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Brief Correspondence

Prognostic Implication of the United States Food and Drug Administration-defined BCG-unresponsive Disease

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Abstract

The category "BCG-unresponsive disease", formulated by experts at the request of the United States Food and Drug Administration, denotes a group of patients with recurrent non-muscle-invasive bladder cancer for whom continued BCG treatment is unlikely to provide benefit. Although quickly adopted for trial design, many of the nuances within the definition lack validation. In this study, we evaluated the prognostic value of BCG unresponsive designation (i.e. recurrence after induction plus at least 1 maintenance course of BCG) by comparing the oncologic outcomes of these patients with those recurring after induction BCG alone. We confirm that appropriately defined, BCG-unresponsive patients are more likely to require salvage radical cystectomy (54.5% vs 17.9%, $p = 0.002$). Moreover, those opting for second-line bladder-sparing therapies are less likely to remain free of tumor recurrence (23% vs 69.2%, $p = 0.003$). On multivariate analysis, BCG-unresponsive disease independently predicts inferior high-grade recurrence-free survival (hazard ratio [HR]: 6.25, 95% confidence interval [CI]: 2.27–16.67; $p < 0.001$) and cystectomy-free survival (HR: 3.85, 95% CI: 1.49–10.0; $p = 0.006$). Our data confirm the prognostic implication of the BCG unresponsive definition i.e. recurrence of high grade disease after induction and one course of maintenance BCG, and support its use in counseling and risk stratification of patients with tumor recurrence after BCG.

Patient summary: Patients who have BCG-unresponsive disease, that is, high-grade non-muscle-invasive bladder cancer recurring after BCG induction and maintenance, have a low likelihood to respond to further BCG treatment and should consider radical cystectomy or clinical trial enrollment.

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The term BCG-unresponsive disease was borne out of the need to define a population with non-muscle-invasive bladder cancer (NMIBC) who will no longer benefit from further BCG therapy [1,2]. To qualify, the patient is required to have high-grade (HG) tumor recurrence after receiving adequate BCG treatment (at least 5/6 induction and 2/3 maintenance doses of BCG, with/without further maintenance therapy) [2]. Since its inception, this definition has been incorporated into documents from the United Stated Food and Drug Administration guiding trial design in the BCG failure setting and has effectively standardized the study population in many ongoing trials [3].

Despite its universal adoption, the prognostic implication of BCG-unresponsive disease is relatively unknown. For

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instance, it is not well established whether tumor recurrence after adequate BCG treatment carried with it a different prognosis than recurrence after induction BCG alone, a disease entity known to be responsive to further intravesical BCG [4–6]. To further elucidate the prognosis of BCG-unresponsive disease and its implication on responsiveness to continued bladder-sparing therapy (BST), we retrospectively analyzed the outcomes in patients with HG recurrence after BCG therapy at our institution.

After Institutional Review Board approval, a retrospective search was conducted in our NMIBC database. Between 2004 and 2015, 83 patients were found to have HG NMIBC recurrence within 6 mo of induction BCG and sufficient information for analysis. Of these, 55 patients recurred after induction and one course of maintenance (satisfying the BCG-unresponsive definition), while 28 patients recurred after induction therapy alone. Tumor staging was based on the TNM staging system and the 2004 World Health Organization grading classification system. Options presented to the patient after tumor recurrence were at the discretion of the treating physician and decisions were made in accordance with our practice of shared decision making. All recurrences were biopsy-proven, and progression was defined as subsequent development of muscle-invasive bladder cancer (MIBC) or distant metastasis. HG recurrence-free survival (RFS), progression-free survival (PFS), cystectomy-free survival (CFS), and cancer-specific survival (CSS) were estimated using the Kaplan-Meier method and compared using the log-rank test. HG RFS was calculated from the time of recurrence, excluding patients who underwent immediate radical cystectomy (RC) after recurrence. PFS, CFS, and CSS were calculated from the time of BCG induction, specifically at the time of the first intravesical instillation [7]. In the analysis of RFS and PFS, patients who underwent RC without pathologic evidence of MIBC/metastasis were censored at the time of cystectomy. Multivariate analysis (MVA) was performed using the Cox regression model adjusting for age, primary tumor grade/stage, and recurrent tumor grade/stage.

Baseline clinicopathologic characteristics prior to BCG induction and the pathologic characteristics of the recurrent tumors are summarized in Supplementary Table 1. Notably, no difference was observed between the two groups in primary and recurrent tumor pathology before and after BCG treatment, respectively. Of the BCG-unresponsive patients, 16 (29%) underwent immediate cystectomy, with seven (44%) found to have MIBC on the pathologic specimen. Of the 39 patients treated with BST (Supplementary Table 2), nine were free of recurrence, 14 underwent delayed RC, and four suffered disease progression and were treated with systemic chemotherapy. Of the patients with failure after induction alone, only two

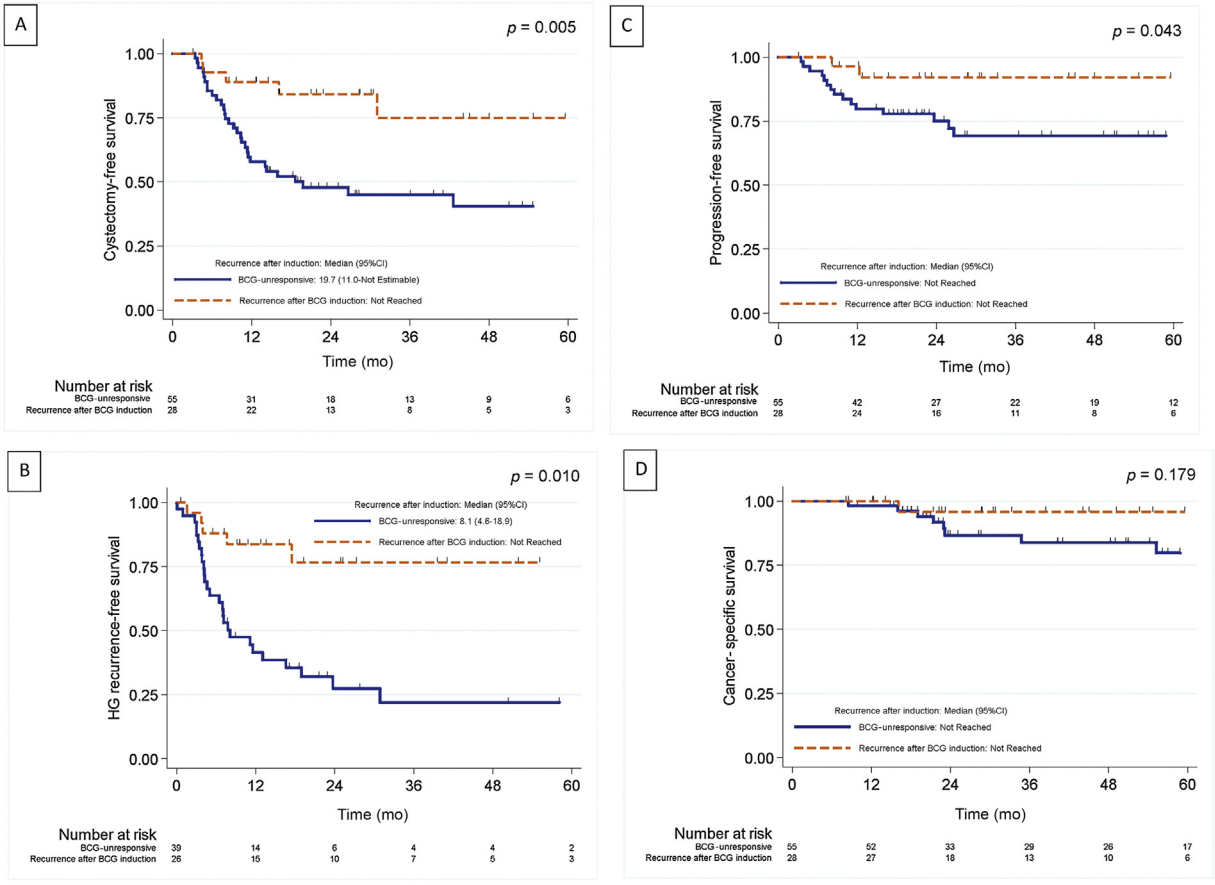

Fig. 1 – Kaplan-Meier analyses of cystectomy-free survival, high-grade (HG) recurrence-free survival, progression-free survival, and cancer-specific survival in patients with bacillus Calmette-Guerin (BCG)-unresponsive disease versus patients with HG recurrence after BCG induction alone. Median follow-up was 25.5 mo (25.5 mo for BCG-unresponsive group and 25.8 mo for recurrence after BCG induction alone group).
BCG = bacillus Calmette-Guerin; CI = confidence interval; HG = high-grade.

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(7.1%) patients underwent immediate cystectomy, and neither was found to have MIBC. Of the remaining 26 patients treated with BST (Supplementary Table 2), 18 remained recurrence-free, three underwent delayed RC, and one was treated with chemotherapy after disease progression.

These results were confirmed on Kaplan-Meier and MVA. BCG-unresponsive patients were more likely to undergo RC (5-yr CFS 40% vs 75%, $p = 0.005$; Fig. 1A). Moreover, among patients treated with BST after recurrence, BCG-unresponsive patients were more likely to develop HG recurrence (5-yr HG RFS 22% vs 77%, $p = 0.01$; Fig. 1B). Likewise, on MVA, BCG-unresponsive disease independently predicted worse CFS (hazard ratio [HR]: 3.85, 95% confidence interval [CI]: 1.49–10.0, $p = 0.006$) and HG RFS (HR: 6.25, 95% CI: 2.27–16.67, $p < 0.001$). Although a lower PFS (5-yr PFS 69% vs 92%, $p = 0.043$) was observed on the log-rank test (Fig. 1C), BCG-unresponsive disease did not predict worse PFS on MVA (HR: 4.07, 95% CI: 0.93–17.81, $p = 0.062$). Finally, no significant difference was seen in CSS (5-yr CSS 80% vs 96%, $p = 0.18$; Fig. 1D).

The current study illustrates the significant clinical difference between HG tumor recurrences after induction plus one maintenance course versus induction alone and confirms the criteria used to qualify patients as BCG-unresponsive. It also demonstrates the futility of currently available intravesical agents after BCG-unresponsive designation and highlights the need for improved therapeutic agents. Equally important, the study also shows the importance of expedient RC in the BCG-unresponsive setting to equalize cancer-specific outcomes. In the light of our findings, we recommend the use of BCG-unresponsive definition for risk stratification and patient counseling [2].

We acknowledge certain inherent limitations of a single-center, retrospective study such as ours. Few patients satisfied the strict definition of BCG-unresponsive disease. Furthermore, as maintenance therapy is increasingly accepted as the standard of care for intermediate- to high-risk NMIBC [8], fewer cases of HG recurrence are seen after induction alone. Despite the small numbers included, we clearly demonstrate a significant difference in HG RFS and CFS.

In summary, HG recurrence after BCG induction and one course of maintenance predicts poor response to additional intravesical therapy. In this setting, expedient RC is recommended for all suitable candidates for surgery. For non-surgical candidates, combination intravesical therapy using gemcitabine and docetaxel is promising [9]. In addition, BCG-unresponsive disease is a distinct clinical entity than recurrence after induction alone, which can be salvaged up to 69.2% of the time with additional intravesical immunotherapy. As such, patients with BCG-unresponsive disease uniquely qualify for future trials investigating efficacies of second-line intravesical agents for BCG-refractory NMIBC.

Author contributions: Ashish M. Kamat 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: Li, Kamat.
Acquisition of data: Li.
Analysis and interpretation of data: Li, González, Kamat.
Drafting of the manuscript: Li, Kamat.
Critical revision of the manuscript for important intellectual content: Li, Tabayoyong, Guo, González, Navai, Grossman, Dinney, Kamat.
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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.09.028.

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