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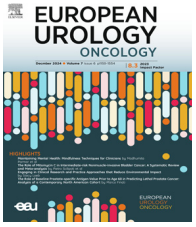

European Association of Urology

Original articles

Clinical Validation of the Intermediate-risk Non–muscle-invasive Bladder Cancer Scoring System and Substratification Model Proposed by the International Bladder Cancer Group: A Multicenter Young Academic Urologists Urothelial Working Group Collaboration

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Abstract

Background and objective: Intermediate-risk (IR) non–muscle-invasive bladder cancer (NMIBC) encompasses a broad spectrum of disease, with heterogeneous outcomes in terms of disease recurrence and progression. The International Bladder Cancer Group (IBCG) recently proposed an updated scoring model for IR substratification that is based on five key risk factors. Our aim was to provide a clinical validation of the IBCG scoring system and substratification model for IR NMIBC.

Methods: This was an international multicenter retrospective study. Patients diagnosed with IR NMIBC between 2012 and 2022 and treated with transurethral resection of the bladder and adjuvant intravesical chemotherapy were included. According to the presence or absence of risk factors, patients with IR NMIBC were further categorized in IR-

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low (no risk factors), IR-intermediate (1–2 risk factors), and IR-high (≥3 risk factors) groups. The 1-yr and 3-yr rates for recurrence-free survival (RFS) and progression-free survival (PFS) were evaluated for each subgroup. Cox regression analyses were used to compare oncological outcomes between the groups.

Key findings and limitations: Of the 677 patients with IR NMIBC included in the study, 231 (34%), 364 (54%), and 82 (12%) were categorized in the IR-low, IR-intermediate, and IR-high groups, respectively. There were significant differences in RFS and PFS rates between these groups.

Conclusions and clinical implications: We provide the first clinical validation of the IBCG scoring system and model for substratification of IR NMIBC.

Patient summary: Our study demonstrates that patients with intermediate-risk non–muscle-invasive bladder cancer can be correctly classified into three distinct subgroups according to their risk of both disease recurrence and progression. Our results support use of this scoring system in clinical practice.

1. Introduction

Risk stratification is a cornerstone in the management of non–muscle-invasive bladder cancer (NMIBC). Intermediate-risk (IR) NMIBC traditionally encompasses patients who do not fall in the low-risk or high-risk category and thus represents a broad spectrum of disease. According to current international guideline definitions, the IR category includes both primary and recurrent disease, as well as Ta and T1 tumors [1,2]. Furthermore, according to the European Association of Urology (EAU) 2021 scoring model, selected high-grade (HG) Ta tumors, namely those with no or only one risk factor, may be classified in the IR category [3]. This substantial heterogeneity contributes to varying guideline recommendations regarding adjuvant treatment after transurethral resection of the bladder (TURB). Recommendations vary from adjuvant intravesical chemotherapy, with or without maintenance, to adjuvant intravesical bacillus Calmette-Guérin (BCG) for up to 1 yr [1]. The decision-making process regarding the choice of adjuvant treatment and the intensity of follow-up is currently left to the discretion of the treating physician, with potential for suboptimal long-term oncological outcomes.

To enhance risk stratification and guide treatment allocation and follow-up scheduling, further substratification of IR NMIBC appears to be warranted. The International Bladder Cancer Group (IBCG) strongly recommends that only low-grade tumors should be considered as IR NMIBC [4,5]. The IBCG has also recently updated their scoring system and substratification model that is based on the absence or presence of clinical risk factors such as multifocality, tumor size, early recurrence, frequent recurrence, and failure of previous intravesical treatment [6]. According to this model, patients with IR NMIBC may be categorized into three different risk groups, which then determines whether they should receive a single chemotherapy instillation, adjuvant chemotherapy, or adjuvant BCG.

However, before considering incorporation of this scoring system and substratification model into international guidelines and adoption in clinical practice, clinical validation is imperative. The aim of our study was to provide the first clinical validation of the IBCG scoring system and substratification model in a large multicenter cohort of patients with IR NMIBC.

2. Patients and methods

2.1. Study population

This was an institutional review board–approved study with all participating sites providing the necessary data-sharing agreements before initiation of the study. Records for patients with pathologically proven primary or recurrent IR NMIBC treated with TURB and adjuvant intravesical chemotherapy between 2012 and 2022 at nine European referral centers of the Young Academic Urologists Urothelial Working Group were included for the purpose of the study. Given the controversy surrounding the inclusion of selected HG Ta tumors in the IR category [7], our study relied on the EAU 2021 risk stratification model, but we intentionally excluded patients with HG disease [3]. In detail, the inclusion criteria were as follows:

- Primary low-grade (LG)/G1 Ta disease with at least two additional risk factors among size ≥3 cm, multifocality, and age >70 yr;
- Recurrent LG/G1 Ta disease;
- Primary or recurrent LG/G2 Ta or G1 T1 disease with at most two additional risk factors among size ≥3 cm, multifocality, and age >70 yr; or
- Primary or recurrent G2 T1 disease with no additional risk factors among size ≥3 cm, multifocality, and age >70 yr.

Only records comprising complete data for baseline, pathological, and oncological outcomes were retained for the purpose of the study. None of the patients had upper tract urothelial carcinoma, prostatic stroma invasion, or metastatic bladder cancer at the time of surgery. After TURB, patients were treated with adjuvant intravesical chemotherapy with either mitomycin C, gemcitabine, or epirubicin, with maintenance therapy administered at the discretion of the treating physician. TURB specimens were

analyzed by experienced uropathologists at each center and were staged according to the TNM classification, while tumor grade was based on the 2004/2016 World Health Organization classification. Owing to the retrospective and multicenter nature of the study, the follow-up protocol was not standardized, but generally aligned with international guideline recommendations. Follow-up usually consisted of ultrasound of the abdomen/pelvis and flexible cystourethroscopy at 3 mo after baseline TURB, every 6 mo for the first 2–3 yr, and every 12 mo thereafter. Cold biopsy/TURB of suspected areas was performed when appropriate to assess disease recurrence or progression.

2.2. Statistical analysis

Categorical variables are reported as the frequency and proportion. Continuous variables are reported as the median and interquartile ranges (IQR). The main endpoint of the study was validation of the IBCG scoring system and substratification model for IR NMIBC. On the basis of the IBCG model, the following risk factors were evaluated: tumor size >3 cm, multifocal disease, early recurrence (<1 yr), frequent recurrence (>1 per year), and failure of previous intravesical treatment [6]. According to the presence or absence of additional risk factors, patients with IR NMIBC were further categorized into IR-low (no risk factors), IR-intermediate (one to two risk factors), and IR-high (three or more risk factors) groups. The 1-yr and 3-yr rates of recurrence-free survival (RFS) and progression-free survival (PFS) for each subgroup were evaluated, and Kaplan-Meyer curves were constructed to evaluate the risk of disease recurrence and progression. Cox regression analyses were used to compare oncological outcomes between the groups. For RFS and PFS, patients without an event were censored at the time of the last negative disease recurrence/progression assessment or at the last negative cystoscopy. Disease progression was defined as the occurrence of muscle-invasive disease or non–organ-confined disease during follow-up. Data were analyzed using STATA 16 (Stata Corp., College Station, TX, USA), and a p value of <0.05 was considered statistically significant.

Table 1 – Descriptive characteristics of the cohort of 677 patients with intermediate-risk non–muscle-invasive bladder cancer treated with transurethral resection of the bladder and adjuvant intravesical chemotherapy

Parameter	Result
Median age, yr (interquartile range)	70 (62–76)
Sex, *n* (%)	
Female	141 (21)
Male	536 (79)
Smoking status, *n* (%)	
Never smoker	180 (28)
Former smoker	295 (47)
Current smoker	156 (25)
Tumor status, n (%)	
Primary	310 (46)
Recurrent	367 (54)
Previous intravesical treatment	186 (51)
Early recurrence (<12 mo)	120 (33)
Frequent recurrence (>1 per year)	61 (16)
Tumor size, *n* (%)	
0–3 cm	630 (93)
≥3 cm	47 (7)
Focality, *n* (%)	
Single	354 (52)
Multiple	323 (48)
Tumor stage, *n* (%)	
Ta	632 (93)
T1	45 (7)
Grade according to WHO 1973, *n* (%)	
Grade 1	259 (38)
Grade 2	418 (62)
Grade according to WHO 2004, *n* (%)	
Low grade	677 (100)

WHO = World Health Organization.

3. Results

Baseline patient characteristics are listed in Table 1. Overall, 677 patients with IR NMIBC treated with TURB and adjuvant chemotherapy were included. Most of the patients were male (79%) and 54% presented with recurrent disease. Of the patients, 93% had Ta tumors, while 7% had T1 tumors. Tumor size >3 cm and multifocal disease were present in 47 (7%) and 323 (48%) patients, respectively. Maintenance was administered in 287 patients (42%) and the median number of maintenance instillations was 6 (IQR 3–10). Among patients with recurrent NMIBC, 120 (33%) experienced early recurrence (<1 yr), 61 (16%) had frequent recurrences (less than one per year), and 186 (51%) had failure of previous intravesical treatment. Thus, 231 (34%), 364 (54%), and 82 (12%) patients belonging to the IR-low, IR-intermediate, and IR-high groups, respectively. Primary tumors were detected in 146 (63%), 147 (40%) and 17 (21%) of patients in the IR-low, IR-intermediate, and IR-high groups, respectively.

Overall, within median follow-up of 36 mo (IQR 20–54), 241 patients (36%) experienced recurrence and 24 (4%) progressed to muscle-invasive disease. The median time to dis-

Table 2 – Probability of disease recurrence and progression at 1 and 3 yr according to the IR substratification model for the cohort of 677 patients with IR non–muscle-invasive bladder cancer treated with transurethral resection of the bladder and adjuvant intravesical chemotherapy

Group	Probability, % (95% confidence interval)			
	1 yr		3 yr	
	Recurrence	Progression	Recurrence	Progression
All patients	14.6 (12.2–17.7)	0.6 (0.2–1.6)	38 (34–42.4)	2.1 (1.1–3.8)
IR low	10.7 (7.7–15.6)	0	29.5 (23.3–37.1)	0
IR intermediate	13.1 (9.9–17.1)	0.6 (0.1–2.2)	36.9 (31.5–42.8)	2 (0.9–4.5)
IR high	33.5 (24.1–45.2)	2.6 (0.7–10.0)	67.5 (55.7–78.8)	8.2 (3.4–19.2)

IR = intermediate risk.

ease recurrence and progression was 24 mo (IQR 12–42) and 36 mo (IQR 20–56), respectively (Fig. 1). The 1-yr and 3-yr survival rates for the entire cohort were 85.4% and 62.0% for RFS, and 99.4% and 97.9% for PFS, respectively (Table 2).

For the IR-low, IR-intermediate, and IR-high groups, the recurrence rates were 10.7%, 13.1%, and 33.5% at 1 yr, and 29.5%, 36.9%, and 67.5% at 3 yr, respectively. The corresponding progression rates for these groups were 0%, 0.6%, and 2.6% at 1 yr, and 0%, 2%, and 8.2% at 3 yr (Table 2). There were significant differences in RFS and PFS rates between the groups, as illustrated in Figure 2.

4. Discussion

In this multicenter retrospective study, we conducted a clinical validation of the IBCG scoring system and substratification model for IR NMIBC. Our findings demonstrate the

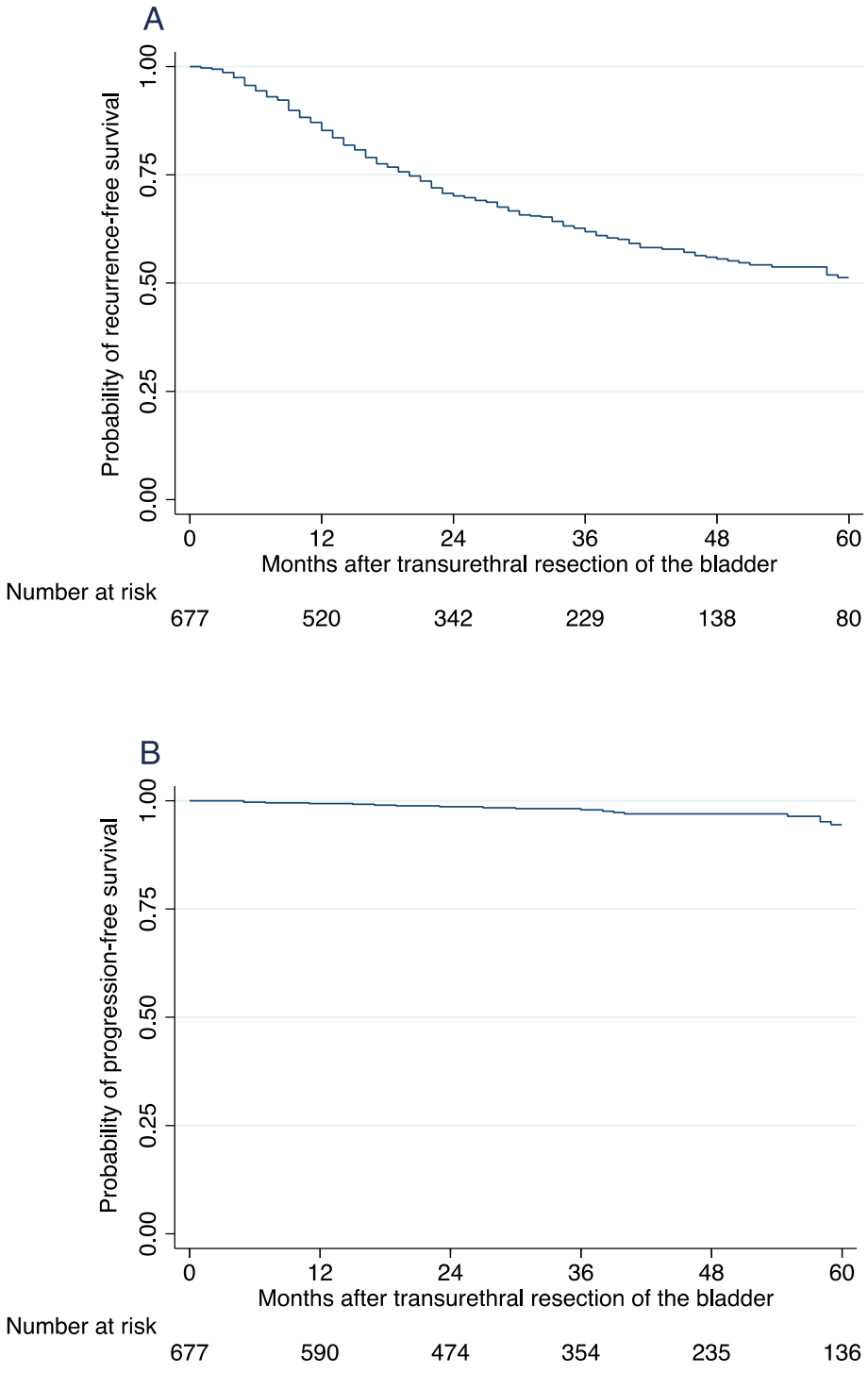
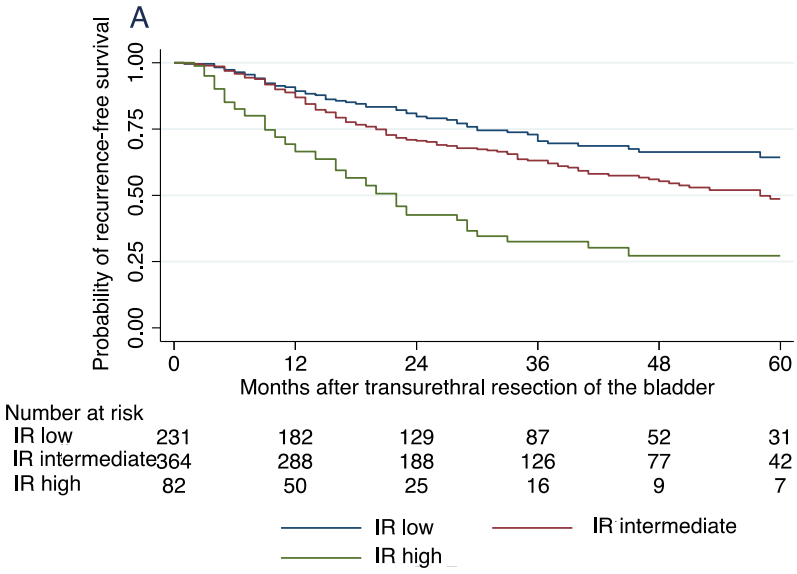
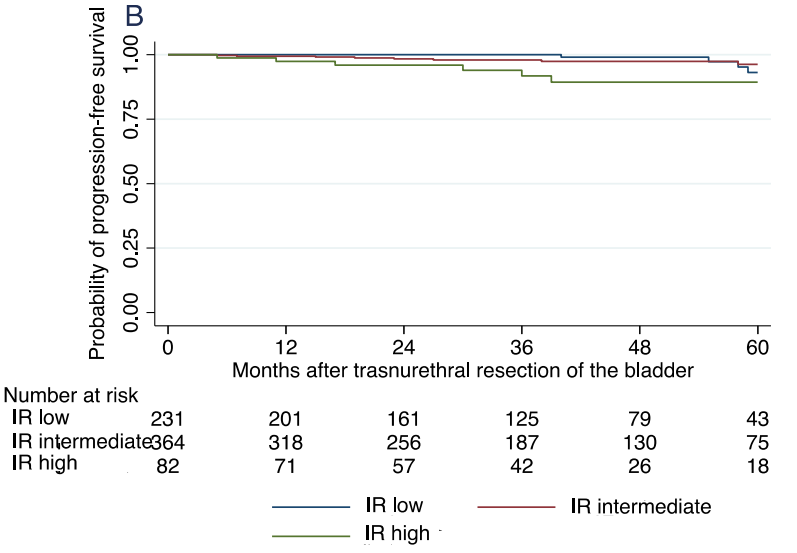


Fig. 1 – Kaplan-Meier estimates of (A) recurrence-free survival and (B) progression-free survival for 677 patients with intermediate-risk non–muscle-invasive bladder cancer treated with transurethral resection of the bladder and adjuvant chemotherapy.



IR low (reference)	HR	95% CI	*p* value
IR intermediate	1.47	1.08–2.01	0.013
IR high	3.36	2.31–4.91	<0.001



IR low (reference)	HR	95% CI	*p* value
IR intermediate	2.09	0.68-6.41	0.2
IR high	4.97	1.45-17.01	0.01

Fig. 2 – Kaplan-Meier estimates of (A) recurrence-free survival and (B) progression-free survival according to the intermediate risk (IR) substratification model for 677 patients with IR non–muscle-invasive bladder cancer treated with transurethral resection of the bladder and adjuvant chemotherapy. HR = hazard ratio; CI = confidence interval.

efficacy of the IBCG model in stratifying patients with IR NMIBC into three distinct groups according to the risk of both disease recurrence and progression. This stratification is based on the presence or absence of five key risk factors: tumor size, focality, previous recurrence, number of recurrences, and frequency of recurrences.

The need for an accurate tool that can substratify IR NMIBC into different subgroups has become imperative in recent years for several reasons. First, IR NMIBC encompasses a broad spectrum of disease with heterogeneous tumor characteristics and outcomes, necessitating a tailored and more personalized approach to disease management and follow-up. Patients with IR NMIBC with a negligible risk of progression may be suitable for de-escalated less morbid therapies such as active surveillance or office fulguration, while those at higher risk of developing HG recurrence or progression to muscle-invasive disease should undergo TURB and adjuvant chemotherapy or BCG treatment [8]. Second, selective use of intravesical BCG for patients with IR disease with a higher risk of disease progression will maximize the treatment benefit and minimize related toxicity. Moreover, in an era characterized by BCG shortage, a resource allocation perspective is fundamental to decision-making regarding adjuvant treatment. Third, as highlighted by Tan and colleagues [6], standardization of the definition and management options for IR NMIBC is essential for clinical trial development and patient recruitment.

Previous efforts have been made to stratify patients with IR NMIBC into different subgroups, primarily focusing on the risk of recurrence or progression to muscle-invasive disease. However, none of these models have been incorporated in clinical practice to date, mainly because of intrinsic study-related limitations or lack of external validation. In 2014, the IBCG conducted a comprehensive review of the literature and introduced an initial expert opinion–based algorithm for stratification of IR NMIBC, defined at the time as multiple and/or recurrent LG Ta tumors [4]. This initial algorithm was updated in 2022 and a new model was proposed [6]. Lammers et al [9] developed and externally validated a model based on five relevant predictors of RFS using data for 724 patients with IR NMIBC, defined as G1/2 Ta tumors without the combination of multiple tumors, recurrent disease, and size >3 cm. This model was built with the aim of predicting disease recurrence, and no data regarding progression to muscle-invasive disease were reported. More recently we provided a decision tree for substratifying recurrent LG Ta tumors into five different classes according to the risk of progression [10]. Despite the high accuracy of the model (C index for disease progression 0.75), its application in clinical practice has been limited by the fact that the study population did not represent the whole IR NMIBC spectrum.

The IBCG updated their first algorithm and developed a new scoring system and substratification model that is based on five key risk factors [6]. Our study provides the first clinical validation of this IBCG scoring system and substratification model. We demonstrated that this model can correctly stratify patients with IR NMIBC into three distinct subgroups according to the risk of both disease recurrence and progression (even though no significant difference in disease progression was observed between the IR-low and IR-intermediate subgroups). Notably, we found that the risk of disease progression in the IR-low group was similar to that for the EAU 2021 low-risk NMIBC group (0.4% at 3 yr), while the IR-high group had a very-high risk of progression (9% at 3 yr), similar to the EAU high-risk NMIBC group. Our findings may form a basis for adoption of this risk stratification in everyday clinical practice and could thus pave the way towards personalized medicine in this setting.

Our study is not devoid of limitations, mainly inherent to its retrospective nature. First, we were not able to evaluate the possible impact of a single postoperative instillation. Second, with the aim of maximizing the homogeneity of the population, we only included patients treated with adjuvant chemotherapy instillations and excluded those who received intravesical BCG. Third, maintenance treatment was administered at the physician's discretion, with a possible impact on oncological outcomes. Fourth, we intentionally decided to exclude HG tumors (ie, selected HG Ta cases) from the study; therefore, it is possible that our results may not be applicable when adopting the EAU 2021 NMIBC risk stratification model for IR disease. In this regard, we are currently running a new study aimed at validating this substratification model specifically for patients with HG Ta NMIBC belonging to the IR group, according to the EAU 2021 risk stratification model. Finally, external validation, ideally with prospectively collected data, is warranted to confirm the validity of our model.

5. Conclusions

We provided the first clinical validation of the scoring system and substratification model for IR NMIBC proposed by the IBCG. Our results demonstrate that this model can correctly categorize IR NMIBC into three subgroups with low, intermediate, and high risk of disease recurrence and progression. These results pave the way towards implementation of this substratification model in clinical practice.

Author contributions: Francesco Soria had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Soria, Rosazza, Moschini, Pradere.
Acquisition of data: Rosazza, Livoti, Dutto, Colucci, Fertitta, Casale, De Angelis, Del Giudice, Pichler, Mancon, Carrion, Krajewski, Mertens, D'Andrea, Mari, Di Maida, Albisinni, Teoh.
Analysis and interpretation of data: Soria, Rosazza.
Drafting of the manuscript: Soria, Rosazza.
Critical revision of the manuscript for important intellectual content: Kamat, Shariat, Briganti, Gontero, Hurle, Laukhtina.
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