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Original Article

Reduced-dose bacillus Calmette-Guérin (BCG) in an era of BCG shortage: real-world experience from a tertiary cancer centre

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Objective

To evaluate the impact of one-third-dose (1/3D) bacillus Calmette-Guérin (BCG) on oncological outcomes in a large cohort of patients with non-muscle-invasive bladder cancer (NMIBC) treated with adequate BCG (as defined by the US Food & Drug Administration (FDA)) in a real-world setting.

Patients and Methods

We performed an institutional review board-approved review of patients with NMIBC treated with adequate BCG at our institution between 2000 and 2020. Patients were stratified according to whether they had received 1/3D BCG or full-dose (FD) BCG. Time to recurrence, time to progression and cancer-specific survival were estimated using Kaplan–Meier methods.

Results

Of 563 patients with NMIBC treated with adequate BCG, 150 (26.6%) received 1/3D and 413 (73.4%) received FD. The use of 1/3D BCG did not adversely affect time to recurrence ($P = 0.449$) or time to progression ($P = 0.716$), and this remained consistent when patients were stratified by individual 2021 European Association of Urology (EAU) prognostic factor risk groups. Cancer-specific survival was similar in patients receiving 1/3D and those receiving FD BCG ($P = 0.320$).

Conclusion

The use of 1/3D BCG was not associated with adverse oncological outcomes in a large cohort of patients receiving adequate BCG for intermediate- and high-risk NMIBC. Based on this real-world experience, risk-stratified split-vial dosing may represent a valuable approach for other institutions facing BCG shortages whilst also providing reassurance to patients who may be concerned about suboptimal outcomes.

Keywords

bacillus Calmette-Guérin, non-muscle-invasive bladder cancer, BCG shortage, reduced dose

Introduction

Bacillus Calmette-Guérin immunotherapy has been the 'gold standard' treatment for intermediate- and high-risk non-muscle-invasive bladder cancer (NMIBC) for almost half a century. Several meta-analyses have demonstrated its superiority over intravesical chemotherapy for recurrence [1–4] and BCG also reduces, or at least delays, progression to muscle-invasive disease [5,6]. Current guidelines support a risk-stratified schedule for maintenance therapy, with 1 and up to 3 years of BCG recommended for patients with intermediate- and high-risk disease, respectively [7,8].

In 2011, the US Food and Drug Administration (FDA) suspended the production of BCG Connaught following the discovery of mould at the Sanofi Pasteur manufacturing plant [9]. This event was the catalyst for a series of problems culminating in several periods of global BCG shortage. Shortly after the suspension of BCG Connaught production, Merck, the sole manufacturer and supplier of BCG Tice to the US market, faced its own production difficulties [9]. Further compounding matters, Sanofi Pasteur subsequently announced that it would indefinitely cease BCG production in mid-2017 [10]. As the Connaught strain supplied a significant proportion of the global market, the end of its

production has led to a BCG shortage both in the USA and worldwide.

These shortages have prompted the use of several alternative treatment strategies including rationing BCG, using intravesical chemotherapy, and upfront cystectomy [11]. In accordance with AUA guidelines, our institution elected to treat patients with one-third-dose (1/3D) BCG, allowing a single vial of BCG to be divided amongst three patients. This approach is based on a randomized trial from the European Organization for Research and Treatment of Cancer (EORTC) that showed no difference in progression rates between full-dose (FD) and 1/3D BCG [12]. Herein, we evaluate the impact of 1/3D BCG on oncological outcomes in NMIBC patients treated with adequate BCG in a real-world setting.

Patients and Methods

This study was conducted with approval from the University of Texas M.D. Anderson Cancer Center institutional review board (IRB number: PA16-1042). We identified 631 patients between January 2000 and January 2020 with NMIBC (cTa, cTis, cT1) who received 'adequate' BCG as defined by the FDA [13], the International Bladder Cancer Group [14] and the European Association of Urology (EAU) [15]: at least five of six induction instillations plus two additional instillations (either as part of three planned maintenance instillations or six planned repeat induction instillations), all taking place within a 6-month period. A total of 68 patients were excluded for the following reasons: primary treatment with BCG plus interferon alpha ($n = 35$), unknown dosing ($n = 21$) and inclusion in trials ($n = 12$).

Patients were only included if pathological information was available from their index transurethral resection of bladder tumour specimen and if they had completed at least one follow-up cystoscopy post-induction BCG at our institution within 6 months from initiation of therapy. A genitourinary pathologist within our institution centrally reviewed all pathology specimens used in clinical treatment decisions. Surveillance schedules were standardized among all providers and based on available NMIBC guidelines.

Medication records were reviewed to determine BCG dosage. The TICE® BCG strain (Merck, Durham, NC, USA) containing 1–8 × 10^8 colony forming units was used. Patients were defined as receiving either FD (50 mg) or 1/3D (16.5 mg) on the basis of the dosage received to ensure adequate BCG treatment (i.e., at least five out of six induction instillations plus two additional instillations). The preparation of 1/3D BCG was performed by dissolving one vial of BCG Tice in 150 mL saline and administering 50 mL of the solution intravesically via a catheter. After removal of the catheter, the patient was instructed to retain the BCG for 2 h.

Study variables in our dataset included age, gender, primary vs recurrent tumour, tumour size and number, T stage, presence of concomitant carcinoma *in situ* (CIS) and grade. The primary endpoints were time to recurrence (calculated as the number of months from first BCG instillation to the date of biopsy-proven disease recurrence) and time to progression to muscle-invasive bladder cancer or metastasis (calculated as the number of months from first BCG instillation to the date of the first increase to stage T2 or higher).

The study population was summarized using descriptive statistics. Pearson's chi-squared tests and Wilcoxon rank-sum tests were used to analyse categorical and continuous data, respectively. Kaplan–Meier methods were used to estimate the time to recurrence and progression. Patients were stratified according to BCG dose. Event-free probabilities were stratified separately in patients receiving 1/3D and FD BCG. The log-rank test was used to assess the statistical significance of these results. For all analyses a P value <0.05 was taken to indicate statistical significance. All statistical analyses were performed with Stata/SE, version 16.1 (Stata Corp. LP, College Station, TX, USA).

Results

A total of 563 patients were treated with adequate BCG at our institution. Of these, 150 (26.6%) received 1/3D BCG and 413 (73.4%) received FD BCG. Table 1 contains a summary of patient and tumour characteristics. Clinicopathological characteristics were similar in the 1/3D and FD groups with three exceptions: 1/3D patients were more likely to have tumours that were solitary (58.0% vs 48.4%; $P = 0.045$), low grade (15.3% vs 8.0%; $P = 0.010$) and not associated with concomitant CIS (83.7% vs 72.9%; $P = 0.017$). However, when patients were stratified according to 2021 EAU prognostic factor risk groups [7], there was no significant difference in distribution of risk ($P = 0.063$). The median number of BCG doses received by patients in the 1/3D and FD groups was 18 and 21 doses, respectively ($P = 0.133$). The median time from index transurethral resection of bladder tumour to first BCG instillation was the same in both groups (53 days; $P = 0.263$).

The median (interquartile range) follow-up for the entire cohort was 54.8 (29.4–88.1) months. Overall, 198 (35.2%) of the 563 patients experienced tumour recurrence, of whom 51 (34.0%) received 1/3D and 147 (35.6%) received FD. There was no significant difference in time to recurrence between the groups ($P = 0.449$; Fig. 1A). Disease progression to muscle-invasive disease or metastasis was seen in 43 patients (7.6%), of whom eight (5.3%) received 1/3D and 35 (8.5%) received FD BCG. Progression to muscle-invasive disease alone occurred in three (2.0%) and 11 (2.7%) patients receiving 1/3D and FD, respectively. Distant metastases occurred in five (3.3%) and 22 patients (5.3%) receiving 1/3D and FD, respectively. There was no significant difference in time to progression between the groups ($P = 0.716$; Fig. 1B).

Table 1 Patient and tumour characteristics.

	1/3D (*n* = 150)	FD (*n* = 413)	*P*
Age at diagnosis			
Median (IQR)	69.00 (63.00–76.00)	68.00 (61.00–75.00)	0.146
Gender, *n* (%)			
Female	24 (16.0)	90 (21.8)	0.131
Male	126 (84.0)	323 (78.2)	
Grade, *n* (%)			
High	127 (84.7)	380 (92.0)	0.010
Low	23 (15.3)	33 (8.0)	
Clinical T stage, *n* (%)			
Ta	78 (52.0)	193 (46.7)	0.153
Tis	14 (9.3)	26 (6.3)	
T1	58 (38.7)	194 (47.0)	
Maximum tumour diameter, *n* (%)			
<3 cm	64 (42.7)	189 (45.8)	0.975
≥3 cm	71 (47.3)	211 (51.0)	
Unknown	15 (10.0)	13 (3.2)	
Lymphovascular invasion, *n* (%)			
Absent	149 (99.3)	408 (98.8)	0.999
Present	1 (0.7)	5 (1.2)	
Concomitant CIS, *n* (%)			
Absent	124 (83.7)	301 (72.9)	0.017
Present	26 (17.3)	112 (27.1)	
Focality, *n* (%)			
Solitary	87 (58.0)	200 (48.4)	0.045
Multifocal	63 (42.0)	213 (51.6)	
Prostatic urethra involvement, *n* (%)			
Absent	143 (95.3)	393 (95.2)	0.931
Present	7 (4.7)	20 (4.8)	
Primary vs recurrent tumour, *n* (%)			
Primary	101 (67.3)	282 (68.3)	0.831
Recurrent	49 (32.7)	131 (31.3)	
Variant histology, *n* (%)			
Present	5 (3.3)	18 (4.4)	0.587
Absent	145 (96.7)	395 (95.6)	
Re-TUR performed, *n* (%)			
No	58 (38.7)	145 (35.2)	0.448
Yes	92 (61.3)	267 (64.8)	
2021 EAU prognostic risk group, *n* (%)			
Intermediate	44 (29.7)	97 (23.8)	0.063
High	85 (57.4)	225 (55.1)	
Very high	19 (12.8)	86 (21.1)	
Total BCG doses			
Median (IQR)	18 (14–24)	21 (15–24)	0.133

1/3D, one-third dose; CIS, carcinoma in situ; EAU, European Association of Urology; FD, full dose; IQR, interquartile range; TUR, transurethral resection.

Subgroup analysis of time to progression stratified by 2021 EAU prognostic factor risk groups showed no significant difference between the 1/3D and FD groups (Fig. 2): intermediate- ($P = 0.847$), high- ($P = 0.536$) and very-high-risk group ($P = 0.603$). Overall, 60 radical cystectomies were undertaken. Fifteen patients (10.0%) in the 1/3D group underwent cystectomy; of these, two (13.3%) had upstaging at the time of cystectomy. Forty-five patients (10.9%) in the FD group underwent radical cystectomy, of whom 18 (40.0%) had upstaging at cystectomy.

Overall, 100 patients (17.8%) died. In the 1/3D group, nine patients (6.0%) died; of these, two deaths (1.3%) were from bladder cancer. Ninety-one patients (22.0%) in the FD group died, of whom 18 (4.4%) died from bladder cancer. The 5-year cancer-specific survival rate was 98.5% (95% CI 90.0–99.8%) in the 1/3D group and 95.7% (95% CI 92.8–97.5%) in the FD group. There was no significant difference in cancer-specific survival between groups ($P = 0.320$; Fig. 1C).

Discussion

Faced with a worldwide BCG shortage, our institution employed split-vial dosing to treat patients with intermediate- and high-risk NMIBC. In the present study, we show that the use of 1/3D BCG was not associated with inferior oncological outcomes compared to FD BCG in patients receiving adequate BCG treatment. To our knowledge, this paper presents the first real-world experience of using split-vial dosing to mitigate the effects of the BCG shortage.

Our results align with the findings of several randomized controlled trials examining the efficacy of reduced-dose BCG

Fig. 1 Kaplan–Meier curves for (**A**) time to recurrence, (**B**) time to progression and (**C**) cancer-specific survival stratified by one-third-dose (1/3D) vs full-dose BCG. *The last patient in the 1/3D group experienced a progression event after the last censoring.

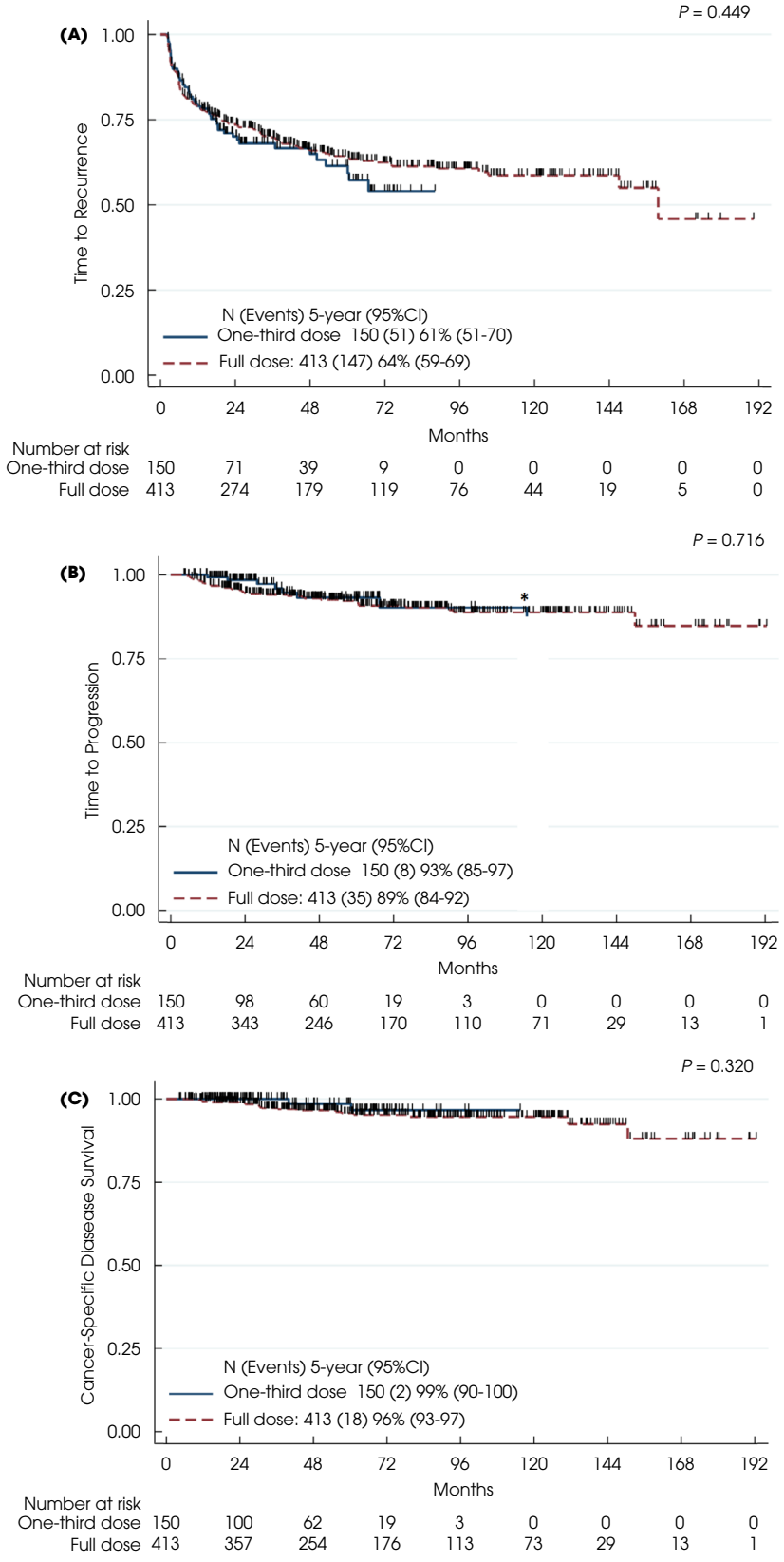
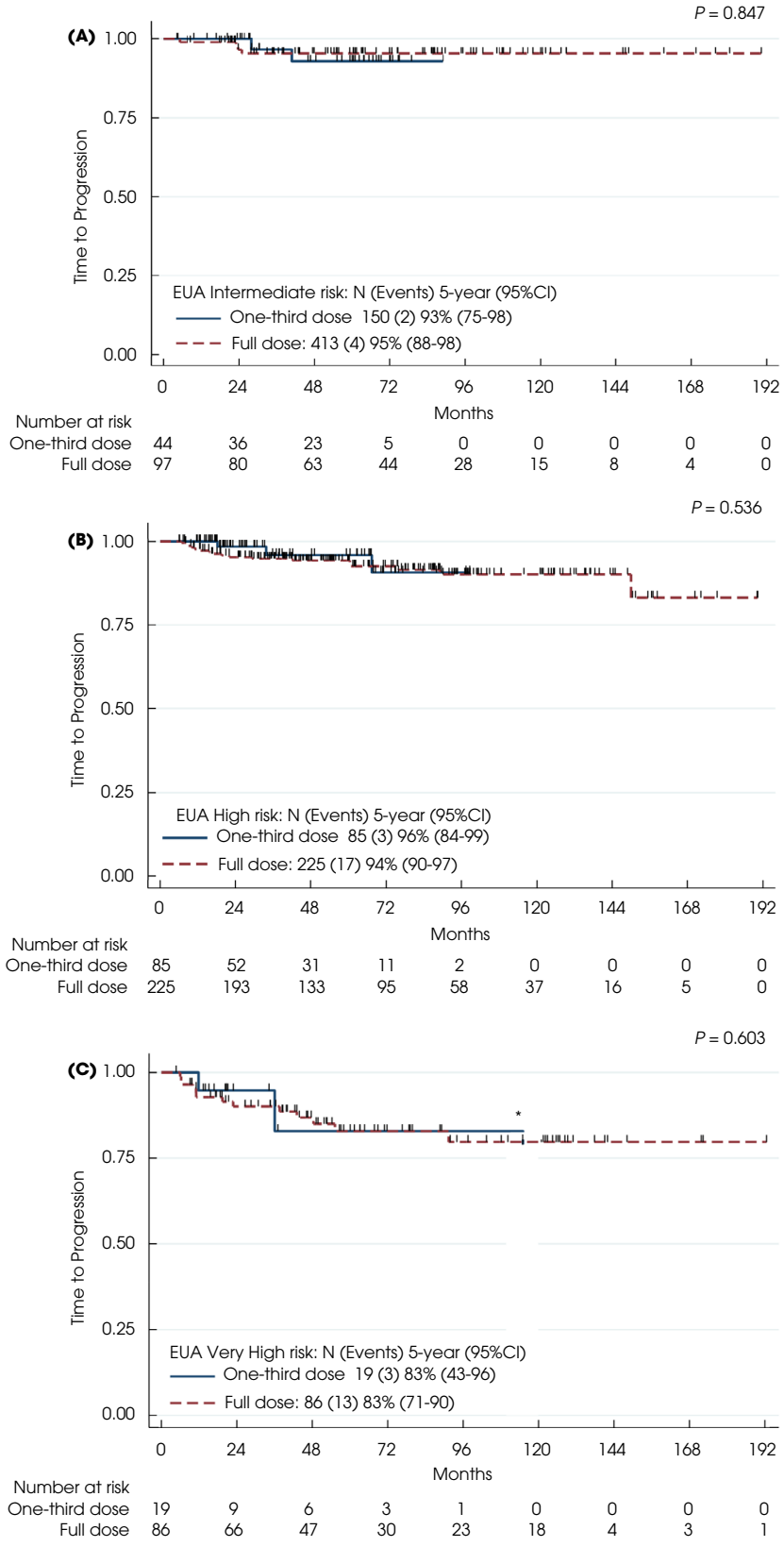


Fig. 2 Kaplan–Meier curves time to progression stratified by 2021 European Association of Urology prognostic factor risk group: (**A**) intermediate risk, (**B**) high risk and (**C**) very-high risk. *The last patient in the one-third-dose group experienced a progression event after the last censoring.



compared to full-dose BCG [12,16,17]. The CUETO group compared FD (81 mg) BCG Connaught with a threefold (27-mg) dose reduction and found no differences in either recurrence or progression between groups [16]. In a subsequent study, the same group found that, in patients with high-risk cancers (G3/T1/Tis), a threefold decreased dose of intravesical BCG was as effective as the standard dose [17]. The EORTC 30962 study examined the use of FD and 1/3D BCG with either a 1- or 3-year maintenance course in patients with intermediate- and high-risk NMIBC [12]. FD BCG was not superior to 1/3D BCG (5-year disease-free rate: 61.7% vs 58.5%; $P = 0.092$). However, subgroup analysis revealed that in high-risk patients, 3 years of maintenance with FD BCG significantly reduced recurrence compared to 1/3D BCG ($P = 0.009$).

The BCG shortage has forced urologists to choose alternative and often suboptimal treatment strategies that deviate from established recommendations. For example, in France, the National Medicines Agency made the decision to restrict BCG therapy to patients with high-grade disease and to only provide an induction course [18]. Ourfali et al. [18]performed a cost–consequence analysis of the medical and financial impact of these restrictions between 2013 and 2016. The authors found a threefold increase in the rate of tumour recurrence and the rate of cystectomy was five times higher. These results are not unexpected given the body of evidence demonstrating that maintenance treatment is required to reduce the risk of recurrence and progression [1,4,5]. The multicentre phase III randomized controlled NIMBUS trial evaluated whether a reduced frequency of standard-dose BCG was non-inferior to the standard-frequency schedule in patients with high-grade NMIBC [19]. The study was halted after an interim safety analysis determined inferiority of the reduced-frequency arm (time to recurrence: hazard ratio 0.40, 95% CI 0.24–0.68). At our centre, split-vial dosing allowed us to maintain the SWOG 8507 regimen [20] during periods of BCG shortage; patients received a median of 18 and 21 BCG instillations in the 1/3D and FD groups, respectively. Our results support the belief that it is the duration of BCG treatment rather than the dose which is more important in the event of BCG shortage.

We observed a similar proportion of cystectomies in both groups (1/3D: 10.0% vs FD: 13.3%), although upstaging at cystectomy was more frequently seen in patients receiving FD than those receiving RD (40.0% vs 13.3%). However, patients receiving 1/3D BCG had shorter follow-up than those receiving FD, and it may be the case that the number of cystectomies in this group increases with time. Interestingly, a recent Surveillance Epidemiology and End Results (SEER) database analysis examining patterns of radical cystectomy use during the BCG shortage found that cystectomy rates were higher pre-shortage, contrary to the authors' hypothesis that the opposite would occur [21].

The present study has limitations inherent in its retrospective single-centre nature, including unmeasured confounding. Selection bias may explain the equivalence in outcomes observed between the 1/3D and FD groups as patients receiving 1/3D BCG were more likely to have tumours that were low-grade, solitary and not associated with concomitant CIS. However, it should be noted that distribution of EAU prognostic factor risk groupings was similar in the two groups (FD and 1/3D) of patients ($P = 0.063$). Furthermore, subgroup analysis of each individual risk group did not reveal any differences in time to progression between patients receiving FD BCG and those treated with 1/3D BCG. Nevertheless, this emphasizes the importance of adopting a risk-stratified approach when managing NMIBC patients during periods of shortage. At our institution, patients with higher-risk disease were prioritized to receive FD BCG where possible. This practice is by no means unique to our centre. A recent analysis of the National Cancer Database assessing trends in BCG utilization before and during national BCG shortages showed that BCG use was rationed according to clinical risk in the years following interruptions to BCG supply, with the steepest declines occurring in lower-risk patients [22]. Another limitation pertains to the classification of BCG dosing; patients were defined as either FD or 1/3D on the basis of the dosage received to ensure adequate BCG treatment (i.e., at least five induction doses plus two additional instillations). This means that instillations received subsequent to this may have been either FD or 1/3D, providing a potential explanation as to why, in contrast to the EORTC trial [12], 1/3D patients did not have inferior time to recurrence compared to FD patients. Additionally, this study does not provide any toxicity data. However, this was never an objective as the association between dose reduction and lower toxicity is already well established [12,16]. We also acknowledge that our institution is a highly specialized cancer centre with expertise in bladder cancer. As such, our results may not be reflective of the community-based NMIBC population. Finally, it should be noted that some centres might be reluctant to employ split-vial dosing on the basis that manufacturer recommendations are to use BCG within 2 h of reconstitution. However, our group has previously addressed this concern, showing that BCG remains viable for at least 8 h and, in some cases, for up to 72 h after reconstitution [23].

Although Merck have announced plans to construct a new BCG manufacturing facility in the USA, BCG supplies are likely to remain limited as it will take several years for the facility to become fully operational [24]. This study provides real-world evidence that 1/3D BCG is not detrimental to patients with intermediate- and high-risk NMIBC treated with adequate BCG. As such, risk-stratified split-vial dosing may represent a valuable approach for other institutions facing shortages whilst also providing reassurance to patients

who may be concerned about the impact of the shortage on their care. It is hoped that future BCG shortages might be mitigated through the use of different BCG strains, alternative intravesical therapies or novel immunotherapies. A more preferable scenario, however, would see the development of a viable alternative to BCG with equivalent or improved anti-tumour activity, thus completely circumventing the significant difficulties associated with BCG production.

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Disclosure of Interests

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Abbreviations: 1/3D, one-third dose; CIS, carcinoma *in situ*; EAU, European Association of Urology; EORTC, European Organization for Research and Treatment of Cancer; FD, full-dose; FDA, US Food and Drug Administration; NMIBC, non-muscle-invasive bladder cancer.