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Management Dilemma for Very High-risk Non–muscle-invasive Bladder Cancer: Real-World Data Challenge the Guideline Recommendation for Upfront Radical Cystectomy

José Daniel Subiela[a,*], *Pietro Scilipoti*[b], *Roberto Contieri*[c], *Nijati Lobo*[d], *Renate Pichler*[e], *Ashish M. Kamat*[d]

[a] *Department of Urology, Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria, Universidad de Alcala, Madrid, Spain;* [b] *Division of Experimental Oncology, Department of Urology, Urological Research Institute, Vita-Salute San Raffaele University, Milan, Italy;* [c] *Department of Urology, Istituto Nazionale Tumori di Napoli IRCCS, Fondazione G. Pascale, Naples, Italy;* [d] *Department of Urology, University of Texas MD Anderson Cancer Center, Houston, TX, USA;* [e] *Department of Urology, Comprehensive Cancer Center Innsbruck, Medical University of Innsbruck, Innsbruck, Austria*

The European Association of Urology (EAU) guidelines recommend upfront radical cystectomy (RC) in patients with very high-risk (VHR) non–muscle-invasive bladder cancer (NMIBC) [1]. However, most patients are not eager to have their bladder removed, and real-world adoption remains limited [2]. The EAU 2021 risk model proposed a 5-yr threshold of 20% for the risk of progression—based on its derivation cohort—as a decision point for considering immediate RC, leading to the formal subclassification of a "very high-risk" NMIBC subgroup. The 2021 EAU update identified a subset with a predicted 5-yr risk of progression to muscle-invasive bladder cancer (MIBC) of 44% [3], although this estimate was derived from patients with primary tumors who had not received bacillus Calmette-Guérin (BCG). Thus, it may not accurately reflect the contemporary VHR population encountered in clinical practice. This raises a critical question: Does the current evidence support upfront RC as a universal strategy for all patients with VHR NMIBC?

A study by the Kamat group in the USA analyzed 529 patients, including 118 classified as VHR, of whom 104 received adequate BCG (induction plus at least one maintenance course) [4]. In this subgroup, the 5-yr progression rate was only 14.9%. Notably, the discriminative ability of the model declined when applied to BCG-treated patients (C index 0.63 vs 0.80 in the original cohort).

Contieri et al [5] conducted a retrospective study at the same center, analyzing data for 235 patients with VHR NMIBC. Only 78 (33%) underwent upfront RC. No significant differences were found in overall survival (BCG 87% vs RC 85%) or cancer-specific mortality (CSM: BCG 10% vs RC 12%).

Miyake et al [6] analyzed data for 3813 patients across multiple institutions in Japan. Among these, 731 cases in the BCG cohort and 130 in the non-BCG cohort were classified as VHR NMIBC. The 5-yr progression-free survival (PFS) rate for BCG-treated patients with VHR NMIBC was 79% (95% CI confidence interval 70–86%), although the discriminative ability of the model was suboptimal (C index 0.617). The authors conducted a subgroup analysis with stratification of VHR NMIBC into five categories:

1. Ta high-grade (HG)/grade 3 (G3) and carcinoma in situ (CIS) with all three risk factors,
2. T1 G2 and CIS with at least two risk factors,
3. T1 HG/G3 and CIS with at least one risk factor,
4. T1 HG/G3 without CIS but with all three risk factors, and
5. Cases with CIS involving the prostatic urethra, variant histology, or lymphovascular invasion (LVI).

Despite these distinctions, no significant differences in recurrence-free survival, PFS, or cancer-specific survival were observed.

Subiela et al [7] conducted a multicenter study across 24 European centers that included 640 patients with VHR

* Corresponding author. Department of Urology, Hospital Universitario Ramón y Cajal, Madrid, Spain. Tel. +34 9 13368000.
E-mail address: jdsubiela@gmail.com (J.D. Subiela).

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NMIBC treated with adequate BCG. The 5-yr PFS rate was 78%, with a CSM rate of 13%. Notably, the group of patients who achieved an early and sustained response to BCG had a 5-yr conditional PFS rate exceeding 90%.

In line with these findings, Scilipoti et al [2] found that upfront RC is rarely performed in Europe. Among 1221 patients, 10% had VHR NMIBC, of whom only 29% underwent upfront RC. After propensity score matching (87 BCG vs 87 RC), the 5-yr CSM rate was similar between the BCG and RC groups (13% vs 16%). However, among 73 patients who underwent delayed RC, the group with disease progression before surgery had worse outcomes (3-yr CSM rate: 31% vs 13%; p = 0.018), underscoring the need to promptly identify patients without a response to BCG.

The generation of level 1 evidence to support upfront RC has proven difficult because of ethical and logistical challenges. The aim of the BRAVO feasibility trial [8] was to compare upfront RC with intravesical BCG in high-risk NMIBC. The study screened 185 patients, but only 51 (27%) consented to randomization. The investigators concluded that a full randomized trial is unlikely to succeed, as some patients (10%) may have lethal disease at diagnosis, while others could benefit from bladder preservation. In addition, RC has a major impact on an individual's quality of life.

Taken together, these data suggest several important considerations.

1. First, VHR NMIBC represents a relatively uncommon disease; even in high-volume centers, and only ten to 12 cases are seen annually [4,5].
2. Second, patients with VHR NMIBC who receive adequate BCG therapy often experience a more favorable prognosis than expected according to the EAU 2021 risk classification, emphasizing the limitations of applying guideline-derived risk stratifications to contemporary BCG-treated cohorts.
3. Third, upfront RC is not a one-size-fits-all solution. Available evidence does not justify its use as the standard of care for all VHR NMIBC cases and suggests that this strategy may lead to overtreatment in many patients. Consequently, upfront RC should not be proposed with the same strength of recommendation as for conservative treatment. Although additional adverse features—such as T1 substaging [9], LVI [10], histological subtypes [11], CIS involving the prostatic urethra or paraurethral ducts [12], and persistent T1 on repeat transurethral resection [13]—have been proposed for refinement of patient selection, their real-world utility seems to be limited, as demonstrated by Miyake et al [6]. This underscores the ongoing uncertainty and the need for more precise risk stratification tools.
4. Although current evidence suggests that outcomes with BCG and upfront RC are comparable in terms of survival, these data are derived from retrospective analyses [5,6] and should therefore be interpreted with caution. There may still be a subset of patients who could benefit from upfront RC, as suggested by the BRAVO feasibility trial [8]. This hypothesis warrants further investigation in a well-designed randomized controlled trial to definitively identify which patients might derive the greatest benefit from early surgical intervention.
5. Additional clinical concerns arise from these studies. First, despite receiving adequate BCG therapy, a proportion of patients classified as having VHR NMIBC may experience very early recurrences (ie, at first surveillance cystoscopy). While most studies were not specifically designed to assess this outcome, data reported by Lobo et al [4] for a consecutive single-center cohort showed that 104/118 patients (88%) with VHR NMIBC received adequate BCG. Similarly, in the expanded cohort from the same institution, Contieri et al [5] found that 90% of patients received adequate BCG treatment. These figures argue against the occurrence of early recurrences in the majority of patients, considering that adequate BCG treatment implies a minimum follow-up duration of approximately 6 mo from initiation of intravesical therapy.

Regarding clinical outcomes for patients treated with upfront RC (defined as RC performed immediately after a diagnosis of VHR NMIBC) or early RC (defined as RC following BCG failure), available data suggest important differences. In the study by Contieri et al [5], among those who underwent upfront RC, 23% were upstaged to MIBC, including six patients (8%) with node-positive disease. In addition, 11% of patients developed metastatic disease during follow-up.

By contrast, in the study by Subiela et al [7], early RC was performed in 169 patients (26.4% of the entire cohort), of whom 82% underwent surgery because of progression to MIBC, while 18% were treated with early RC at the NMIBC stage following BCG failure. Among all patients who underwent early RC, only four (2%) had nodal involvement, all of whom had MIBC at the time of surgery. Notably, among those treated at the NMIBC stage, only 7.7% were upstaged to MIBC. These findings suggest that although upfront RC is often offered to patients perceived to have worse clinicopathologic features according to clinical judgment, those undergoing early RC after BCG failure may still experience acceptable pathological outcomes, particularly when surgery is performed before progression to MIBC [2].

These insights reinforce the limitations of current clinicopathologic risk models and underscore the need for more accurate and dynamic tools to guide clinical decision-making. Emerging strategies may help in closing this gap. For instance, detection of minimal residual disease using urine-derived tumor DNA has shown promise in identifying patients at higher risk of relapse and may guide therapeutic decision-making [14]. In parallel, multiomics approaches have identified molecular subtypes of NMIBC with distinct clinical outcomes [15]. These tools may enable a biologically informed framework for selecting patients most likely to benefit from early RC.

Until such precision models have been clinically validated and are widely accessible, treatment decisions should be individualized and made in close consultation with the patient. These findings highlight the need for a more personalized approach to the management of VHR NMIBC. Predictive models integrating molecular biomarkers and real-time response data may enhance treatment precision. At the same time, there is a pressing need to explore new ther-

apeutic options. Ongoing trials in the BCG-naïve setting—such as BCG combined with immune checkpoint inhibitors (CREST with sasanlimab, ALBAN with atezolizumab, POTOMAC with durvalumab, and KEYNOTE-676 with pembrolizumab), or TAR-200, a sustained-release gemcitabine system, in combination with BCG or cetrelimab (SunRISe-3)—may offer promising bladder-preserving alternatives that are oncologically safe.

Conflicts of interest: The authors have nothing to disclose.

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