



European Association of Urology

Bladder Cancer

Bladder-sparing Treatment in Patients with Bacillus Calmette-Guerin-unresponsive Non-muscle-invasive Bladder Cancer: An Analysis of Long-term Survival Outcomes

Wei Shen Tan^a, Valentina Grajales^a, Roberto Contieri^a, Patrick Hensley^b, Kelly Bree^a, Pavlos Msaouel^c, Charles C. Guo^d, Graciela M. Noguerras-Gonzalez^e, Neema Navai^a, Colin P. Dinney^a, Ashish M. Kamat^{a,*}

^a Department of Urology, University of Texas MD Anderson Cancer Center, Houston, TX, USA; ^b Department of Urology, University of Kentucky, Lexington, KY, USA; ^c Department of Genitourinary Medical Oncology, Division of Cancer Medicine, University of Texas MD Anderson Cancer Center, Houston, TX, USA; ^d Department of Genitourinary Pathology, University of Texas MD Anderson Cancer Center, Houston, TX, USA; ^e Department of Biostatistics, University of Texas MD Anderson Cancer Center, Houston, TX, USA

Article info

Article history:

Accepted April 20, 2023

Associate Editor:

M. Carmen Mir

Keywords:

Bacillus Calmette-Guerin
Intravesical
Non-muscle-invasive bladder cancer
Radical cystectomy
Survival

Abstract

Background: Data for bladder-sparing treatment (BST) in bacillus Calmette-Guerin (BCG)-unresponsive non-muscle-invasive bladder cancer (NMIBC) patients report short-term outcomes limited to 1–2 yr.

Objective: To assess long-term survival outcomes of BCG-unresponsive NMIBC patients treated with BST.

Design, setting, and participants: BCG-unresponsive NMIBC patients diagnosed between January 2000 and September 2021 from an institutional NMIBC registry were evaluated.

Intervention: Long-term survival outcomes for patients receiving BST, early radical cystectomy (RC), and delayed RC were compared.

Outcome measurements and statistical analysis: The primary endpoints were overall survival (OS) and cancer-specific survival (CSS).

Results and limitations: In total, 114 patients with a median follow-up of 71.2 mo (interquartile range: 32.6–132.2) were analyzed. There were no significant differences in OS (hazard ratio [HR]: 1.40, 95% confidence interval [CI]: 0.68–2.89, $p = 0.4$) or CSS (HR: 0.88, 95% CI: 0.22–3.55, $p = 0.9$) between patients undergoing early RC ($n = 38$) and BST ($n = 76$). At 60 mo, BST patients had a high-grade recurrence-free rate, muscle-invasive disease/metastasis progression-free rate, and avoidance of RC rate of 37%, 83%, and 58%, respectively. Current smoker status (HR: 4.44, 95% CI: 1.41–13.97, $p = 0.011$) was the only variable predictive of high-grade recurrence following a multivariable analysis. The median time to RC from BCG-unresponsive date was 2.1 and 11.7 mo for those undergoing early RC and delayed RC (after BST), respectively. Patients treated with early RC had a higher

* Corresponding author. Department of Urology, MD Anderson Cancer Center, The University of Texas, Houston, TX, USA. Tel. +1-713-792-3250; Fax: +1-713-794-4824.
E-mail address: akamat@mdanderson.org (A.M. Kamat).



incidence of cT1 disease (53% vs 36%, $p = 0.049$) and lymphovascular invasion (LVI; 11% vs 0%, $p = 0.011$) compared to patients treated with BST. Survival outcomes were similar between groups: 10-yr OS—58% versus 50% (HR: 1.40, 95% CI: 0.68–2.89, $p = 0.4$), and 10-yr CSS—81% versus 85% (HR: 0.88, 95% CI: 0.22–3.55, $p = 0.9$). **Conclusions:** An analysis of long-term survival of BCG-unresponsive NMIBC patients receiving BST suggests that it may be safe in patients without LVI and/or variant histology and nonsmokers. Survival outcomes for patients treated with BST may not be inferior to those receiving early RC.

Patient summary: Bladder-sparing treatment can be offered to appropriately selected patients who have bacillus Calmette-Guerin (BCG)-unresponsive non-muscle-invasive bladder cancer. Long-term outcomes may not be inferior to those for patients who opt for early radical cystectomy.

© 2023 The Author(s). Published by Elsevier B.V. on behalf of European Association of Urology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

BCG-unresponsive non-muscle-invasive bladder cancer (NMIBC) patients represents a group of patients who have high-grade (HG) refractory or early relapsing disease despite adequate bacillus Calmette-Guerin (BCG) for whom radical cystectomy (RC) is the reference standard as recommended by guidelines [1–3]. However, most patients are reluctant to undergo RC and seek alternative bladder-sparing treatment (BST). This disease state was hence recognized by the US Food and Drug Administration (FDA) in 2018, to allow single-arm trials, some of which have reported results recently and have led to regulatory approval for drugs in this space [4–6].

With emerging data for BST, an unanswered question remains—are we sacrificing cancer-specific survival (CSS) of our patients in attempts at bladder preservation? In the trial that led to the approval of pembrolizumab in 2020, the 12-mo disease-free survival rate was 19% with an avoidance of cystectomy rate of 51% at a median of 36 mo [5]. Similarly, the trial that led to the recent approval (December 2022) of nadofaragene fidenovec reported a 12-mo HG disease-free rate of 24% and, ultimately, a cystectomy-free rate of 65% at 24 mo [6]. Since no long-term data are available for BST in BCG-unresponsive patients, this coupled with the small but significant risk of developing metastatic disease compels physicians to continue to recommend early RC [7].

To attempt to address this knowledge gap, herein we report the long-term outcomes of patients with BCG-unresponsive NMIBC at our institution over a 20-yr period. We further elucidate the outcomes of patients who receive early RC (at diagnosis of BCG-unresponsive state) versus those who underwent BST.

2. Patients and methods

This study was conducted with approval from our institutional review board. An institutional database of consecutive patients diagnosed with NMIBC between January 2000 and September 2021 was queried, and patients meeting the criteria for BCG-unresponsive disease, as established by the FDA, International Bladder Cancer Group, and European Association of Urology, were included [1,4,8]. To summarize, BCG-unresponsive disease was defined as (1) persistent/residual carci-

noma in situ (CIS) with/without papillary disease (Ta and T1) within 12 mo of completion of adequate BCG and (2) recurrent HG papillary disease (Ta and T1) within 6 mo of completion of adequate BCG or HG T1 disease at first evaluation following induction-only BCG. Adequate BCG was defined as the receipt of at least five of six induction BCG instillations and of two of three planned maintenance instillations, or two induction treatment of at least five of six BCG instillations. All patients had a minimum of 12 mo follow-up.

All patients had pathology review by subspecialty trained urologists at our institution. Typically, the default at our institution is to offer RC to patients who are fit enough. BST is discussed as an option for those who refuse (more commonly) or are unfit for RC. Where BST was administered, cystoscopy surveillance and imaging schedule were standardized as per the high-risk NMIBC guidelines [2]. Patients treated with RC received follow-up including computed tomography imaging in accordance to our institutional guidelines [9]. Patient demographics, gender, and histopathological characteristics such as tumor stage, grade, presence of concurrent CIS, and BST type were determined.

The primary endpoints were CSS and overall survival (OS). CSS was defined as the number of months between diagnosis of BCG-unresponsive disease and death attributed to bladder cancer. OS was defined similarly for death from any cause. The secondary endpoints included progression-free rate. For patients undergoing RC, this was calculated from the date of BCG-unresponsive diagnosis until the development of local disease recurrence or metastasis on cross-sectional imaging to account for the lead time bias. For patients treated with BST, other secondary endpoints included HG recurrence-free rate, progression to muscle-invasive bladder cancer (MIBC)/metastasis-free rate, and avoidance of RC rate. Patients without an event were censored at the date of their last follow-up when they were free of an event. Early RC was defined receiving RC following a diagnosis of BCG-unresponsive disease, while delayed RC was defined as receiving BST after a diagnosis of BCG-unresponsive disease followed by salvage RC following treatment failure.

Statistical analysis was performed using Stata/SE version 17 (Stata-Corp, College Station, TX, USA). Statistical significance threshold was set at 0.05. Descriptive statistics were used to summarize the study cohort. Categorical variables were analyzed using Pearson's chi-square test or Fisher's exact test, while Wilcoxon rank-sum test was used to test continuous variables. The median follow-up of the study was determined by the reverse Kaplan-Meier method. Survival estimates were calculated using the Kaplan-Meier method. For time points with five or fewer patients at the time at risk, estimates were not reported. A proportional odds ordinal regression analysis was used to determine interactions. A multivariable Cox proportional hazard model was used

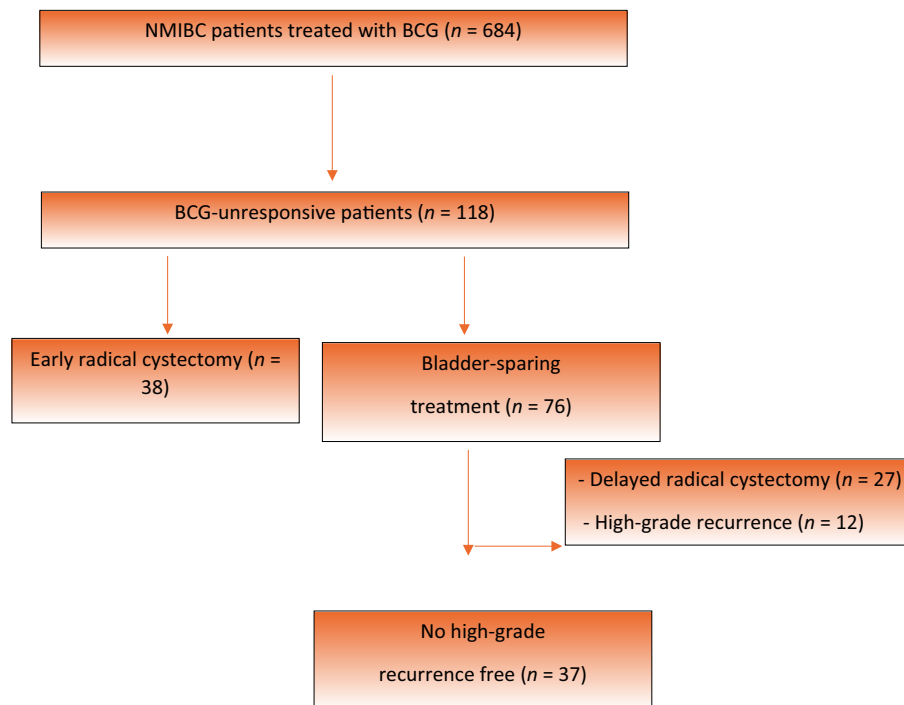


Fig. 1 – CONSORT diagram of study cohort. BCG = bacillus Calmette-Guerin; NMIBC = non-muscle-invasive bladder cancer.

Table 1 – Baseline characteristics following BCG-unresponsive diagnosis of patients treated with early radical cystectomy versus bladder-sparing treatment

Variables	Early radical cystectomy (n = 38)	Bladder-sparing treatment (n = 76)	p value
Age, median (IQR)	69 (63–78)	70 (63–78)	0.5
Male, n (%)	28 (73.7)	60 (79.0)	0.5
Smoking history, n (%)			0.012
Nonsmoker	19 (50.0)	20 (26.3)	
Ex-smoker/current smoker	19 (50.0)	56 (73.7)	
Number of previous BCG instillations (%)			<0.001
<10	25 (65.8)	5 (6.6)	
≥10	13 (34.2)	71 (93.4)	
T stage, n (%)			0.049
CIS only	13 (34.2)	23 (30.3)	
Ta	5 (13.2)	26 (34.2)	
T1	20 (52.6)	27 (35.5)	
CIS with/without papillary disease, n (%)	20 (52.6)	38 (50.0)	0.8
Lymphovascular invasion, n (%)	4 (10.8)	0 (0)	0.011
Variant histology, n (%)	2 (5.3)	2 (2.6)	0.6
Bladder-sparing treatment, n (%)			
Additional BCG		28 (36.8)	
BCG interferon		22 (28.9)	
Gemcitabine-docetaxel		10 (13.2)	
Other		16 (21.1)	

BCG = bacillus Calmette-Guerin; CIS = carcinoma in situ; IQR = interquartile range.

to adjust for confounding factors. An ordered logit model was used to determine the association between stage and RC treatment (delayed vs early).

3. Results

A total of 114 patients fulfilling the criteria for BCG-unresponsive disease with at least 1 yr of follow-up were identified from our institutional registry of patients treated with BCG. Of the 114 patients, 76 (67%) received BST and 38 (33%) underwent early RC (Fig. 1). The median follow-up

was 71.2 mo (interquartile range [IQR]: 32.6–132.2). As shown in Table 1, patient age and sex were matched evenly. Patients treated with early RC were more likely to be non-smokers (50% vs 26%, $p = 0.012$), have cT1 stage (53% vs 36%, $p = 0.049$), have lymphovascular invasion (LVI; 11% vs 0%, $p = 0.011$), and have received fewer BCG instillations (nine or fewer instillations: 66% vs 7%, $p < 0.001$) compared with patients managed by BST.

Figure 2 describes the distribution of all patients in the study with their outcome. There were no significant difference (inconclusive difference) between patients undergoing

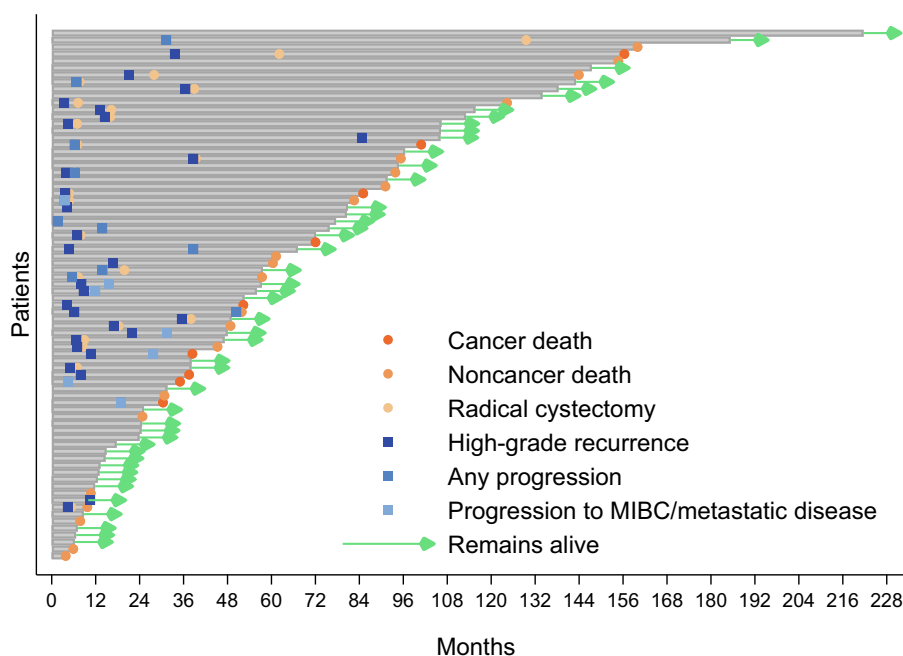


Fig. 2 – Swimmer plot describing the outcomes of all patients in the study labeled by their initial treatment following diagnosis of BCG-unresponsive NMIBC. BCG = bacillus Calmette-Guerin; MIBC = muscle-invasive bladder cancer; NMIBC = non-muscle-invasive bladder cancer.

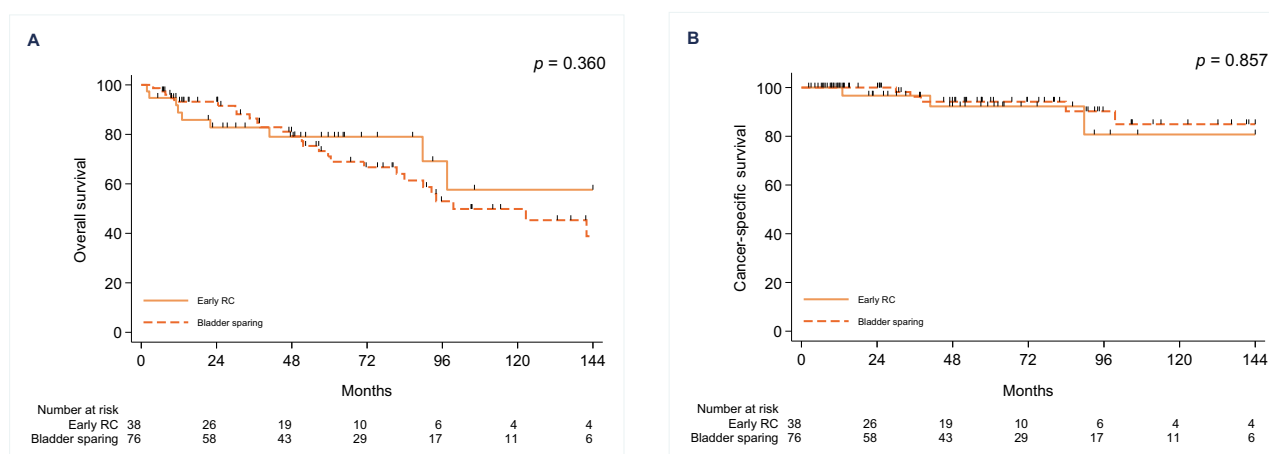


Fig. 3 – Kaplan-Meier survival estimates comparing early radical cystectomy versus bladder-sparing treatment: (A) overall survival (HR: 1.40, 95% CI: 0.68–2.89, $p = 0.4$) and (B) cancer-specific survival (HR: 0.88, 95% CI: 0.22–3.55, $p = 0.9$). CI = confidence interval; HR = hazard ratio; RC = radical cystectomy.

BST or early RC with regard to OS (HR: 1.40, 95% CI: 0.68–2.89, $p = 0.4$) or CSS (HR: 0.88, 95% CI: 0.22–3.55, $p = 0.9$; Fig. 3 and Table 2). Results were constant following adjustment for age, T stage LVI, and variant histology even when stratified for CIS with/without papillary disease or papillary-only disease (Supplementary Table 2). The median time to receipt of BST was 0.9 mo (IQR: 1.3–2.1), and there was no difference in the median time to receipt of BST and any event endpoint. For patients undergoing BST, freedom from HG recurrence was 49% at 24 mo and 37% at 60 mo (Supplementary Fig. 1 and Table 2). The rates of freedom from MIBC/metastasis progression were 90% at 24 mo and 83% at 60 mo. In all, 55% of patients treated with BST had avoided RC at 120 mo (Table 2). When adjusted for age, T

stage, and type of BST, the only variable that was associated with the risk of HG recurrence was “current smoker” status (HR: 5.06, 95% CI: 1.63–15.66, $p = 0.005$).

Supplementary Table 1 report patients stratified by early versus delayed RC (following a trial of BST). The timing of surgery was at a median of 2.1 mo (IQR: 1.4–2.6) for patients treated with early RC and a median of 11.9 mo (IQR: 7.0–27.6) for delayed RC. There was no difference in survival outcomes between the two groups: 10-yr OS—58% versus 51% (HR: 1.23, 95% CI: 0.53–2.86, $p = 0.6$) and 10-yr CSS—81% versus 80% (HR: 1.14, 95% CI: 0.25–5.21, $p = 0.9$; Fig. 4 and Table 2). Freedom from progression rates was also similar for patients treated with early versus delayed RC (HR: 1.63, 95% CI: 0.39–6.84, $p = 0.5$; Supple-

Table 2 – Survival function (%) for patients treated with early radical cystectomy ($n = 38$) versus bladder-sparing treatment ($n = 76$) and early ($n = 38$) versus delayed ($n = 27$) radical cystectomy, and outcomes of bladder-sparing treatment ($n = 76$)

Endpoint	Treatment arm	12 mo (95% CI)	24 mo (95% CI)	60 mo (95% CI)	120 mo (95% CI)
OS	Early RC	89 (73–96)	83 (66–92)	79 (61–90)	58 (27–79)
	Bladder-sparing treatment	93 (84–97)	93 (84–97)	71 (57–81)	50 (34–64)
CSS	Early RC	100	97 (79–100)	92 (72–98)	81 (44–95)
	Bladder-sparing treatment	100	100	94 (83–98)	85 (65–94)
<i>Early RC versus delayed RC</i>					
Freedom from progression	Early RC	97 (80–100)	97 (80–100)	88 (67–96)	
	Delayed RC	100	96 (76–99)	87 (64–96)	80 (53–92)
OS	Early RC	89 (73–96)	83 (66–92)	79 (61–90)	58 (27–79)
	Delayed RC	96 (77–99)	96 (77–99)	80 (58–91)	51 (28–71)
CSS	Early RC	100	97 (79–100)	92 (72–98)	81 (44–95)
	Delayed RC	100	100	96 (75–99)	80 (47–93)
<i>Bladder-sparing treatment</i>					
Freedom from high-grade recurrence rate		66 (54–76)	50 (37–62)	37 (23–50)	32 (18–47)
Freedom from any progression rate		88 (78–94)	80 (66–88)	62 (44–76)	62 (44–76)
Freedom from muscle-invasive/metastasis progression rate		95 (86–98)	90 (77–96)	83 (66–92)	83 (66–92)
Avoidance of radical cystectomy rate		80 (69–88)	72 (59–81)	58 (44–70)	55 (40–68)

CI = confidence interval; CSS = cancer-specific survival; OS = overall survival; RC = radical cystectomy.
Shaded column denotes too few patients (fewer than five) to provide valid results.

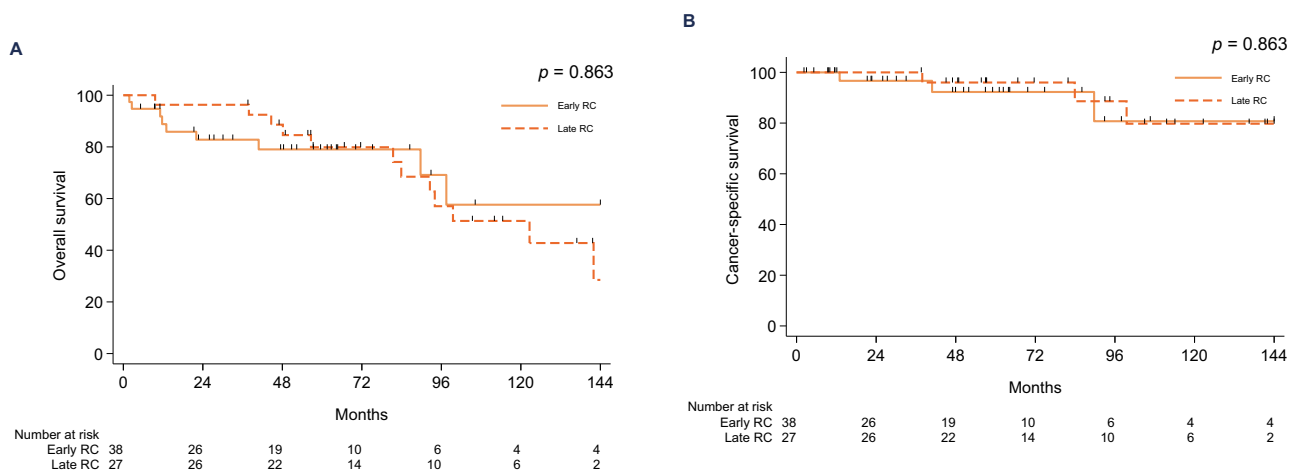


Fig. 4 – Kaplan-Meier survival estimates comparing early versus delayed radical cystectomy: (A) overall survival (HR: 1.23, 95% CI: 0.53–2.86, $p = 0.6$) and (B) cancer-specific survival (HR: 1.14, 95% CI: 0.25–5.21, $p = 0.9$). CI = confidence interval; HR = hazard ratio; RC = radical cystectomy.

mentary Fig. 2 and Table 2). There was no difference in outcomes following adjustment for age, T-stage LVI, and variant histology (Supplementary Table 2). A proportional odds ordinal regression analysis suggests that there was no significant difference in the final RC T stage between patients treated with early versus delayed RC (odds ratio: 0.98, 95% CI: 0.40–2.41, $p = 0.966$). T stage for patients who underwent delayed RC is reported in Supplementary Table 3.

4. Discussion

Our report suggests that for patients with BCG-unresponsive NMIBC, a trial of BST does not confer poorer survival outcomes versus early RC over the long term (a median follow-up period of 72 mo).

Most guidelines are unanimous on the recommendation that BCG-unresponsive NMIBC should be treated with RC [1–3]. At the same time, most patients are reluctant to undergo RC without a trial of BST. Since no long-term data are available for BST in BCG-unresponsive patients, many physicians continue to recommend early RC. Furthermore, in recently reported trials of approved agents, the duration of follow-up was truncated at 36 mo for pembrolizumab and 24 mo for nadofaragene firadenovec.

We recognize that our report is based on patients who received BST prior to the availability of agents that have been approved recently. Pembrolizumab was approved in January 2020 based on a phase II trial that reported a 3-mo complete response rate of 41%, but only 19% of patients of the entire cohort remaining recurrence free at a median of 36 mo [5]. An interim analysis of the CORE1 study suggests that combination therapy of pembrolizumab with

CG0070 achieves a 58% complete response rate at 12 mo [10]. Intravesical nadofaragene firadenovec gene therapy was recently approved (December 2022) based on a 3-mo complete response rate of 53% and an overall response rate of 24.3% at a median follow-up of 20 mo [6]. More recently, results of a single-arm study of BCG-unresponsive patients treated with combination intravesical IL-15R α Fc plus BCG reported a papillary 24-mo complete response rate of 48% [11]. However, the initial complete response rate at 3 mo was 55%, and another 16% of patients achieved a complete response following reinduction therapy. In a retrospective assessment of combination intravesical chemotherapy with gemcitabine-docetaxel (Gem-Doce), the HG recurrence-free survival at 2 yr in the subgroup of patients who met the BCG-unresponsive criteria was 50% for CIS-containing tumors and 58% for papillary-only tumors [12]. In our cohort, which included 10 patients who received Gem-Doce, the HG recurrence-free rates were 50% at 2 yr, 37% at 5 yr, and 32% at 10 yr, with CSS of 100% at 2 yr, 94% at 5 yr, and 85% at 10 yr. Thus, our data suggest that the long-term risk of cancer-related death in patients who have elected to undergo BST is low. Clearly, given that this is a retrospective analysis, patient selection played a key role, with the aim to quantify the long-term outcomes of patients who are appropriately selected for BST.

It is important to acknowledge that we are not advocating for the indiscriminate delay in radical treatment in BCG-unresponsive NMIBC patients because of the undue risk of disease progression to MIBC/metastatic disease where patients would have missed the opportunity for curative intent [7]. Rather, we are suggesting that selected patients who elect to avoid early RC and its accompanying morbidity have comparable outcomes with those who elect to undergo BST with delayed RC under the care of vigilant physicians. It is important to appreciate, for example, that no patient in our BST had evidence of LVI, and there were few patients with variant histology in their specimen from transurethral resection of bladder tumor, as these patients would have been recommended RC. Our results are not alone in supporting this notion: in an analysis of 117 recurrent NMIBC patients following BCG therapy (not all BCG unresponsive) who were treated by RC, Haas and colleagues [13] also found that 5-yr CSS was not different between 61 patients who had early RC and 56 patients who received intravesical BST.

Although not the aim of our study, our results highlight the importance of smoking cessation in patients with bladder cancer. Smoking was an independent predictor of HG recurrence following BST. Other studies have reported that smoking attributes up to a 50% increased risk of bladder cancer recurrence compared with nonsmokers [14,15]. In the BCG-unresponsive patient cohort, the need to recommend smoking cessation is even more crucial due to the risk of cancer progression and the requirement for RC following treatment failure.

Study limitations include the single-center retrospective nature of the study. This cohort represents a well-selected patient cohort and is subjected to a case selection bias. The fact that there were few patients with LVI and variant histology in our BCG-unresponsive NMIBC cohort would

suggest that these patients likely would have been treated with RC even before fulfilling the criteria for being BCG unresponsive, which is typically our institutional practice. It is also important to appreciate that these results represent outcomes of a tertiary institution where patients treated with BST received treatment promptly, and there were minimal delays once decision for RC were made.

5. Conclusions

An analysis of long-term survival outcomes for BST shows that it may be a safe option in patients without LVI and/or variant histology and nonsmokers. Survival outcomes for patients treated with BST may not be inferior to those receiving early RC. This would support the use of recently approved agents that are arguably more efficacious and help allay fears in selected patients who would appreciate a trial of BST following a diagnosis of BCG-unresponsive NMIBC.

Author contributions: Wei Shen Tan and 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: Tan, Kamat.

Acquisition of data: Tan.

Analysis and interpretation of data: All authors.

Drafting of the manuscript: Tan.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Tan, Nogueras-Gonzalez.

Obtaining funding: None.

Administrative, technical, or material support: None.

Supervision: Kamat.

Other: None.

Financial disclosures: Ashish M. Kamat certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Ashish M. Kamat is a consultant or advisory board member for Abbott Molecular, Arquer Diagnostics, ArTara Therapeutics, Asieris Pharmaceuticals, AstraZeneca, BioClin Therapeutics, Bristol Myers Squibb, Cepheid, Cold Genesys, Eisai, Engene, Ferring Pharmaceuticals, FerGene, Imagine Pharma, Janssen, MDxHealth, Medac, Merck, Pfizer, Photocure, ProTara Therapeutics, Roviant Sciences, Seattle Genetics, Sessen Bio, Theralase Technologies, TMC Innovation, and US Biotest; has received grants and/or research support from Adolor Corporation, Bristol Myers Squibb, FGD Industries, Heat Biologics, Merck, Photocure, SWOG/NIH, Specialized Programs of Research Excellence (SPORE), and AIBCCR; and holds the patent for Cytokine Predictors of Response to Intravesical Therapy (CyPRIT) jointly with UT MD Anderson Cancer Center. Wei Shen Tan was a consultant to Combat Medical. Kelly Bree was a consultant to Stratify genomics. Pavlos Msaouel has received honoraria for service on scientific advisory boards for Mirati Therapeutics, Bristol Myers Squibb, and Exelixis Inc.; consulting for Axiom Healthcare Strategies; nonbranded educational programs supported by Exelixis Inc. and Pfizer; and research funding for clinical trials from Takeda, Bristol Myers Squibb, Mirati Therapeutics, Gateway for Cancer Research, and

the University of Texas MD Anderson Cancer Center. Colin P. Dinney receives funding from the Cancer Center Support Grant funding from the National Institutes for Health/National Cancer Institute (award number P30CA016672) at MD Anderson Cancer Center, has received grant and personal fees from FKD Therapies, and is a creator of intellectual property owned by UT/MDACC related to the use of genetic alterations as a predictive biomarker for response to nadofaragene firadenovec. The other authors have nothing to disclose.

Funding/Support and role of the sponsor: This research was supported by the Wayne B. Duddleston Professorship in Cancer Research and the Raymond and Maria Floyd Bladder Cancer Research Foundation Grant to Ashish M. Kamat, and by National Institute of Health/National Cancer Institute UT MD Anderson SPOR in Genitourinary Cancer (Bladder; P50CA091846) to Colin P. Dinney.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.euro.2023.04.013>.

References

- [1] Babjuk M, Burger M, Capoun O, et al. European Association of Urology guidelines on non-muscle-invasive bladder cancer (Ta, T1, and carcinoma in situ). *Eur Urol* 2022;81:75–94.
- [2] Chang SS, Boorjian SA, Chou R, et al. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO guideline. *J Urol* 2016;196:1021–9.
- [3] Tan WS, Rodney S, Lamb B, Feneley M, Kelly J. Management of non-muscle invasive bladder cancer: a comprehensive analysis of guidelines from the United States, Europe and Asia. *Cancer Treat Rev* 2016;47:22–31.
- [4] US Department of Health and Human Services Food and Drug Administration. BCG-unresponsive nonmuscle invasive bladder cancer: developing drugs and biologics for treatment guidance for industry. 2018. <https://www.fda.gov/media/101468/download#:~:text=For%20the%20purposes%20of%20this,completion%20of%20adequate%20BCG%20therapy>.
- [5] Balar AV, Kamat AM, Kulkarni GS, et al. Pembrolizumab monotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open-label, single-arm, multicentre, phase 2 study. *Lancet Oncol* 2021;22:919–30.
- [6] Boorjian SA, Alemozaffar M, Konety BR, et al. Intravesical nadofaragene firadenovec gene therapy for BCG-unresponsive non-muscle-invasive bladder cancer: a single-arm, open-label, repeat-dose clinical trial. *Lancet Oncol* 2021;22:107–17.
- [7] Tan WS, Kelly JD. Is delay to radical cystectomy following BCG failure oncologically safe? *Nat Rev Urol* 2021;18:323–4.
- [8] Kamat AM, Sylvester RJ, Böhle A, et al. Definitions, end points, and clinical trial designs for non-muscle-invasive bladder cancer: recommendations from the International Bladder Cancer Group. *J Clin Oncol* 2016;34:1935.
- [9] The University of Texas MD Anderson Cancer Center. Urothelial carcinoma of bladder and upper tract treatment algorithm. 2022.
- [10] Li R, Steinberg GD, Uchio EM, et al. CORE1: Phase 2, single-arm study of CG0070 combined with pembrolizumab in patients with nonmuscle-invasive bladder cancer (NMIBC) unresponsive to bacillus Calmette-Guerin (BCG). *J Clin Oncol* 2022;40:4597.
- [11] Chamie K, Chang SS, Gonzalgo M, et al. Final clinical results of pivotal trial of IL-15R α Fc superagonist N-803 with BCG in BCG-unresponsive CIS and papillary nonmuscle-invasive bladder cancer (NMIBC). *J Clin Oncol* 2022;40:4508.
- [12] Steinberg RL, Thomas LJ, Brooks N, et al. Multi-institution evaluation of sequential gemcitabine and docetaxel as rescue therapy for nonmuscle invasive bladder cancer. *J Urol* 2020;203:902–9.
- [13] Haas CR, Barlow LJ, Badalato GM, DeCastro GJ, Benson MC, McKiernan JM. The timing of radical cystectomy for bacillus Calmette-Guerin failure: comparison of outcomes and risk factors for prognosis. *J Urol* 2016;195:1704–9.
- [14] Lammers RJ, Witjes WP, Hendricksen K, Caris CT, Janzing-Pastors MH, Witjes JA. Smoking status is a risk factor for recurrence after transurethral resection of non-muscle-invasive bladder cancer. *Eur Urol* 2011;60:713–20.
- [15] Wyszynski A, Tanyos SA, Rees JR, et al. Body mass and smoking are modifiable risk factors for recurrent bladder cancer. *Cancer* 2014;120:408–14.