancer patients compared with patients treated with early radical cystectomy. Given the conflicting findings on the impact of variant histology in smaller studies, the association of variant histology with prognosis deserves further evaluation in larger studies.

RISK STRATIFICATION BASED ON MOLECULAR BIOMARKERS

For molecular biomarkers to be of clinical use, they should be able to increase the predictive accuracy beyond the standard clinical and pathological parameter models.[41] Several investigators have attempted to use molecular biomarkers as prognostic factors to predict outcomes in patients with NMIBC.[10,13,42-44] However, molecular biomarkers have shown mixed results so far and are not sufficiently validated to be used in clinical practice at this time.[45]

It is becoming clear that superficial low-grade cancers and invasive or high-grade cancers harbor distinctive genetic defects: The low-grade, non-invasive papillary tumors are characterized by activating mutations in the H-Ras gene and fibroblast growth factor receptor 3 (FGFR3) gene and the high-grade invasive tumors are characterized by structural and functional defects in the p53 and retinoblastoma

protein (Rb) tumor-suppressor pathways.[46] The deletion of both arms of chromosome 9 occurs frequently in bladder cancer during the earliest stages of tumorigenesis. However, these chromosomal aberrations do not seem to distinguish between the two tumor development pathways.[47] Tumor invasion and progression in the bladder seems to be a multifactorial process, promoted by micro-environmental changes that include the up-regulation of N-cadherin, the down-regulation of E-cadherin, the overexpression of matrix metalloproteinases 2 and 9, an imbalance between angiogenic and anti-angiogenic factors and increased synthesis of prostaglandin.[46]

In patients with T1 bladder cancer, nuclear overexpression of p53 protein has been reported to have a higher probability of disease progression.[43] In a meta-analysis, p53 was a predictor for recurrence, progression and mortality in patients with bladder cancer.[48] However, investigators of this meta-analysis had concerns of overestimating findings because of publication and reporting bias, and suggested that current evidence is not sufficient to conclude whether changes in p53 act as markers of outcome in patients with bladder cancer.[48] Hernandez *et al.*,[49] in a prospective cohort of 772 patients with NMIBC, showed that FGFR3 mutations are prevalent in low-grade Ta and that these mutations are independent predictors of recurrence in patients with low-grade Ta tumors. Van Rhijn *et al.*[42] showed that molecular grading, the grading system based on FGFR3 and MIB-1 (Ki-67) status, is an independent predictor for recurrence, progression and disease-specific survival. Van Rhijn *et al.*[44] validated the utility of molecular grading as a prognostic factor to predict outcomes in patients with NMIBC. The addition of molecular grade to the multivariable model for progression increased the predictive accuracy from 74.9% to 81.7%.[44] Shariat *et al.*[50] evaluated NMP22 for detecting recurrence and progression in patients with NMIBC in a large multi-institutional international cohort. There was a substantial degree of heterogeneity in the diagnostic performance among institutions. There was no clearly defined NMP22 cut-off that could indicate higher risk disease, but there was a continuum of risk for recurrence and progression.

The international consensus panel on cytology and bladder tumor markers evaluated the prognostic utility of molecular markers for bladder cancer.[45] Molecular markers were classified into six groups, i.e. microsatellite-associated markers (e.g. FISH, LOH), proto-oncogenes/oncogenes (e.g. Her-2/neu, H-Ras, BCL-2, MDM-2, FGFR-3, C-MYC) tumor suppressor genes (e.g., p53, Rb), cell cycle regulators (e.g., p21, p27, Ki-67, Cyclin-D1, Cyclin-E), angiogenesis-related factors (VEGF, COX-2, TSP-1) and extracellular matrix adhesion molecules (e.g. E-cadherin, MMPs, TIMPs, CD44, U-PA). The panel concluded that although certain biomarkers, such as Ki-67 and p53, appear to be promising in predicting recurrence and progression in patients with bladder cancer, the data are still heterogeneous.[45] The panel recommended that identifying definitive criteria for test positivity, a clearly defined patient population, standardization of techniques used to evaluate markers and clearly specified endpoints and statistical methods will help to bring accurate independent prognostic indicators into the clinical management of patients with bladder cancer.[45]

CONCLUSIONS

NMIBC comprises of a heterogeneous group of patients and includes pathological stage Ta, T1 and CIS. Patients with low-grade Ta disease have very low risk of progression while patients with T1 disease with concurrent CIS have a much higher risk of progression, approaching 50%. The EORTC and CUETO risk tables are the two best-established predictive models for recurrence and progression risk calculation in patients with NMIBC. However, both the EORTC and the CUETO risk tables exhibit a poor discrimination for prognostic outcomes and overestimate the risk of disease recurrence and progression in high-risk patients in external validation. Additional prognostic factors such as depth of lamina propria invasion should be added to new prognostic models to enhance their usefulness. Molecular biomarkers such as Ki-67, FGFR3 and p53 appear to be promising in predicting recurrence and progression, but need further validation prior to using them in clinical practice. Future research should focus to enhance the predictive accuracy of the risk assessment tools by incorporating additional prognostic factors such as depth of lamina propria invasion and molecular biomarkers after rigorous validation in multi-institutional cohorts.

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Conflicts of interest
There are no conflicts of interest.

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