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Original Article

The value of maintenance therapy in intermediate-risk non-muscle-invasive bladder cancer

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Objective

To evaluate which subgroups of patients with intermediate-risk non-muscle-invasive bladder cancer (IR-NMIBC) benefit from maintenance therapy based on the International Bladder Cancer Group (IBCG) risk stratification, as the role of a maintenance course in patients with IR-NMIBC is debated.

Patients and Methods

We relied on a prospectively maintained database of patients with IR-NMIBC who received intravesical chemotherapy or Bacillus Calmette–Guérin (BCG) (2010–2023). Patients were stratified according the IBCG prognostic algorithm (no, one to two, and three or more risk factors). All patients received at least six induction instillations after index transurethral resection of bladder tumour. We used 3-month landmark stacked cumulative incidence and multivariable Cox regression models to assess the benefit from a maintenance course in terms of risk of recurrence and progression according to the IBCG risk groups stratification.

Results

Among 464 patients, 205 (44%) received BCG treatment and 259 (56%) received intravesical chemotherapy. The median (interquartile range) number of maintenance instillations was 9 (5–11). Over a median follow-up of 57 months, 139 (30%) patients had a recurrence. Patients with no IBCG risk factors had a similar risk of 5-year disease recurrence according to treatment duration (7.7% vs 7.3%; hazard ratio [HR] 0.78, 95% confidence interval [CI] 0.49–1.37, for induction only vs induction plus maintenance, respectively), whereas patients with one to two (5-year risk: 16% vs 13%; HR 0.65, 95% CI 0.48–0.82) or three or more IBCG risk factors (5-year risk: 21% vs 17%; HR 0.48, 95% CI 0.25–0.85) were associated with lower hazards of recurrence if treated with an induction plus maintenance course.

Conclusions

The IBCG algorithm effectively stratifies patients with IR-NMIBC by recurrence risk. In this observational cohort, maintenance therapy was associated with lower recurrence rates in patients with one to two or three or more IBCG risk factors, but not in those with no risk factors. These findings suggest that the IBCG stratification may inform risk-adapted treatment decisions in patients with IR-NMIBC.

Keywords

bladder cancer, intermediate-risk, non-muscle-invasive bladder cancer, International Bladder Cancer Group, intravesical chemotherapy, Bacillus Calmette–Guérin, maintenance

Introduction

Non-muscle-invasive bladder cancer (NMIBC) is a heterogeneous disease, characterised by a wide spectrum of recurrence and progression rates [1,2]. Within this context, the intermediate-risk (IR) category defined by the European Association of Urology (EAU) encompasses patients who do not fit into either the low- or high-risk groups, thereby including a broad range of clinical presentations [3,4]. Given the substantial heterogeneity within the IR-NMIBC

population, the International Bladder Cancer Group (IBCG) has recently proposed a refined risk stratification algorithm aimed at improving clinical decision-making [5,6]. This algorithm classifies patients according to five key risk factors: early recurrence (<1 year), frequent recurrence (more than one per year), tumour multifocality, tumour size (≥3 cm), and recurrence despite prior intravesical therapy. Although not yet prospectively validated, the IBCG stratification has been retrospectively evaluated in a multicentre cohort, confirming that recurrence and progression risks vary significantly across the defined subgroups [7].

According to current EAU guidelines, patients with IR-NMIBC may be offered either a 1-year course of BCG or intravesical chemotherapy following transurethral resection of bladder tumour (TURBT), although the recommendations are not tailored to specific patients' risk profiles. In contrast, the IBCG algorithm offers a more nuanced approach: patients with one to two risk factors may receive either induction-only chemotherapy or a 1-year BCG course, while those with three or more risk factors may be considered for induction plus maintenance chemotherapy, or a 1-year BCG course if prior chemotherapy has already been administered [5,6].

Despite these proposed frameworks, the use, duration, and scheme of a maintenance therapy in IR-NMIBC remains a matter of debate. A recent systematic review, and other retrospective studies have suggested that maintenance therapy may be beneficial in this setting [8–10]. However, it remains unclear whether this benefit applies uniformly across all IR-NMIBC subgroups, or whether some patients may be suitable candidates for treatment de-escalation, potentially reducing both costs and treatment-related burden [11].

To address this question, we analysed a single-centre cohort of patients with IR-NMIBC, stratified according to the IBCG algorithm, to evaluate whether outcomes differed based on treatment strategy (induction only vs induction plus maintenance), particularly in terms of recurrence and progression.

Patients and Methods

Study Population

After Institutional Review Board approval, we relied on a prospectively maintained database including patients diagnosed with NMIBC from 2010 to 2023 who underwent TURBT at our centre. We included patients with histologically confirmed IR-NMIBC (defined as any patients not included in the low-, high-, and very high-risk groups) according to the EAU 2021 prognostic risk group classification who had complete follow-up data and without a history of upper tract urothelial carcinoma [4]. Patients with missing data on oncological outcomes were excluded. This process led to the selection of 464 patients (Fig. S1).

Clinical Variables of Interest

The dataset included demographic and pathological characteristics such as age, gender, tumour history (e.g., primary or recurrent), tumour stage and grade at TURBT. Tumour grade was defined according to both the WHO 1973 and WHO 2004/2016 grading systems [4]. Other factors recorded were tumour size, multifocality, early instillation after TURBT, and details of chemotherapy and BCG instillations (start date, end date, number of instillations).

Patients treated with chemotherapy received at least one induction course of six intravesical instillation (one instillation per week for 6 weeks after TURBT) of epirubicin 50 mg/50 mL or mitomycin C 40 mg/40 mL according to EAU guidelines [12], followed in some cases by a maintenance chemotherapy course (one instillation per month, started at least 2 weeks after the end of the induction course). BCG therapy after TURBT was administered following the Southwest Oncology Group (SWOG) protocol, starting with an induction course of six weekly instillations [13]. Patients treated with BCG received at least one induction course of six instillations, which was followed in some cases by maintenance therapy consisting of three weekly instillations at 3, 6, and 12 months. The follow-up strategy included in-office cystoscopy, CT scans, and urinary cytology, tailored according to the risk stratification and in line with EAU-recommended follow-up protocols [12]. The duration of maintenance cycle, when performed, was at the discretion of the treating physician.

Patients were stratified according to the IBCG prognostic algorithm based on the number of risks features they harboured (no, one to two, and three or more risk factors) in reference to the index TURBT, which was defined as the TURBT performed at our centre where the IR-NMIBC was identified [6]:

- Frequent recurrence (defined as more than one recurrence per year);
- Early recurrence (defined as a recurrence that occurs earlier than 1 year);
- Recurrence despite prior intravesical instillations;
- Multifocality (more than one lesion);
- Tumour size ≥3 cm.

Outcomes

Recurrence was defined as any NMIBC recurrence at any intravesical site occurring during follow-up, whereas progression was defined as the time to diagnosis of MIBC or metastatic disease. Patients who did not experience the event at last contact were censored at their last date of follow-up.

Statistical Analysis

First, main clinical characteristics were presented using medians and interquartile ranges (IQRs) for continuous

variables. To assess difference within groups, proportions differences were evaluated using the chi-square test and the Fisher's exact test. For continuous variables, differences clinical patient characteristics in distribution of ranks across the different groups were evaluated using the Wilcoxon rank-sum test.

Follow-up began at the start of treatment and continued until the occurrence of one of the outcomes (i.e., recurrence, progression) or censoring. Censoring occurred at the date of last contact with the patient with no evidence of recurrence and progression during follow-up. To account for competing risk events, avoid outcomes' underestimation, and reduce reverse causality bias, which is generally obtained when competitive events are not considered in outcomes' analysis, we computed the 3-month landmark competing event cumulative incidence stacked proportion of recurrence and progression for each IBCG risk group (no vs one to two vs three or more risk factors), overall and stratified by treatment duration (induction only vs induction plus maintenance). The stratification of patients was performed in accordance with IBCG stratification algorithm, as previously reported [6]. We considered death from other causes as a competing event for each of the outcomes included in the incidence proportion analysis. The median follow-up was estimated using a reverse Kaplan–Meier approach [14,15].

Then, we performed a multivariable Cox regression analysis to predict the risk of any recurrence and progression according to treatment duration (induction only vs induction + maintenance) for different IBCG risk groups (no vs one to two vs three or more risk factors), after accounting for clinically relevant variables that are not included in the IBCG algorithm (namely, early instillation after TURBT and tumour grade [as per WHO 2004 Grade Group stratification]), in order to investigate the potential benefits of a maintenance treatment in relation to IBCG risk groups. Effect sizes were visualised using a forest plot. In this analysis, in the event of death from any causes, patients were censored.

Statistical significance was set at $P < 0.05$. For all statistical analyses, R software environment for statistical computing and graphics was used (version 4.3.2; http://www.r-project.org/) [16].

Results

Baseline Characteristics

Of the 464 patients with IR-NMIBC included, the median (IQR) age at TURBT was 67 (63–75) years and 297 (64%) patients had a pathological (p)Ta low-grade (LG) tumour (Table 1). A total of 205 (44%) patients received BCG treatment and 259 (56%) received intravesical chemotherapy. There were no differences among baseline characteristics for patients who received induction only (196 [42%]) and patients who had an induction plus maintenance course (268 [58%]) after TURBT. In total, there were 146 (31%) patients with no IBCG risk factors, 215 (46%) patients with one to two IBCG risk factors, and 103 (23%) patients with three or more IBCG risk factors.

Table 1 Characteristics of the 464 patients diagnosed with IR-NMIBC according to treatment duration (induction only vs induction plus maintenance) at a single tertiary referral centre.

Characteristic	Induction only, *N* = 196	Induction plus maintenance, *N* = 268	*P*
Age at TURBT, years, median (IQR)	69 (63–76)	66 (64–73)	0.2
Gender, *n* (%)			
Female	35 (18)	68 (25)	0.054
Male	161 (82)	200 (75)	
Primary tumour	119 (61)	141 (53)	0.082
Tumour size (cm), *n* (%)			
<3	164 (84)	215 (80)	0.3
≥3	32 (16)	53 (20)	
Multifocality	66 (34)	96 (36)	0.6
Tumour grade WHO 1973, *n* (%)			
Grade 1	59 (30)	77 (29)	0.3
Grade 2	112 (57)	142 (53)	
Grade 3	25 (13)	49 (18)	
Tumour grade WHO 2004, *n* (%)			
LG	126 (64)	154 (57)	0.14
HG	70 (36)	114 (43)	
Histology, *n* (%)			
Ta LG	133 (68)	164 (61)	0.3
Ta HG	61 (31)	101 (38)	
T1 LG	2 (1)	3 (1)	
Early instillation at TURBT, *n* (%)	41 (21)	48 (18)	0.4
Type of treatment, *n* (%)			
BCG	79 (40)	126 (47)	0.2
Chemotherapy	117 (60)	142 (53)	
Number of total instillations, median (IQR)	6 (6–6)	15 (11–17)	<0.001
Number of maintenance instillations, median (IQR)	–	9 (5–11)	–
>6 maintenance instillations, *n* (%)	–	166 (62)	
IBCG risk stratification, *n* (%)			
No risk factors	57 (29)	89 (33)	0.4
One to two risk factors	90 (46)	125 (47)	
Three or more risk factors	49 (25)	54 (20)	

The median (IQR) number of maintenance instillations in the induction plus maintenance group was 9 (5–11) and was consistent among all IBCG risk groups. Full details regarding the maintenance number of instillations according to IBCG risk groups are provided in Table S1.

Recurrence Free Survival Outcomes

The median (IQR) follow-up was 57 (36–75) months and 139 (30%) patients experienced any recurrence. There were four

(0.8%) patients who had a recurrence and two (0.4%) patients who had a high-grade (HG) recurrence within 3 months from the start of treatment, thus were excluded from landmark incidence stacked analysis. The 5-year cumulative incidence proportion of any recurrence was 15% (95% CI 12–19%) in patients with no IBCG risk factors, 29% (95% CI 24–36%) in patients with one to two IBCG risk factors, and 38% (95% CI 28–50%) in patients with three or more IBCG risk factors (Fig. 1). Patients with no IBCG risk factors who were treated with induction only had a similar 5-year cumulative incidence proportion of recurrence (7.7%, 95% CI 6–9.7%) compared to patients who received induction plus maintenance (7.3%, 95% CI 5.7–9.3%; Fig. 2). Conversely, patients with one to two IBCG risk factors who received induction only had a higher risk of 5-year recurrence (16%, 95% CI 14–20%) compared to those who received induction plus maintenance (13%, 95% CI 10–15%). Similarly, patients with three or more IBCG risk factors who underwent induction only had a 5-year risk of recurrence of 21% (95% CI 15–26%), which was higher than the 17% (95% CI 13–23%) observed in patients with three or more risk factors who received induction plus maintenance.

Progression Free Survival Outcomes

A total of 47 (10%) patients experienced disease progression during follow-up. None experienced disease progression within 3 months from treatment start. The 5-year cumulative incidence proportion of progression was 3.8% (95% CI 2.9–5%), 5.3% (95% CI 4.2–6.6%), and 7.4% (95% CI 5.6–9.8%) for patients with no, one to two, and three or more IBCG risk factors, respectively. Among the latter group, patients who received induction only had a 5-year risk of progression of 4.2% (95% CI 3.1–5.8%), whereas patients who had induction plus maintenance had a 5-year risk of progression of 3.1% (95% CI 2.2–4.3%; Fig. 3).

Oncological Outcomes Assessed Using Multivariable Cox Regression Models

At the 3-month landmark multivariable Cox regression model, we found no difference in terms of recurrence among patients with no IBCG risk factors according to the type of treatment received (induction only vs induction plus maintenance; hazard ratio [HR] 0.78, 95% CI 0.49–1.37;

Fig. 1 Cumulative incidence proportion of any recurrence among patients with IR-NMIBC identified at our centre according to IBCG risk groups.

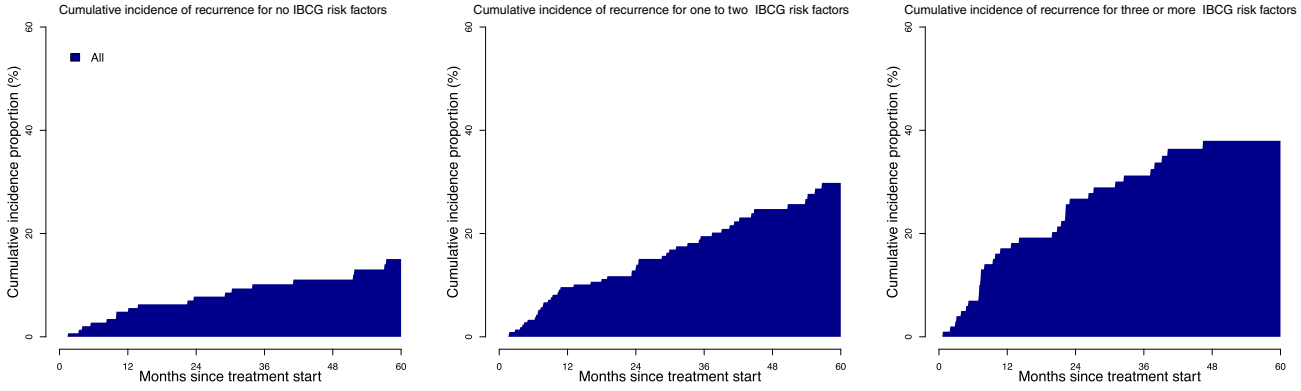


Fig. 2 Cumulative incidence proportion of any recurrence among patients with IR-NMIBC identified at our centre according to IBCG risk groups and treatment duration (induction only vs induction plus maintenance).

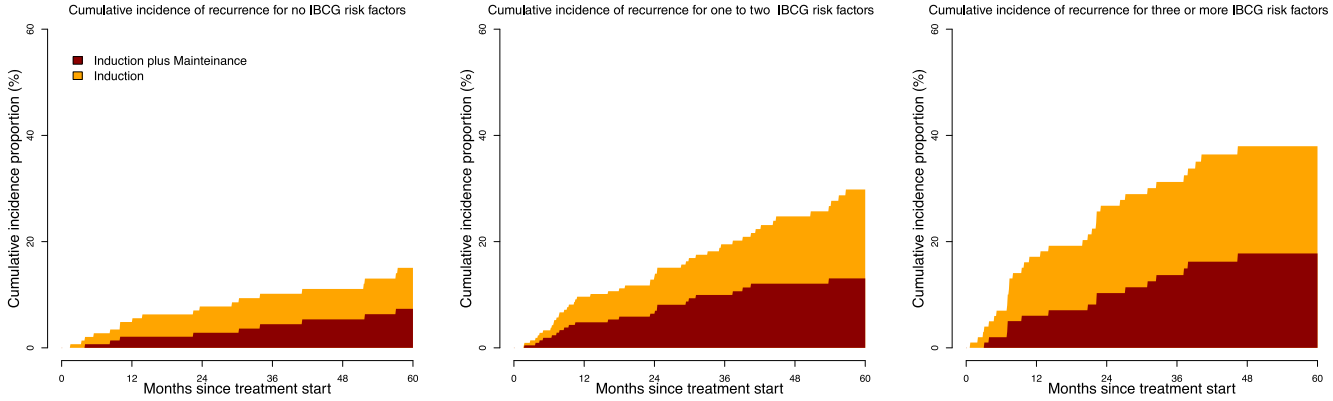


Fig. 3 Cumulative incidence proportion of progression among patients with IR-NMIBC identified at our centre according to IBCG risk groups and treatment duration (induction only vs induction plus maintenance).

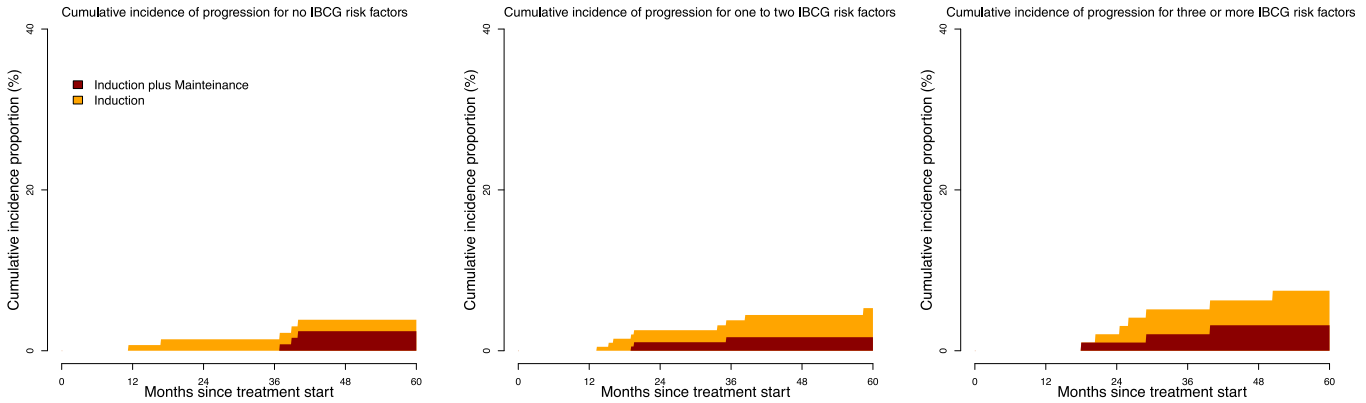
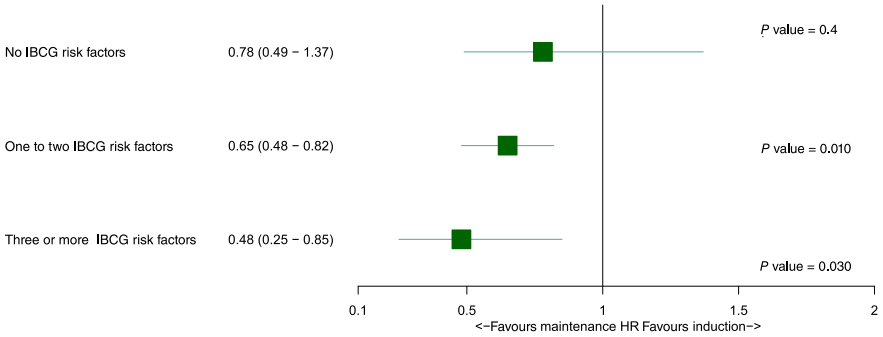


Fig. 4 Forest plot showing the HRs and 95% CIs derived from three separate multivariable Cox regression models testing the association of maintenance and the risk of any recurrence using induction as a reference. The model was adjusted for tumour grade and early instillation performed at TURBT.



P = 0.4). Instead, patients with one to two and three or more IBCG risk factors had a significant lower risk of recurrence if induction was followed by a maintenance course (HR 0.65, 95% CI 0.48–0.82, P = 0.010 for one to two IBCG risk factors; HR 0.48, 95% CI 0.25–0.85, P = 0.030 for three or more IBCG risk factors; Fig. 4, Table S2). Even if maintenance lowered the risk of progression compared to induction only, no significant differences at cox regression models were assessed among IBCG groups (Table S2).

Discussion

We conducted a retrospective analysis investigating the benefit of a maintenance course in terms of recurrence and progression among patients with IR-NMIBC treated with intravesical chemotherapy or BCG at our centre, particularly we assessed the benefit of a prolonged treatment (induction plus maintenance) over a shorter one (induction only) according to the IBCG scoring system risk groups.

The latest EAU 2021 classification includes in the IR-NMIBC group patients not in the low- or high-risk NMIBC groups, which may include some Ta HG cancers without additional risk factors, (e.g., tumour size ≥3 cm or multifocality) [3,4]. Soria et al. [7] have recently tested the IBCG scoring system in a multicentre retrospective cohort, showing significant differences in recurrence-free survival and progression-free survival when patients with IR-NMIBC were stratified into three risk groups based on IBCG risk factors and, therefore, supporting the use of the IBCG scoring system in clinical practice. Currently, the IBCG recommends at least the use of intravesical chemotherapy induction or BCG up to 1 year for patients with one to two IBCG risk factors, whereas patients with three or more IBCG risk factors should be treated with intravesical chemotherapy induction plus maintenance or BCG up to 1 year [6]. Up to now, no study has ever assessed if there is a benefit from performing a maintenance plus induction course compared to an induction course only according to the IBCG stratification system. In this context, our study has revealed several noteworthy findings.

First, we analysed the efficacy of the IBCG scoring system in assessing the risk of recurrence in patients with IR-NMIBC. Our results showed that the increasing presence of IBCG risk factors is associated with an increased risk of any recurrence, thus confirming the results of recent studies assessing the

prognostic role of the IBCG stratification system [7]. In our cohort, the 5-year risk of any recurrence ranged from 15% for patients with IR-NMIBC with no IBCG risk factors to 38% for those with three or more IBCG risk factors. Moreover, our analysis evaluated the risk of recurrence according to both treatment duration (induction only vs induction plus maintenance) and the IBCG stratification system, testing the benefit of a prolonged treatment among different IBCG risk groups. In particular, patients with no IBCG risk factors had a similar risk of 5-year recurrence according to treatment duration (induction only: 7.7% vs induction plus maintenance: 7.3%), thus suggesting no evidence for a benefit from a prolonged treatment for this group of patients. As patients with IR-NMIBC with no IBCG risk factors have a relatively low 5-year recurrence and progression rate, recent evidence suggests the possibility of using the IBCG scoring system to select candidates for active surveillance (AS) among patients with IR-NMIBC [17,18]. In particular, a lower recurrence rate has been reported for patients with IR-NMIBC selected for AS according to the presence of no IBCG risk factors, emphasising the potential use of the IBCG scoring system to select some patients for AS to avoid some possible complications of TURBT, anaesthesia, and in-hospital stay, which can be especially concerning in elderly patients [19,20].

Second, we found a lower risk of disease recurrence among patients with one to two IBCG risk factors who received a maintenance course after induction compared to patients with one to two IBCG risk factors who had an induction only course. Patients with one to two and three or more IBCG risk factors who received a prolonged treatment (i.e., induction plus maintenance) had a 35% and 52% reduced risk of any recurrence compared to patients in the same categories who received only an induction course, respectively (all $P < 0.05$). These findings suggest that both these IBCG groups probably benefit of a prolonged treatment compared to patients with no IBCG factors, for whom a shorter treatment seems sufficient. Despite the guidelines being unclear about the optimal duration of maintenance therapy in patients with IR-NMIBC, the results of the NIMBUS trial confirm the benefit of administering at least 1 year of BCG for patients with high-risk NMIBC, reducing recurrence and progression rates [21]. Thus, we confirm that not all patients with IR-NMIBC are the same in terms of oncological outcomes, and not all patients benefit equally from a maintenance course. For patients with IR-NMIBC with no IBCG risk factors, maintenance therapy appears to be unnecessary. However, for patients with one to two IBCG risk factors, and especially for those with three or more IBCG risk factors, a prolonged treatment regimen seems to improve significantly their oncological outcomes. However, the question regarding how long this treatment should be given remains unanswered and further prospective evidence will be needed.

Our study is not without limitations. The long accrual period and retrospective design may have introduced bias, including potential confounding by indication and recall bias. For instance, we were unable to determine the rationale guiding the choice between BCG and intravesical chemotherapy in patients with IR-NMIBC, nor could we ascertain the reasons behind the decision to administer maintenance therapy vs induction alone. While one might hypothesise that patients selected for maintenance therapy had more aggressive disease features, Table 1 does not reveal any significant clinical differences between the two groups. Furthermore, the duration of maintenance therapy was left to the discretion of the treating physician, and we are unable to provide standardised reasons for shorter or longer treatment durations. Nevertheless, among the 58% of patients who received maintenance therapy, the median (IQR) number of instillations was 9 (5–11). Assuming a regimen of one instillation per month starting roughly 3 months after the index TURBT and the induction cycle, this corresponds approximately to 1 year of treatment, thereby suggesting sufficient exposure to maintenance therapy. Furthermore, we did not analyse separately the outcomes of patients treated with BCG vs those who received chemotherapy, resulting in findings that reflect a mixed-treatment population. However, this approach mirrors current guideline recommendations, which endorse either intravesical chemotherapy or BCG for IR-NMIBC. Recent evidence also suggests that treatment-naïve patients with IR-NMIBC have comparable oncological outcomes whether treated with chemotherapy or BCG [8], supporting the inclusion of both groups in our analysis. Moreover, this strategy reflects real-world clinical practice, where treatment decisions are influenced by patients' characteristics and physician preferences. With respect to disease progression, although adjusted HR from Cox models suggested a possible benefit for patients receiving induction plus maintenance therapy—and despite the retrospective validation of prognostic differences between IBCG risk groups [7]—the *P* values were not statistically significant. This is likely due to the limited number of progression events in each group (~10%), which may have reduced the statistical power of our analysis. It is conceivable that larger cohorts with more events could reveal significant differences. Similarly, in our risk stratification analysis, the benefit of maintenance therapy may not have reached significance due to the same limitation for patients with no IBCG risk factors. That said, the HR was 0.78 with a reasonably narrow CI (0.49–1.37), suggesting fair precision, and the cumulative incidence of progression was nearly identical between groups (7.7% vs 7.3%). The low number of patients who received an early instillation after TURBT (89 [20%]) may appear ambiguous considered the significant number of pTa LG tumours (297 [64%]); however, we observed an increasing trend in the use of early instillation from 2010 to 2023, in line with the growing body of evidence supporting its use

over the years [22]. Overall, primary tumours received an early instillation three times more often than recurrent tumours in our cohort. Additionally, the occurrence of intraoperative complications such as bladder perforation or bleeding, and the clinical decision to prioritise BCG in recurrent IR-NMIBC previously treated with intravesical chemotherapy, may have also influenced the observed rates [23]. Finally, although retrospective evidence continues to support the validity of the IBCG classification algorithm, a prospective validation remains lacking—highlighting the need for further research in this area.

In conclusion, among patients with IR-NMIBC, the IBCG prognostic algorithm correctly identifies patients with different disease prognoses who should be treated accordingly. For patients with no IBCG risk factors, induction alone seems sufficient after TURBT, whereas maintenance therapy reduced significantly the risk of recurrence in patients with one to two and three or more IBCG risk factors, with a 35% and 52% risk reduction, respectively. Although these findings need to be validated prospectively, they should be considered when informing treatment decision in patients with IR-NMIBC.

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Disclosure of Interests

All authors declare no conflict of interest relative to the content of the paper.

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Study concept and design: Paolo Zaurito, Pietro Scilipoti, Marco Moschini. Acquisition of data: Paolo Zaurito, Pietro Scilipoti, Mattia Longoni, Alessandro Viti, Mario de Angelis, Alfonso Santangelo, Giovanni Tremolada, Leonardo Quarta, Andrea Cosenza, Angelo Occhi, Armando Galdieri, Natasha Disabato, Michele Brancaccio, Giusy Burgio. Analysis and interpretation of data: Paolo Zaurito, Pietro Scilipoti, Marco Moschini. Drafting of the manuscript: Paolo Zaurito, Pietro Scilipoti, Marco Moschini. Critical revision of the manuscript for important intellectual content: Mattia Longoni, Mario de Angelis, Andrea Necchi, Maurizio Colecchia, Andrea Salonia, Francesco Montorsi, Alberto Briganti, Marco Moschini. Obtaining funding: None. Supervision: Marco Moschini.

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Abbreviations: EAU, European Association of Urology; HG, high-grade; HR, hazard ratio; IBCG, International Bladder Cancer Group; IQR, interquartile range; IR, intermediate-risk; LG, low-grade; (N)MIBC, (non-)muscle-invasive bladder cancer; pT, pathological T stage; TURBT, transurethral resection of bladder tumour.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Flowchart demonstrating the selection process of patients including in the study.

Table S1. Number of maintenance instillations of BCG or intravesical chemotherapy.

Table S2. Multivariable Cox regression analyses to assess the risk of any recurrence.

