THE JOURNAL of UROLOGY®
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Contemporary Outcomes of Patients with Nonmuscle-Invasive Bladder Cancer Treated with bacillus Calmette-Guérin: Implications for Clinical Trial Design

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Abbreviations and Acronyms

AUA = American Urological Association
BCG = bacillus Calmette-Guérin
CFS = cystectomy-free survival
CIS = carcinoma in situ
EAU = European Association of Urology
FDA = U.S. Food and Drug Administration
HG = high grade
IBCG = International Bladder Cancer Group
LG = low grade
MIBC = muscle-invasive bladder cancer
NMIBC = nonmuscle-invasive bladder cancer
OS = overall survival
PFS = progression-free survival
RFS = recurrence-free survival
RFS-HG = recurrence-free survival—high grade
TUR = transurethral resection

Purpose: Recurrent disease after bacillus Calmette-Guérin treatment presents a therapeutic challenge. To aid trial development, the U.S. Food and Drug Administration defined "adequate bacillus Calmette-Guérin" therapy and adopted the "bacillus Calmette-Guérin unresponsive" disease state. Available data for efficacy benchmark comparison are outdated, leading to concerns about appropriate control arms and sample size calculations. We describe a contemporary cohort of patients with nonmuscle-invasive bladder cancer treated with intravesical bacillus Calmette-Guérin, and provide benchmark outcomes data.

Materials and Methods: We retrospectively reviewed patients receiving adequate bacillus Calmette-Guérin therapy at a tertiary cancer center between January 2004 and August 2018. Unadjusted univariable analysis was conducted using the Pearson chi-square test. Kaplan-Meier estimates for recurrence-free survival—high grade, progression-free survival—muscle-invasive bladder cancer and overall survival were used to create survival curves and compared using the log-rank test.

Results: Of the 542 patients who received adequate bacillus Calmette-Guérin, 518 (90%) had European Association Urology high risk disease, with carcinoma in situ present in 175 (32%). With a median followup of 47.8 months, freedom from high grade recurrence at 1, 3 and 5 years was 81%, 76% and 74%, respectively, and progression-free survival was 97%, 93% and 92%. Progression to muscle invasion at 5 years was exclusively seen in patients with high risk disease (progression-free survival 91%; log-rank test, $p=0.024$).

Conclusions: A contemporary cohort of patients with nonmuscle-invasive bladder cancer treated with adequate bacillus Calmette-Guérin demonstrated markedly better outcomes than seen in prior studies. These data could be used in the design of clinical trials, to guide power calculations, as well as serve as benchmarks for comparison to evaluate nonrandomized studies.

Accepted for publication December 24, 2020.

Funding Source: This research was supported by the Wayne B. Duddlesten Professorship in Cancer Research, the Raymond and Maria Floyd Bladder Cancer Research Foundation Grant (AMK), and Grant P50CA091846 from the NIH/NCI UTMD Anderson SPORE in Genitourinary Cancer (Bladder) (CPND).

* Financial interest and/or other relationship with AUA Urology Care Foundation.

† Financial interest and/or other relationship with NIH and FKD.

‡ Financial interest and/or other relationship with FKD, Merck, BMS, Photocure, NIH, AIBCCR, Arquer, Theralase, Medac, Pfizer, Astra Zeneca, Imagin, Eisai/H3 Biomedicine, Cold Genesys, Sessen Bio, enGene, Janssen, ArTara, Seattle Genetics, FerGene

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0022-5347/21/2056-1612/0
THE JOURNAL OF UROLOGY®

https://doi.org/10.1097/JU.0000000000001633
Vol. 205, 1612-1621, June 2021
Printed in U.S.A.

Key Words: urinary bladder neoplasms, immunotherapy, BCG vaccine

THE annual incidence of bladder cancer was on pace to exceed 81,000 new diagnoses in 2020, with an estimated 60,000 cases being nonmuscle-invasive disease on presentation.[1] The use of intravesical immunotherapy with bacillus Calmette-Guérin vaccine for the treatment of intermediate and high risk nonmuscle-invasive bladder cancers is a clinical standard recommended by leading urological guideline committees.[2,3] Unfortunately, while BCG immunotherapy is highly efficacious, there are patients who will develop recurrences and require additional therapies.

Part of the challenge in finding efficacious BCG alternatives has been inconsistency in defining what constitutes "BCG failure", as well as variability in what is considered to be a clinically meaningful outcome. To address this issue, a consensus definition of "BCG unresponsive disease" was developed by experts.[4,5] This disease state has been adopted by the FDA to allow single-arm registration studies with no control group, and to benchmark results to historical controls of CIS response rates.[6]

Due to increased activity in this space, there has been a similar surge of trials that seek to evaluate agents such as checkpoint inhibitors in earlier disease states (eg BCG refractory or BCG relapsing patients).[7–9] Indeed, trials such as ALBAN (atezolizumab plus BCG in BCG-naïve high risk NMIBC)[10] and KEYNOTE-676 (pembrolizumab plus BCG in patients with persistent or recurrent disease after adequate BCG induction)[11] are recruiting. Common themes that arise during the design of these studies is the necessity of control arms, and that the trialists and statisticians must rely on historical data to help guide sample size calculations. Furthermore, the statistics that are currently available are from strictly regulated non-U.S. clinical trials and do not factor in current real-world practices (eg use of blue light cystoscopy, restaging TUR etc).[12,13]

The aim of our study is to provide outcomes information from patients treated under real-world conditions with at least induction BCG and at least 2 additional instillations constituting maintenance or repeat induction courses—what is considered to be the minimum required for "adequate BCG" per the FDA—at a high volume bladder cancer center outside the confines of a clinical trial. Ultimately, our hope is that this information can be used to inform clinical trial design by serving as a benchmark for sample size calculations, as well as providing a benchmark for comparison when evaluating results from nonrandomized studies.

MATERIALS AND METHODS

This study was conducted with approval from the University of Texas M.D. Anderson Cancer Center institutional review board (PA16-1042). We identified patients between January 2004 and August 2018 (to allow adequate followup time) with NMIBC (*c*Ta, *c*Tis, *c*T1) who received induction BCG ($\geq$5 of 6 instillations). The cohort was further refined to include those receiving "adequate" initial course of BCG as defined by the FDA and the IBCG: at least 5 of 6 induction instillations plus 2 additional instillations (either as part of 3 planned maintenance instillations or 6 planned repeat induction instillations), all taking place within a 6-month time frame.[4,6] Patients were included only if pathological information was available from their primary, pre-induction BCG TUR specimen and if they had completed at least 1 followup cystoscopy post-induction BCG at our institution within 6 months from initiation of therapy. We included patients who received additional BCG therapy (maintenance or re-induction) or ongoing surveillance outside M.D. Anderson only if there were interval followup visits with updated outside records available. If not, patients were censored at the time of their last clinic visit or cystoscopy. All pathology specimens used in clinical treatment decisions were centrally reviewed by a genitourinary pathologist within our institution.

Risk stratification to identify those patients who met intermediate or high risk criteria was applied retrospectively to each patient based on disease stage, grade, and histology of the primary and/or repeat TUR specimens prior to induction BCG in accordance with the published American Urological Association and European Association of Urology NMIBC Guideline risk categories.[2,3] Clinicopathological information was collected for all patients and included age, gender, race, family history, smoking history, clinical staging, pathological staging, number of BCG instillations, BCG failures, subsequent therapies and disease outcomes. BCG failure included refractory, relapsing and intolerant patients, according to published guidelines.[4] Disease outcomes of interest were RFS-HG, PFS, CFS and OS. All temporal end points were timed from the date of first instillation of BCG during induction. The PFS end point includes freedom from progression to muscle-invasive bladder cancer or metastasis. Management decisions regarding therapy duration, discontinuation and escalation (ie radical cystectomy) were made at the discretion of each individual urological oncologist.

Unadjusted univariable analysis was conducted using the Pearson chi-square test. Kaplan-Meier estimates for RFS-HG, PFS, CFS and OS were used to create survival tables with various time cutoffs. Survival curves specifically for PFS are presented and the survival distribution was compared using the log-rank test. For all comparisons, a p value of <0.05 was considered statistically significant.

RESULTS

Overall Demographics

The final cohort included 542 patients who received an adequate course of intravesical BCG (an

additional 38 patients received induction BCG only and were excluded from analysis). Among those receiving adequate BCG the median overall followup was 47.8 months (IQR 25.3–87.8). Clinicopathological characteristics are exhibited in table 1: median age was 68.4 years old (IQR 61.2–75.0) and most patients (80%, 432) were men. Clinical T stage was evenly distributed between cTa (47%, 253) and cT1 (47%, 252), with an additional 6.8% (37) comprised of pure cTis. Concomitant CIS (with Ta or T1 tumor) was present in an additional 25% patients (138), resulting in 32% (175) of all patients having some component of CIS at initial diagnosis. In total, BCG intolerance led to discontinuation of therapy in 8.5% (46).

Outcomes

All Patients. At 1 year, 81% of patients who received adequate BCG remained free of HG disease recurrence (RFS-HG; table 2). During prolonged followup, this rate remained high at 3 years (76%) and 5 years (74%). Progression to MIBC or metastasis was an uncommon event during followup among these patients, with PFS at 92% over a 5-year period (fig. 1). Over the same 5-year time period, 14% of the cohort ultimately underwent radical cystectomy.

Table 1. *Baseline demographics and disease characteristics in 542 nonmuscle-invasive bladder cancer cases treated with "adequate" BCG*

No pts.	542	
Median yrs age (IQR)	68.4	(61.2–75.0)
No. gender (%):		
Female	110	(20.3)
Male	432	(79.7)
No. grade (%):		
LG	68	(12.5)
HG	476	(87.5)
No. clinical T stage (%):		
cTa	253	(46.7)
cTis	37	(6.8)
cT1	252	(46.5)
No. histology (%):		
Pure urothelial Ca	521	(96.1)
Variant	21	(3.9)
No. lymphovascular invasion (%):		
Absent	536	(98.9)
Present	6	(1.1)
No. any CIS (%):		
Absent	367	(67.7)
Present	175	(32.3)
No. prostatic urethra (%):		
Uninvolved	516	(95.2)
Involved	26	(4.8)
No. location (%):		
Solitary	231	(42.8)
Multifocal	311	(57.2)
No. EAU risk group (%):		
Intermediate	56	(10.3)
High	486	(89.7)
No. AUA risk group (%):		
Intermediate	120	(22.1)
High	421	(77.9)
No. maintenance BCG (%):		
<1 yr	230	(42.4)
1–3 yrs	222	(41.0)
>3 yrs	90	(16.6)
No. BCG failure (%):		
Refractory	26	(4.8)
Relapsing	78	(14.4)
Intolerant	46	(8.5)

BCG was deemed "adequate" based on definition supported by IBCG and FDA.

Stratification by EAU Risk Classification. As expected, outcomes with BCG varied with EAU risk classification, which paralleled tumor grade prior to beginning therapy. For patients starting with intermediate risk NMIBC, the RFS-HG was 95%, 92% and 86% at 1, 3 and 5 years, respectively (table 2). Importantly, no patients with LG disease within the entire cohort progressed to MIBC at any point during followup, as is reflected by the 100% PFS seen with EAU intermediate risk disease (fig. 2). The PFS at 1, 3 and 5 years for high risk NMIBC was 96%, 92% and 91%, respectively.

Stratification by AUA Risk Group. The AUA risk classification differs from the EAU risk groups since it includes solitary HG Ta tumors <3 cm and LG T1 tumors within intermediate risk. For the AUA risk groups, the 1, 3 and 5-year RFS was 89%, 85% and 82% for intermediate risk and 79%, 73% and 71% for high risk, respectively. The 1, 3 and 5-year PFS was 98% at all time points for intermediate risk and 96%, 94% and 93% for high risk, respectively. Progression was statistically significantly higher in high risk patients, with a 5-year KM estimate of progression to MIBC or metastasis of 7% vs 2% for intermediate risk (fig. 3; log-rank test, $p < 0.020$). As expected, the progression events for the AUA intermediate risk group were driven by the high grade patients.

Stratification by Presence of CIS. The presence of CIS was an independent driver of response to BCG. The combination of Ta or T1 with concomitant CIS was associated with a statistically significant decrease in both RFS-HG (log-rank test, $p = 0.04$) and cystectomy-free survival (log-rank test, $p = 0.002$). We found that PFS was statistically similar for patients with HG Ta/T1 without concomitant CIS compared to either CIS alone or CIS in combination with Ta/T1 (fig. 4; log-rank test, $p = 0.971$ and $p = 0.863$). This finding confirms the FDA stance that CIS should be considered for registration studies regardless of whether CIS is present alone or in combination with Ta or T1 disease.

DISCUSSION

For over 50 years, intravesical BCG therapy has remained a cornerstone of management of patients with NMIBC, with recent interest in new drug

Table 2. *Survival analysis based on Kaplan-Meier estimates at 1, 3 and 5-year time points*

	RFS-HG			PFS			CFS			OS			
	1 Yr	3 Yrs	5 Yrs	1 Yr	3 Yrs	5 Yrs	1 Yr	3 Yrs	5 Yrs	1 Yr	3 Yrs	5 Yrs	Median Mos Followup
% Overall	81	76	74	97	93	92	95	89	86	99	93	86	47.8
% EAU risk group:													
Intermediate	95	92	86	100	100	100	98	96	90	98	94	79	43.1
High	80	74	72	96	92	91	95	88	86	99	93	87	49.4
% AUA NMIBC risk group:													
Intermediate	89	85	82	98	98	98	93	91	88	99	96	86	46.9
High	79	73	71	96	94	93	96	89	86	99	92	86	48.2
% Presence of CIS:													
LG Ta/T1 only	94	90	85	100	100	100	98	96	92	98	94	82	43.0
HG Ta/T1 only	81	77	75	97	93	92	96	91	89	99	94	88	44.8
CIS only	77	70	66	91	91	91	81	74	74	97	90	80	42.3
Ta/T1+CIS	77	68	67	96	92	89	94	85	81	99	91	86	65.3

development for BCG-naïve and unresponsive disease. It is in this context that we present a high volume, single institutional experience of BCG treated NMIBC patients. The overall rate of HG recurrence among patients who received "adequate" BCG (as defined by FDA and IBCG) ranged from 19% at 1 year up to 26% after 5 years of followup, but was as high as 34% among patients with any CIS present. Disease progression over 5 years was relatively low at 8% overall, with the highest rate observed among HG Ta/T1 tumors with concomitant CIS (11%). As expected, no progression (or metastasis) events occurred in any patient with baseline low grade disease only, regardless of other factors, including size, focality and grade of subsequent

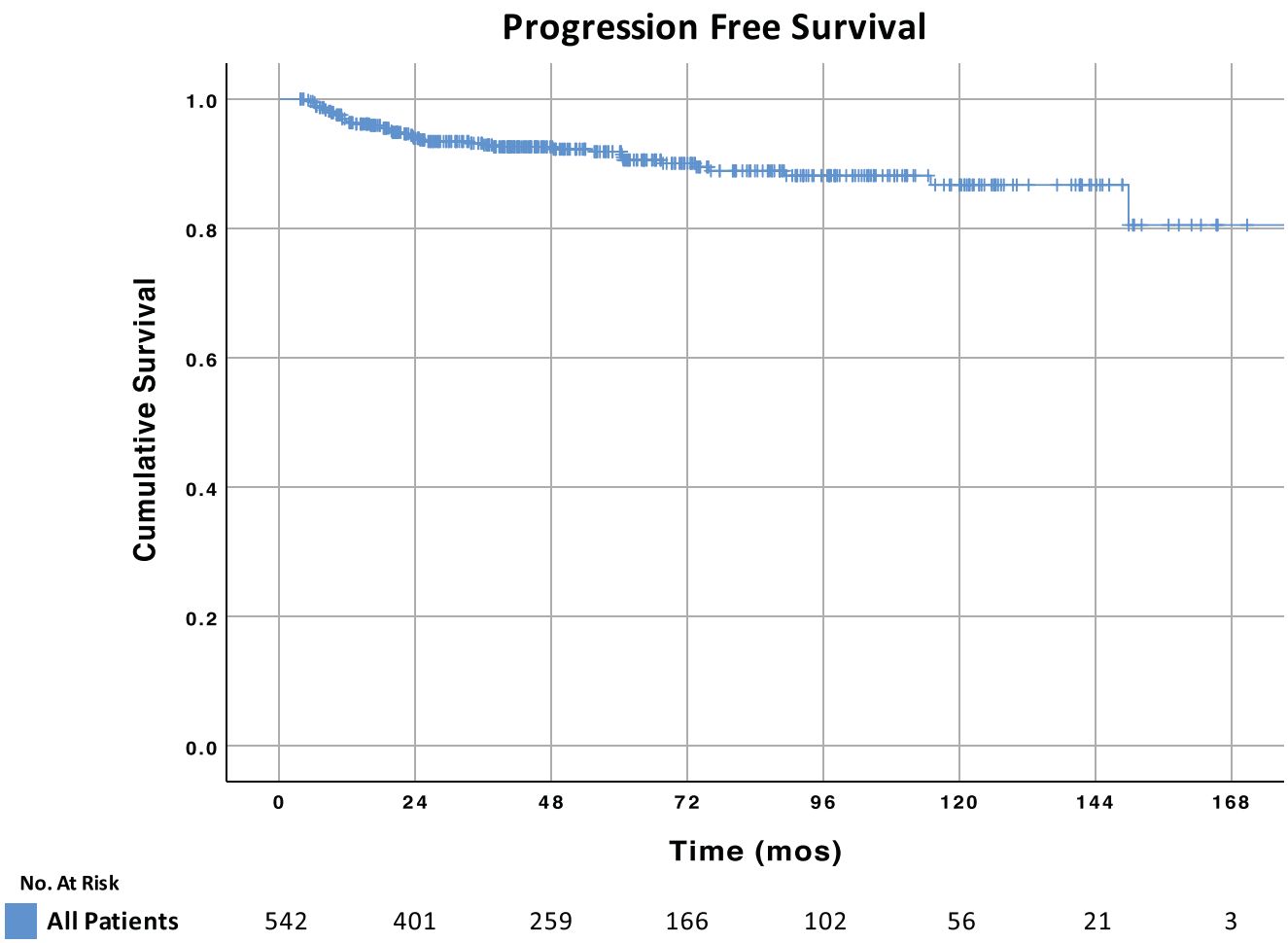


Figure 1. Kaplan-Meier survival analysis of progression to muscle-invasive bladder cancer or metastatic disease among all patients treated with "adequate" intravesical bacillus Calmette-Guérin.

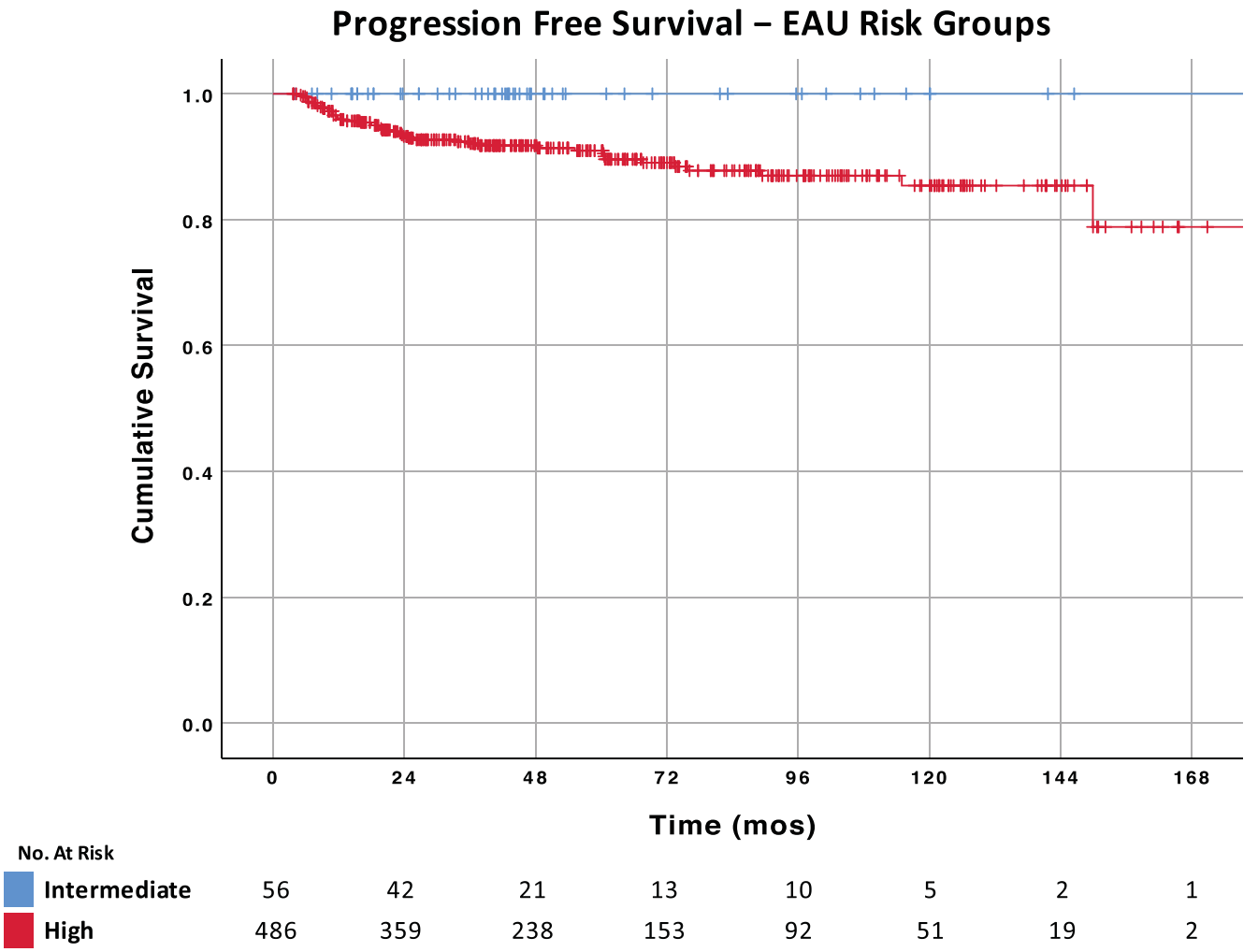


Figure 2. Kaplan-Meier survival analysis of progression to muscle-invasive bladder cancer or metastatic disease based on nonmuscle-invasive bladder cancer risk groups as defined by European Association of Urology, where all high grade tumors are included in high risk group.

recurrences, lending support to the notion of de-escalation in the long-term management of such tumors[14] as well as refinement of the AUA risk classification, which currently include Ta high grade tumors in the intermediate risk category.

Historically, studies have been hampered by lack of appropriate control arms and consensus on trial end points among regulatory bodies.[15,16] These factors have been addressed through publication of consensus statements for an inclusive disease state known as "BCG unresponsive disease."[4,5] The FDA has since approved prospective, single-arm registration trials in BCG unresponsive CIS, with response rates from historical cohorts serving as a control.[6] The primary objective of our report is to establish contemporary, robust benchmarks for expected outcomes of patients receiving intravesical BCG therapy outside the confines of a clinical trial. Combined with the published literature, these data have the potential to inform clinical trial design, especially with regards to sample size calculation.

Kamat et al utilized historic bladder cancer recurrence and progression rates from prior EAU trials and meta-analyses to make sample size recommendations for trials in BCG-naïve and BCG-failure patients.[4] Notably, patients in our cohort exhibited similar, albeit slightly better 12-month RFS and PFS in both intermediate risk and high risk patients compared to the EAU trials (eg 12-month RFS for high risk patients receiving induction with maintenance BCG was 79% in our cohort vs 75% in EAU trials; RFS was 89% vs 75% for intermediate risk disease at 12 months). These differences can be accounted for by nuanced variations in risk stratifications systems implemented (AUA vs IBCG definitions) but illustrate the power of these retrospective cohorts to inform decisions regarding clinical trial design.

For patients who are BCG-naïve, inclusion criteria for clinical trials consist of high grade disease and/or CIS never treated with intravesical BCG. Also included are patients who previously received BCG

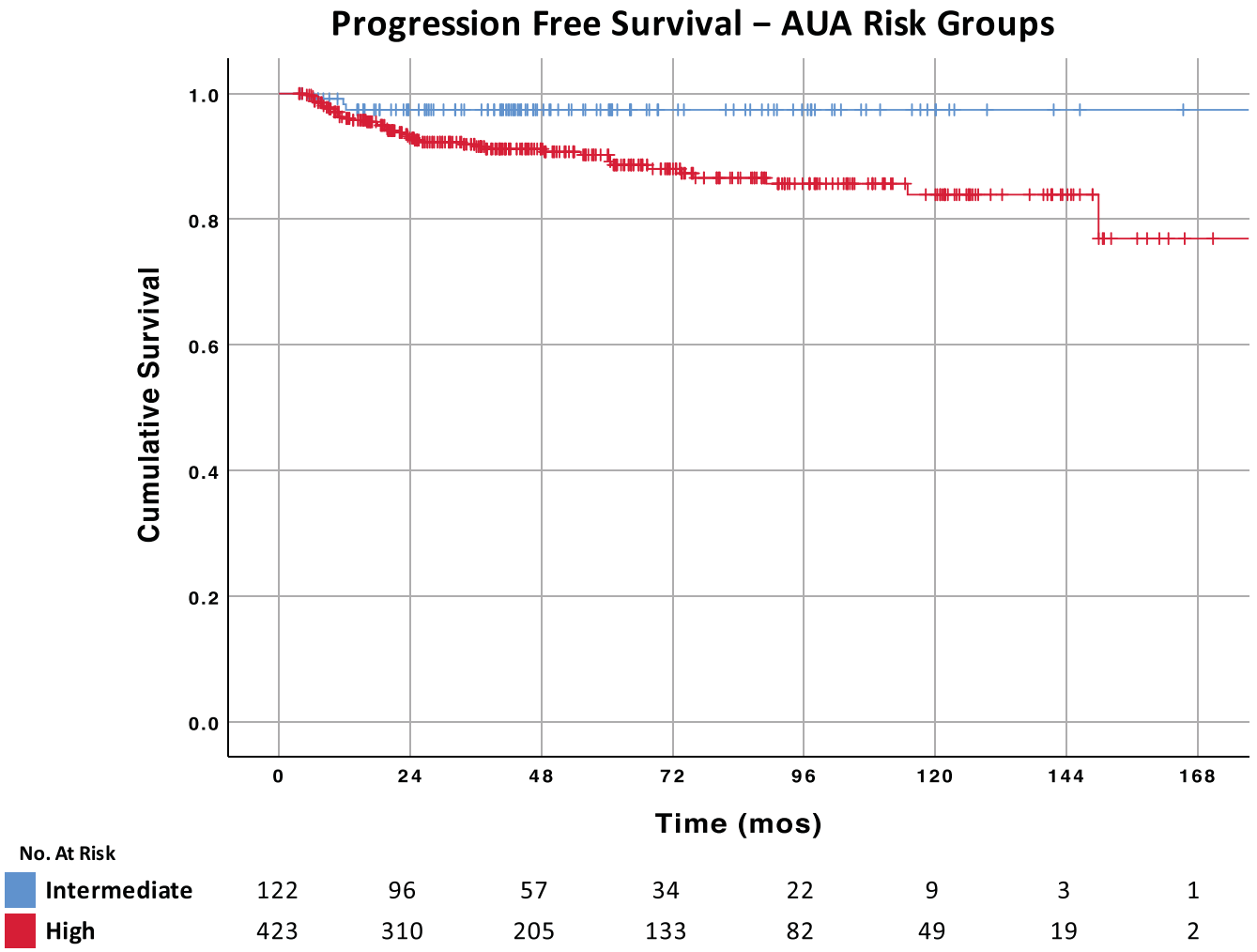
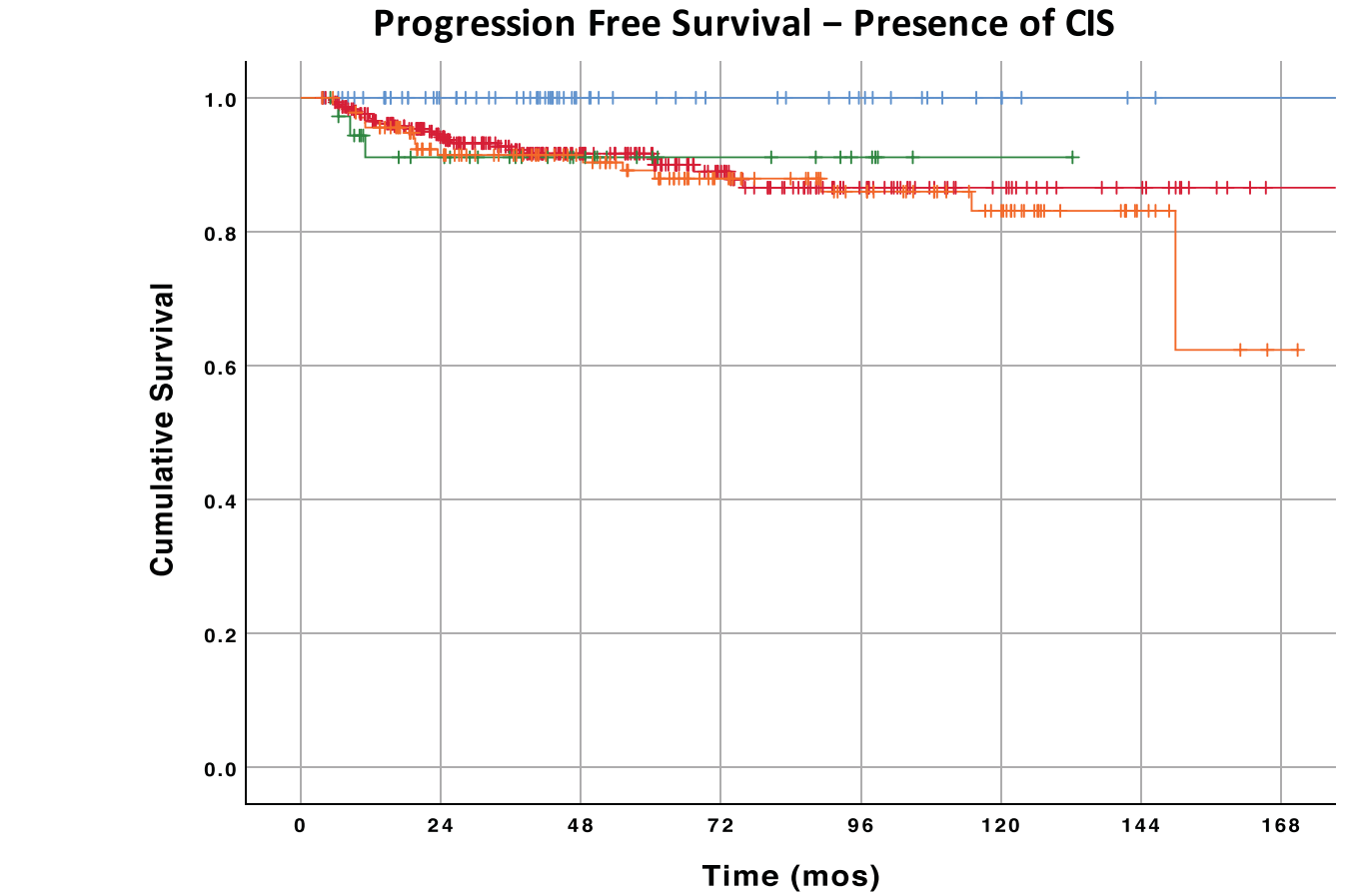


Figure 3. Kaplan-Meier survival analysis of progression to muscle-invasive bladder cancer or metastatic disease based on nonmuscle-invasive bladder cancer risk groups as defined by American Urological Association, where high grade papillary tumors may be included in intermediate risk group if they are primary and less than 3 cm.

more than 3 years before study enrollment, since these patients respond similarly to BCG-naïve patients.[4] Most experts advocate for superiority trials for intravesical agents, as they are designed to show that the new agent is more effective than the current standard (BCG). On the other hand, noninferiority studies are designed to show that a new treatment/regimen is not unacceptably worse than the standard. These are commonly implemented when the new treatment exhibits characteristics beyond clinical efficacy making them attractive alternatives; for NMIBC, these may include improved cost, access, side effect profiles, dosing schedules, duration of therapy etc. Others have proposed noninferiority trials due to the high benchmark that is set by BCG. For these noninferiority studies, the margin is subjective and difficult to set, and small margins require a larger number of patients relative to superiority studies. In high risk NMIBC, placebo controlled trials are unethical owing to high rates of progression and mortality when left untreated. Control arms are more appropriately comprised of BCG, when available, as the universally accepted standard of care per guidelines.[2,3]

Based on our data, we recommend that the primary end points in table 2 be used to power future prospective studies. Patients with fully resected papillary disease could be included in studies, with time to recurrence or recurrence-free survival as clinical end points. For example benchmarks for RFS-HG at 1 year, 3 years and 5 years would be 79%, 73% and 71%, respectively, for AUA high risk NMIBC treated with adequate BCG. For patients with concomitant papillary disease with CIS, appropriate end points would be complete response rate and duration of response for CIS (because these patients have active disease at study entry). Here we found CR rates of 77%, 68% and 67% at 1, 3 and 5 years, respectively. Given the high efficacy of BCG with regard to disease recurrence, the IBCG has previously recommended an absolute reduction in high grade recurrence of 10% at 2 years as the



No. At Risk							
LG Ta/T1 only	67	49	26	18	13	6	2	1
HG Ta/T1 only	300	220	134	82	43	22	12	1
CIS only	37	26	16	9	5	1	0	0
Ta/T1 + CIS	139	106	83	57	41	27	7	1

Figure 4. Kaplan-Meier survival analysis of progression to muscle-invasive bladder cancer or metastatic disease based on stage and grade of index tumor prior to treatment with intravesical bacillus Calmette-Guérin.

magnitude of effect for a clinical trial to be considered positive.[4] Applying this benchmark to our cohort, to detect a 10% difference in 1 year, 3 year and 5 year RFS-HG in AUA high risk patients who received adequate BCG (79%, 73% and 71%, respectively), a sample size of 420, 536 or 570 patients, respectively, would be needed to achieve statistical power of 80%. Additionally, historical data suggest that up to 35% of patients with high risk NMIBC have disease progression.[17] Our data suggest that these numbers are much lower (6%–7% at 3–5 years); hence, progression should be a secondary end point of any trial since powering for progression will otherwise require immensely large numbers of patients in the trial.

There are multiple limitations to this study. The use of a retrospective cohort exposes our analysis to influence from unmeasured confounders that cannot be fully controlled for, including significant selection bias that may have excluded patients at especially high risk for poor outcomes (ie immediate RC for T1 plus CIS or early cystectomy for T1 patients with recurrent or persistent disease after induction BCG only). Second, the fact that our institution is a highly specialized cancer center with urological oncologists whose clinical focus is predominantly (if not exclusively) bladder cancer can be considered a limitation on the generalizability of our results. Patients treated at our institution have access to clinical trials, salvage bladder preserving intravesical therapies, and surgical expertise for early radical cystectomy not otherwise readily accessible in community settings. However, we present a real-world description of the outcomes achievable with the current standard of care for comparison against novel agents. Additionally, there was no standardized treatment algorithm in place during the study period, including use of second line agents for BCG failures.

CONCLUSIONS

We present contemporary clinical outcomes in patients managed with adequate (as defined by the FDA and the IBCG) intravesical BCG for intermediate and high risk bladder cancer in an ideal, real-world, off-protocol setting. This contemporary cohort of NMIBC patients treated with adequate intravesical BCG therapy demonstrated markedly better outcomes than seen in prior studies. In an effort to facilitate and inform clinical trial design, we provide benchmark rates of recurrence and progression-free survival stratified across a number of stages, grades and risk stratifications with accompanying examples of statistical power and sample size calculations for future single-arm registration studies. These data could be used in the clinical trial design of studies to guide power calculations as well as serve as benchmarks for comparison to evaluate non-randomized studies.

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EDITORIAL COMMENTS

The aphorism "if you can't measure it, you can't improve it" is an appropriate summary of why there are so many persistent and unanswered questions in the treatment of nonmuscle-invasive bladder cancer in 2021. For decades, lack of standardization in the diagnosis and management of NMIBC has precluded our ability to make meaningful comparisons among patient cohorts and treatment outcomes. Fortunately, recent efforts to standardize disease state definitions and treatment terminology will help alleviate these problems and will be used to guide future trial design (reference 4 in article). All of this is especially important in the era of BCG shortages since radical cystectomy provides excellent cancer control in high risk patients, and the use of single arm-studies of novel agents requires quality benchmarking data to make meaningful comparisons. However, the heterogeneity of historical data makes comparison difficult, and this has significant implications for approval of these novel therapies.

In this study the authors report outcomes for patients with NMIBC treated with BCG according to the newly standardized definitions of "adequate BCG" treatment and "BCG unresponsive" disease. They contribute important data that can inform many aspects of bladder cancer care by demonstrating how excellent outcomes can be achieved with BCG in contemporary practice that includes re-TUR of bladder tumor, photodynamic enhanced cystoscopy and use of maintenance BCG. However, many gaps in knowledge remain since their findings are limited to BCG-naïve patients, and the superior results seen in this cohort may reflect patient selection (for either intravesical therapy or "early cystectomy") at a single high volume center. There is a persistent unaddressed need to establish similar standardized outcomes for patients with BCG unresponsive disease since many single-arm studies are currently underway.[1] Moving forward, multi-institutional collaborative efforts will be required to address these important gaps in knowledge given the heterogeneity of these patient populations.

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Studies in NMIBC are some of the most complex in urological oncology. In most malignancies, we review the effect of treatment in simple, dichotomous terms, eg recurrence-free survival, metastasis-free survival, progression and OS. However, NMIBC represents a heterogeneous disease, evolving sometimes over the course of years, with outcomes ranging from clear disease progression as evidenced by muscle invasion or distant disease to more benign events such as low grade recurrences. The multiple iterations of definitions of "BCG failure" are a manifestation of this complexity.[1] Moreover, although the basics of NMIBC management remain the same, there has been interval evolution in techniques and technologies.

All this is to say that an accurate understanding of outcomes in patients with NMIBC is still lacking.[2] Furthermore, the treatment landscape of NMIBC is shifting; the FDA approval of pembrolizumab and pending approval for nadofaragene firadenovec are examples in the BCG unresponsive space, while novel agents are being trialed currently in the BCG-naïve space. It is in this context that these authors from M.D. Anderson Cancer Center have provided a timely benchmark of contemporary outcomes in patients with NMIBC receiving BCG.

There are some caveats to their analysis that should be acknowledged. M.D. Anderson is a well-known bladder cancer center, and patients traveling to seek care are more likely to be highly motivated (and compliant with recommendations) and have access to clinical trials for salvage and surgical expertise for early radical cystectomy that might not always be be present in the "real world." It would be good for other institutions to follow suit and report their own outcomes in the contemporary era.

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REPLY BY AUTHORS

We appreciate the insightful comments that optimal outcomes such as ours may only be possible in the "real world" with focus on expertise, use of advanced cystoscopic techniques, and appropriate use of and

access to BCG. Nonetheless, we must as a community expect—demand, even—that the traditional variation in patient outcomes between the academic and real worlds be overcome, and aim to provide all of our patients with the benchmark outcomes demonstrated in this study. Hence, we reiterate our findings here: in a contemporary cohort of appropriately managed patients who received adequate BCG, even in the high risk setting, the 12-month RFS was 79% and 12-month PFS was 96%. It is, indeed, reassuring that this is in concordance with benchmarks set forth by meta-analyzed EORTC (European Organization for Research and Treatment of Cancer) trial data (75% 12-month RFS and 95% 12-month PFS for high risk patients; reference 4 in article). Contrast these to the often-quoted longitudinal outcomes from older reports, eg the "one-third rule" (one-third of patients with high risk NMIBC die of bladder cancer, one-third are alive and one-third die of other causes; reference 18 in article).

Our data reflect outcomes obtained using contemporary standards of care, and guideline and evidence-based approaches to patient selection and appropriate use of BCG immunotherapy. We urge the ongoing single-arm BCG unresponsive trials supported by the FDA, as well as those in the BCG-naïve setting, to use such contemporary benchmarks for sample size calculations (references 4 and 6 in article). Otherwise, we risk conducting underpowered studies or worse, approving agents with suboptimal outcomes.