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Review

Bacillus Calmette-Guérin (BCG) Treatment Failures in Non-Muscle Invasive Bladder Cancer: What Truly Constitutes Unresponsive Disease

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Abstract. Bacillus Calmette-Guérin (BCG) remains the most effective intravesical therapy for non-muscle invasive bladder cancer but will fail in up to 40% of patients. The ability to identify patients who are least likely to respond to further BCG therapy allows urologists to pursue secondary treatments more likely to convey a recurrence or survival benefit to the patient. We examined the literature to determine what constitutes BCG unresponsive disease. After review, we believe that BCG unresponsive disease should be defined as (1) patients with recurrent high grade T1 disease within 6 months of their primary tumor after at least one course of BCG or patients who have failed at least 2 courses of BCG with either (2) persistent or recurrent pure papillary (Ta) disease within 6 months or (3) persistent or recurrent carcinoma in situ (CIS) within 12 months.

Keywords: Urinary bladder neoplasms, *Mycobacterium bovis*, BCG vaccine, administration, intravesical, treatment failure

INTRODUCTION

Bladder cancer is currently the fifth most common cancer in the United States and an estimated 74,000 new cases are expected in 2015 [10], with the vast majority (70%) being non-muscle invasive (NMI) disease [11]. For high grade NMIBC, a thorough transurethral resection of the bladder tumor (TURBT) followed by an induction course of intravesical Bacillus Calmette-Guerin (BCG) is considered the standard of care per the American Urological Association (AUA) [11] and European Association of Urology (EAU) [12] guidelines. The recommendation for BCG use as adjuvant therapy is based upon the results of numerous studies that have demonstrated clear superiority in preventing tumor recurrence and disease progression (to muscle-invasive) as compared to TURBT alone [13, 14] and intravesical chemotherapy [9, 15–21].

Unfortunately, BCG therapy still fails in 40% of patients followed for 2 years [22]. Many of these patients will go on to cystectomy but some will be either unfit for cystectomy or desire bladder-preserving therapies. In patients who proceed with bladder conservation, urologists must weigh the expected efficacy of repeat immunotherapy (BCG monotherapy or BCG-based regimen) with the use of other intravesical treatments (i.e., chemotherapy, device-assisted therapy, photodynamic therapy). The exact combination of variables that indicate the disease is unlikely to respond to further BCG therapy (what was previously denoted as "BCG refractory" disease, now termed

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"BCG unresponsive" disease) remains a much-debated topic among urologic oncologists and is a critical distinction to make in a patient's treatment course.

As noted by Herr, appropriate and consistent nomenclature is crucial, not only to avoid unnecessary and ineffective treatments, but also to standardize the interpretation of results for salvage therapies [23]. In this review, we will revisit the origins of BCG therapy, as well as those studies examining repeat BCG-based intravesical therapy for failure patients in an attempt to identify what truly constitutes BCG unresponsive disease.

DEVELOPMENT OF THERAPEUTIC BCG FOR BLADDER CANCER

The anti-tumor potential of BCG was first noted in 1929 when an autopsy series by Pearl noted a lower rate of cancer in patients who had tuberculosis (TB) [24]. Around the same time, Holmgren [25] also published a description of the anti-neoplastic nature of BCG. Further studies of BCG revealed its ability to retard transplanted tumor growth, first in mice systemically infected with BCG [26] and later with direct injection of BCG into the tumor [27, 28]. This work also specifically found that close contact between BCG and the tumor was needed for efficacy. A later study by Bast determined that a lower tumor burden (i.e. maximal tumor resection) led to improved treatment efficacy [29]. With these studies in mind, Morales surmised that instilling BCG into the bladder via a catheter, the same route utilized for thiotepa, after TURBT, would allow for similar BCG-tumor direct contact. He began recruiting patients for his research in 1972.

In 1976, Morales published his series of 10 patients (only 7 eligible for analysis) treated with intradermal and intravesical (120 mg) BCG weekly for 6 weeks [30]. The decision to treat patients for 6 weeks was arbitrary, per his own report, and likely due to the fact that each package of BCG vaccines included 6 separate vials. The study found no tumors during the 47 patient-months of follow up. In light of these exciting results, a larger study by Lamm et al. randomized patients to TURBT alone vs. TURBT with intravesical and intradermal BCG. They found a significant reduction in tumor recurrence (50% vs 21%, $p = 0.027$) and a prolonged median time to recurrence (29 vs. 16 months, $p = 0.014$) in the cohort receiving BCG [13]. Intradermal administration was later discontinued after a separate randomized controlled trial revealed that the local effect of intravesical therapy alone was responsible for the reduced recurrence rate [31]. Further, while an initial investigation found no benefit to maintenance BCG instillations in enhancing the durability of therapy [32], later trials have demonstrated clear improvement in recurrence and progression rates [33]. This difference is possibly due to the difference in BCG maintenance schedules, as the initial trial utilized one instillation monthly for 2 years while later trials administered 3-week "mini-courses" (weekly instillations for 3 weeks) at 3, 6, 12, 18, 24, 30, and 36 months.

The efficacy of BCG was clear but needed to be compared to the optimal therapy of the time, thiotepa. In 1982, Brosman reported the results of his randomized trial in which 49 patients received either BCG or thiotepa weekly for 6 weeks with subsequent maintenance and were followed for 2 years [15]. BCG showed superiority with no recurrences, while 9 patients treated with thiotepa had a recurrence (40%). Another larger, randomized study, performed by the Southwest Oncology Group (SWOG), compared the efficacy of BCG to doxorubicin and found superiority with BCG treatment (37% vs. 17% for papillary, 70% vs. 34% for carcinoma in situ (CIS) at 5 years) [17]. These results and pooled analysis of toxicities ultimately led to approval of BCG by the Federal Drug Administration (FDA) in 1990 for the treatment of non-muscle invasive bladder cancer. This ushered in a new era of intravesical therapy for NMIBC but also invariably created a new disease classification, BCG failure.

INITIAL EXPERIENCE IN TREATING BCG FAILURES WITH NON-MUSCLE INVASIVE DISEASE

Like today's failure patient, patients who developed recurrent high-grade non-muscle invasive disease after BCG posed a big challenge to treating urologists, namely due to the large disparity in treatment options. Radical cystectomy could be pursued but risked the possibility of overtreatment given that the disease remained non-muscle invasive, as well as significant perioperative morbidity and mortality [3]. Conversely, repeat intravesical therapy risked poor efficacy and the development of metastatic disease, bypassing the ability for a potentially curative procedure (radical surgery). The first study of further intravesical instillations for failure patients was reported by Haaff et al. who found that repeat BCG induction was effective in eradicating disease in 56% of patients (5 of 9 patients with CIS, 3 of 7 patients with residual papillary

tumors and 6 of 9 patients treated adjuvantly) [34]. Two larger series of 60 and 57 patients found similar recurrence-free survival (RFS) rates of 53% and 59.6%, respectively, with repeat BCG therapy when followed for more than 3 years [4, 5].

Given the effectiveness of repeat BCG therapy for patients with one BCG failure, new studies examining patients with multiple failures were performed. Catalona et al. assessed the response of 100 patients who underwent multiple repeated BCG induction with any recurrence [6]. The authors found that patients treated with a second induction course of BCG had a RFS of 35% at 2 years, while further BCG induction courses rendered only a minority of patients disease free (<20%). A similar rate was later published in a pooled analysis of smaller studies [35]. By identifying the low rate of durable efficacy of BCG beyond 2 induction courses, these studies began to lay the foundation for defining BCG unresponsive disease.

EARLY DEFINITION OF REFRACTORY DISEASE

The first mention of bladder cancer "refractory" to intravesical therapy was in 1984 and described patients refractory to thiotepa who went on to receive doxorubicin for post-TURBT adjuvant therapy [36]. The term "BCG refractory" first appeared in 1989 in a study assessing the efficacy of BCG in patients with non-muscle invasive bladder cancer and concomitant prostatic CIS [37]. The term was quickly adopted, particularly by those studying photodynamic therapy for non-muscle invasive disease [38–41]. In these studies, patients described as refractory had received from one to six prior BCG courses.

As investigation of alternative intravesical agents (both immunotherapy and chemotherapy) progressed during the 1990 s and early 2000 s, the use of the term BCG refractory expanded, but the definition continued to be variable and anecdotal. The differences between definitions were usually used to describe the number of prior BCG courses and the time to recurrence. The number of prior BCG courses ranged from 1 [2, 42–44] to 3 [45] with many studies including a combination (i.e. 1-2 courses). With regard to the time to recurrence, this ranged from 3 months (consistent with 1 prior BCG course) to greater than 24 months. For all intents and purposes, the term BCG refractory became synonymous with BCG failure.

It was not until 2003 that Herr and Dalbagni attempted to formally define BCG refractory disease [23]. Their retrospective study assessed a cohort of 93 BCG-naïve patients with NMIBC who were treated with induction BCG and then randomized to no further therapy or monthly BCG maintenance. Surveillance included repeat cystoscopy, bladder biopsies and cytologies at 3 and 6 months from initial BCG administration. Multivariate analysis revealed that the presence of tumor at the 6-month evaluation was the only variable predictive of further tumor recurrence. To date, this remains the only study that has attempted to formally define BCG refractory disease.

Given the variable definition of BCG refractory disease and broad, generic nature of using the term BCG failure, an International Consensus Panel discussed and agreed upon more specific definitions to further stratify BCG failure patients [46]. The consensus definition for BCG refractory disease was "failure to achieve a disease-free state by 6 months after initial BCG therapy with either maintenance or retreatment at 3 months because of either persistent or rapidly recurrent disease," as well as "progressive disease in stage, grade or extent at 3 months after first cycle of BCG." Unfortunately, since publication in 2005, the utilization of this definition in the literature has been minimal. Expanding upon the review of BCG refractory definitions created by Herr and Dalbagni [23], Table 1 presents the major studies since 1990 which have assessed BCG refractory patients, including the definitions of BCG refractory, therapies used and outcomes of these studies.

More recently, a panel of experts was convened at the 2015 Genitourinary Symposium of the American Society of Clinical Oncologists (GU-ASCO) annual meeting and decided that, given the variability of nomenclature regarding BCG refractory disease, future patients felt to no longer benefit from further BCG therapy should be referred to as BCG unresponsive [1]. This definition included "patients who did not respond to BCG treatment and have a new (if previously treated for a low-grade NMIBC) or persistent high-grade (HG) recurrence at our around 6 months after BCG was initiated, and those who despite an initial complete response to BCG, relapse with HG NMIBC within 6 months of their last intravesical treatment with BCG." Further clarification detailing the criteria for these patients specified the number of prior BCG induction courses (at least 2, receiving 5/6 induction instillations of 2/3 maintenance instillations), timing of recurrence (within 6 months of last exposure), no maximum limit of BCG to be administered (though did recommend BCG maintenance), have Ta/T1 with or without CIS or CIS of the prostatic urethra, and persistent T1HG

Table 1
Major studies since 1990 which have assessed second line therapies for BCG refractory patients, including the study definition of BCG refractory and well as the therapies used and outcomes

		Definition of Refractory		Study Population		Study Intervention			Efficacy of Salvage Therapy (%)		
Year Published	Study Author	# Prior BCG Courses	Timing of Recurrence After Prior BCG (months)	# Patients	Disease Stage	Intravesical Agent Studied	Induction Schedule	Maintenance x Schedule	Response to Therapy	1 year	2 year
1990	Glashan	1	3	87	CIS	IFN	Weekly × 12	Monthly to 1 year	43*	21*	–
1996	Sardosy	2+	6	60	CIS	Bropirimine	3 days/week × 6	Weekly to 1 year	24	–	–
1992	Klein	1	3	41	Mixed	BCG, Methotrexate, Interferon, Thiotepa,or Doxorubicin	Weekly × 6	None	–	–	–
1995	Merz	1	3	115	Mixed	BCG	Weekly × 6	None	42	–	–
1998	Nseyo	1–6	NS	34	CIS	Photodynamic Therapy (Intravenous 5-ALA)	Single Treatment	None	58	31	–
2001	Waidelich	2	NS	24	Mixed	Photodynamic Therapy (Oral 5-ALA)	Single Treatment	None	79	–	36 (3 years)
2000	Steinberg	1–3	3–24	90	CIS	Valrubicin	Weekly × 6	None	21	17	8 (2.5 years)
2001	Luciani	1-2	5–288	24	Mixed	BCG/IFN or Valrubicin	Weekly × 6–8	3 week mini cycles every 3 months	17	–	–
2001	O'Donnell	1-2	6	40	Mixed	BCG/IFN	Weekly × 6–8	3 week mini cycles at 3, 9, 15 months	–	56	48
2006	Joudi	1-2	6	467	Mixed	BCG/IFN	Weekly × 6	3 week mini cycles at 3, 9, 15 months	–	–	45
2009	Malmstrom	1	3	19	Mixed	MMC	Weekly × 6	None	–	–	23
2002	Dalbagani	1-2	6	30	Mixed	Gemcitabine	Twice weekly × 3 weeks	None	50	21	–
2013	Skinner	2	6	58	Mixed	Gemcitabine	Weekly × 6	Monthly to 1 year	47	28	21
2006	McKiernan	Mean 3	NS	18	Mixed	Docetaxel	Weekly × 6	None	56	–	–
2013	Barlow	1–4+	NS	54	Mixed	Docetaxel	Weekly × 6	Monthly to 1 year	59	40	25 (3 years)
2014	Morales	1-2	6	129	Mixed	Mycobacterial Cell Wall-Nucleic Acid Complex	Weekly × 6	3 week courses at 3, 6, 12, 18, and 24 months	34	23	15
2014	McKiernan	1	NS	28	Mixed	Nanoparticle Albumin Bound Paclitaxel	Weekly × 6	Monthly to 6 months	36	36	–
2014	Lightfoot	1-2	6	47	Mixed	Gemcitabine/Mitomycin	Weekly × 6	Monthly to 1 year	68	48	38
2015	Steinberg	1-2	6	45	Mixed	Gemcitabine/Docetaxel	Weekly × 6	Monthly to 2 years	66	54	34

*High Dose Group Only (100 Million Units). NS = Not specified.

disease on repeat TUR. In this review, we aim to review the literature and provide the basis for which this decision was built upon.

DEFINING BCG UNRESPONSIVE DISEASE

So what truly constitutes BCG unresponsive disease? In defining this, we should first consider the reasoning for creating such a definition. The goal with any intravesical therapy is to prevent recurrence, progression, and metastatic disease, as these require dramatic changes in management and put the patient at high risk of poor long-term survival [3]. Identifying the point at which BCG is less likely to be effective at preventing these outcomes is crucial so as not to delay delivery of alternative agents or radical surgery that can confer an improved survival benefit. In formulating this definition, many different disease-specific elements must be considered which affect the likelihood of disease recurrence and progression. In an attempt to identify these variables, Herr et al. examined 221 men with non-muscle invasive disease (both CIS and papillary) treated with BCG and followed for 2 years. The investigators considered both disease-independent and disease-dependent variables prior to intravesical therapy, at the 3-month surveillance cystoscopy and at the 6-month surveillance cystoscopy. Variables found to be predictive of progression included stage T1 disease at all time points (prior, 3 months, 6 months) and disease duration of less than 1 year [47]. This early study highlighted two of the key elements of BCG unresponsive disease, disease stage and timing of recurrence. Other factors not considered in this study, but critical to consider, include patient age, the number of prior BCG courses and extent of disease (focality and size).

Prior BCG therapy

As previously discussed, two prior studies have demonstrated durable eradication of disease (at 2 years) in 35% of patients treated with a second course of BCG [6, 35]. In the National Phase 2 BCG/IFN study, the addition of interferon-α 2B (IFN) to BCG showed an absolute disease-free rate at 2 years of 45%, suggesting there may be up to a 10% improvement when considering all BCG failure patients [48]. This data suggests that nearly half of those patients who fail initial BCG therapy will have a durable response to BCG/IFN. Multivariate analysis from this study found that patients with 2 or more BCG failures performed significantly worse (HR = 1.56, $P = 0.0002$) than those with 1 prior BCG failure. This further supports Catalona's original finding that repeat BCG administration beyond 2 courses is often ineffective [6]. Thus, in most cases, non-muscle invasive disease can be considered to respond to up to 2 induction courses of BCG prior to being considered BCG unresponsive. Specific caveats to this statement, namely recurrent T1 high grade disease, are discussed later in this review.

Disease timing

In the previously mentioned study by Herr and colleagues [47], patients found to have persistent disease at 3 months but resolution at 6 months had a 0% 1-year and 16% 3-year risk of progression. Conversely, patients with no evidence of disease at 3 months and recurrence at 6 months had higher rates of progression with 11% at 1 year and >57% at 3 years. Patients with persistent disease throughout all 6 months had similar progression rates to those with recurrent disease at 6 months (25% at 1 year and 61% at 3 years), identifying 6 months as a key time point in the disease process. However, as this study cohort was a BCG naïve population that only received 1 induction course of BCG, the effect of maintenance instillations, which have been shown to reduce recurrence and worsening disease [33], or a second course of BCG is unknown.

Merz et al. also evaluated the effect of early BCG failure on the efficacy of repeat BCG administration in patients with pure or concomitant CIS. They evaluated 115 patients with a median follow-up time of 44 months. Early failure was defined as those with recurrence within 9 months of BCG initiation [2]. Seven of 23 patients with an early recurrence had progressive disease, as compared to 1 of 92 in those with a late recurrence. Of those who progressed, four had failed a second course of BCG. While Herr found that 6 months was a critical time point in all patients, this finding intimates that a longer recurrence interval is needed for patients with CIS.

The notion of recurrence timing was again evaluated as part of the National Phase 2 BCG/IFN trial [49]. In this study, 467 patients with prior BCG failure received 6 weekly BCG/IFN instillations, followed by 3-week mini-cycle maintenance at 3, 9 and 15 months after completing induction. When stratified by timing of disease recurrence after prior BCG, patients with persistent disease were 1.83 times as likely to fail therapy, as compared to BCG-naïve patients, and only 34% were disease-free at 2 years ($p < 0.001$). Patients with recurrence within 1 year had a 2-year disease-free rate of 41–43% (HR 1.58), while those with a recurrence beyond 1 year responded similarly to naïve patients

(53–66% 2-year disease-free rate, HR 0.98). Unfortunately, this study did not evaluate the stage of disease at the time of recurrence and thus only recurrence, and not progression, can be considered.

Given the above findings, it appears clear that patients who fail intravesical BCG within the first 6 months are at a higher likelihood of progression and less likely to respond to further BCG. However, the data also suggests that the 6-month time point is not equally applicable to all patients with non-muscle invasive disease. Recurrence within 1 year of initial BCG treatment, in conjunction with certain disease elements, appears to also predict a worse response to further BCG.

Disease stage

The risk of disease progression is closely linked to the stage and grade of disease present. Patients with low grade papillary disease have the lowest risk of progression at 1 year (<1%), while patients with high-grade disease have the highest risk (8%) [50]. Yet, even within the classification of high-grade disease, there is still significant variability in the rate of progression, median time to progression and expected efficacy of BCG in preventing progression of each disease state. In reviewing high-risk disease, as it pertains to BCG unresponsive disease, we will primarily focus on CIS and high grade T1 (T1HG) disease, as these carry the highest risk of recurrence and progression.

CIS

CIS was first described by Melicow [51] in 1952. Early reports of patients diagnosed with CIS were quite variable, as the clinical course depended on the extent of disease. Prior to BCG, up to 80% of patients with CIS would ultimately progress to muscle-invasive disease [52, 53]. The high rate of progression in CIS patients later became more clear as genetic analysis revealed a common genetic alteration (loss of p53) in both CIS and T2 tumors [54]. This differs from cyclin D activation, which has been identified in analysis of papillary tumors. Further studies have also demonstrated spatial and temporal relationships between CIS and the later development of T2 disease [55].

To date, BCG remains the clearly superior therapeutic agent for the treatment of bladder CIS [9]. The reported short-term efficacy of a single course of BCG is variable, depending upon the length of cohort follow up. Studies with long-term follow-up have identified durable efficacy in 40–46.7% of patients [9, 56] at 3.6–7.6 years. Further improvement in efficacy has been demonstrated with additional BCG instillations, either via maintenance (6 + 3) or repeat induction (6 + 6) [33]. However, Gofrit et al. have reported that even in patients with a complete response (CR) to 1-2 BCG induction courses, as proven by post treatment biopsies, 40.4% will have a recurrence at a median of 18 months [7]. Unfortunately, the authors did not specifically report the RFS of those who required 1 vs. 2 BCG induction courses separately, though the majority of patients (88.5%) had only 1 prior BCG course. While the recurrence rate is high, meta-analyses have reported a progression rate of 13.9–15.4% [8, 9] in CIS patients. In addition to bladder recurrence, patients with CIS are also at high risk of developing extravesical disease, particularly after BCG failure. Upper tract disease is the most common site of extravesical disease, estimated to occur in 21–32% of cases, while prostatic disease will occur in 8–19% of patients [57, 58]. We will not expound further on these disease processes in this article but consideration of these alternative sites of disease is crucial as it can drastically change patient management independent of the BCG failure classification (i.e., prostatic invasion without bladder involvement requiring cystoprostatectomy).

In patients who develop a CIS recurrence after a single prior BCG failure, repeat BCG-based therapy should be administered. Repeat BCG monotherapy has demonstrated a 2-year disease-free rate of 30–42% in two small studies [2, 59]. BCG/IFN combination therapy with maintenance resulted in a 2-year disease-free rate of 57% [60], but sub-analysis revealed that those with 2 or more failed BCG courses attained a disease-free status in only 23% of cases at 2 years. The same study also evaluated the effect of recurrence timing from prior BCG. The authors found that patients with persistent disease retreated with BCG/IFN were disease-free in only 23% of cases at 2 years, as compared to 42% in patients with recurrence within 1 year and 59% in those with recurrence beyond 1 year. Further sub-analysis of this population has revealed that patients with recurrence at 6–12 months (disease-free 42% at 1 year, 29% at 2 years) respond similarly to patients with persistent or recurrent disease within 6 months (45% and 38%) (O'Donnell, unpublished data). Given these results, it appears that patients with a CIS recurrence have an improved response with the use of BCG/IFN but efficacy is still reduced relative to naïve patients when the recurrence occurs within 1 year of initial therapy. In considering the timing of recurrence, these results, combined with those previously published by Merz [2], continue to suggest that the

often used 6 month time point, used most recently by the GU-ASCO consensus panel to define "BCG unresponsiveness", is too short of a time interval to capture patients with CIS who are unlikely to derive benefit from further treatment.

High grade T1 disease

In any patient with T1HG disease, re-resection must be performed. This identifies the 29–40% of patients that will be upstaged to muscle-invasive disease [61, 62], thus requiring more radical intervention, and ensures complete tumor resection to maximize the effect of adjuvant therapy. One study demonstrated that re-resection itself reduces the rate of recurrence but not progression [63], likely a result of a more complete resection. In those with confirmed T1HG disease after re-resection, pooled group analysis of multiple small studies identifies a progression rate of 27.2% in patients treated with BCG induction alone [64–72], while those treated with induction and maintenance had a 19.0% progression rate [73–79] (Table 2). Recently, a large multicenter retrospective individual patient data analysis of 2451 patients reported a progression rate of 19% at a median of 5.2 years follow-up[80].

In the case of recurrent T1HG disease after BCG, minimal data is available about the expected efficacy of repeat BCG therapy. One study by Raj et al. retrospectively compared a historical and contemporary cohort of patients with recurrent T1HG disease [81]. In the historical group, 85 patients with recurrent T1HG disease were treated with repeat TUR and BCG, of which 60 (71%) experienced progression to muscle-invasive disease at 5 years. Of note, 84 of these patients had concomitant CIS. Of the 129 patients with recurrent T1HG disease in the contemporary group, 65 underwent immediate cystectomy and over half (33) were upstaged to T2 disease. The remaining 64 patients underwent repeat TUR and BCG, and 33 (52%) had progression at 5 years. However, 13 patients (10%) in the contemporary group had T2 disease prior to initial BCG and thus should not be considered as having progressed. Cumulative incidence of disease-specific death at 5 years for these groups (historical and contemporary) was 48% and 31%, respectively, suggesting a survival benefit in the contemporary group with immediate cystectomy. However, there was a substantial disparity in median follow-up times (13.3 vs. 2.7 years), which may account for some of this difference. Direct comparison of the historical group with the contemporary group undergoing TUR+BCG was not reported. Finally, all patients treated in this study were enrolled prior to the recommendation for re-resection of T1 disease. Thus, the number of patients found to have progressive disease, which was actually just initially understaged, is unclear.

In another study primarily populated with BCG failure patients (81% with at least 1 prior BCG treatment

Table 2
Pooled analysis of multiple small studies assessing rate of disease progression for patients with high grade T1 disease treated with (A) BCG induction alone or (B) BCG induction and maintenance

Author	No. of Patients (n)	Rate of Progression (%)	Median Follow-Up (months)
(A) High Grade T1 disease Treated With BCG Induction But No Maintenance			
Gohji [62]	45	4.4	63
Pfister [63]	26	27	54
Hara [64]	97	45	25
Herr [65]	25	40	184
Kulkarni [66]	69	19	45
Lebret [67]	35	20	45
Patard [68]	50	22	60 (mean)
Shahin [69]	92	33	64
Brake [70]	44	16	28
Total/Weighted Average:	483	27.2	–
(B) High Grade T1 disease Treated With Induction BCG And Maintenance			
Hurle [71]	51	18	85
Thanos [72]	17	24	36
Iori [73]	31	6.5	40
Margel [74]	78	18	107
Pansadoro [75]	81	17	76
Peyromaure [76]	57	23	53
Zhang [77]	23	35	45 (mean)
Total/Weighted Average:	338	19	–

course), Herr et al. reported a CR rate of 45% in 80 patients found to have T1 disease on repeat TURBT for high grade papillary disease [82]. Over 5 years, 61 of these patients (76%) were found to have progressive disease. Multivariate analysis did not specifically address specific pathology types (i.e., T1 disease) but identified that any pathology on re-resection TURBT (non-T0) was predictive of recurrence and progression. Though, a major limitation of this study was that the outcomes reported included only those with T1 disease on re-resection and did not report on the outcomes of the 220 patients found to have T1 high grade disease on initial resection. Thus, these results likely only represent the outcomes of select, extremely high-risk patients with T1 disease. Other factors that further complicate interpretation of these results include the exclusion of BCG exposure (number of prior courses) in the multivariate analysis, as well as lack of maintenance BCG.

In reviewing unpublished data from the National Phase 2 BCG/IFN study, 61 BCG failure patients with recurrent T1 disease were identified, of which 51% were disease-free at 1 year and 38% at 2 years (O'Donnell personal communication). While this demonstrated a good response to therapy, we caution over-interpretation of this data, given the small number of patients and unknown rate of progression in the group.

Given the small amount of published data, we feel that patients with T1HG recurrence first require a careful re-evaluation prior to any further therapy. As with naïve patients, those with recurrent T1HG should undergo a repeat TURBT for the same reason. While a potentially curative response to further BCG or BCG/IFN is possible, as in the BCG/IFN results, there is an added risk of disease progression that could compromise survival.

After reviewing the above-noted studies, none considered recurrence timing as a factor for analysis. Given that patients who recur beyond 12 months respond similarly to BCG naïve patients [49], we feel that this similarly applies to T1HG patients and would not consider them BCG unresponsive. Conversely, patients with T1HG recurrence within 6 months represent a group with clearly aggressive disease, which is either rapidly recurrent or locally worsening. Thus, we feel that these patients should be considered BCG unresponsive after only a single course of BCG and proceed to second-line intravesical therapies or cystectomy. T1HG patients with recurrence at 6–12 months remain a group who may potentially respond to repeat BCG-based therapy. As such, we feel it premature to consider them BCG unresponsive without further data.

Extent of disease (Focality and Size)

Multiples studies of naïve patients, failure patients, and mixed populations have clearly demonstrated that tumor multiplicity is predictive of both recurrence [48, 49, 83] and progression [84, 85]. The notion that multifocal disease puts a patient at higher risk for intravesical failure is not surprising since the more tumors present, the larger the surface area of diseased bladder mucosa. As BCG is only effective if in contact with tumor cells and a larger area of disease is present, the possibility that some bladder mucosa will go untreated during BCG therapy remains a real possibility. While identified as a risk factor for recurrence and progression, the true effect of multifocal disease requires evaluation of multiple other associated factors, including the specific stage, grade and size of each tumor, presence of CIS, distribution of tumors in relation to one another and distribution of tumors within the bladder. Only after these variables have all been assessed will we be able to fully understand the increased risk and complexity of multifocal disease. We are unaware of any studies that have performed such an analysis to date.

In addition, the effect of tumor size on the risk of recurrence and progression has been a heavily debated topic. Multiple studies have reported an increased risk of recurrence [48] or recurrence and progression [83, 84, 86] with larger tumors (specifically greater than 3 cm), while others have found no effect [87, 88]. As with any large high-grade tumor, re-resection should be considered to rule out occult T2 disease, as well as to maximally debulk for optimal efficacy of adjuvant therapy.

Both multifocal disease and large tumor size are variables used to estimate recurrence and progression rates in the European Organization of Research and Treatment of Cancer (EORTC) Bladder Cancer Risk calculator, which is based upon the risk tables published by Sylvester et al. [86]. However, these risk tables were constructed utilizing data from seven studies, none of which assessed the effect of BCG. Thus, the known reduction in recurrence and progression with BCG utilization is not accounted for in this calculator. We acknowledge the importance of these factors with respect to recurrence and progression but do not feel, given the evidence currently available, that these factors should be included in any definition of BCG unresponsive disease at this time.

Age

Given that BCG efficacy is dependent upon the generation of a strong immune response, specific

populations with depressed immune function, including the elderly, are less likely to respond to therapy. The effect of age has been assessed in only a few studies, of which two have demonstrated no prognostic significance to this variable [89, 90]. However, these studies utilized 65 and 70 years of age as cutoffs and did not consider patients categorically. In the latter study, while age did not predict recurrence or progression, it did predict patient survival (HR 4.34, $p = 0.0006$). Age was evaluated categorically (based on decade of age) as part of the National Phase 2 BCG/IFN trial [91]. Multivariate analysis identified age as an independent risk factor for treatment failure with patients over the age of 80 old less likely to respond to therapy. When considering prior BCG exposure, those who were BCG naïve patients over the age of 80 had a 2-year RFS of 47%, as compared to 65% in the 61- to 70-year age group (adjusted HR = 1.564, $p = 0.02$). For those with prior BCG failures, patients over the age of 80 were disease-free in only 32% of cases at 2 years as compared to 55% in the 61- to 70-year age group. In light of these results, it would appear that BCG is less effective in this subset of patients, though further meta-analyses are warranted.

Review limitations

As with any review, inter-study variability in methods and reporting limits the interpretation and comparative value. In most reports discussed above, there were few studies that reported on the presence of variant histology, particularly aggressive variants such as micropapillary disease. In addition, other reports, such as those assessing for CIS, combined patients with pure and concomitant disease for analysis without reporting sub-group outcomes. The most important limitation, though, involves the under-utilization of repeat TUR for patients with T1HG disease. Even in a large analysis, such as the >2000 patient multicenter database, only 38.2% of T1HG patients received restaging TUR, likely understaging a substantial number of patients with invasive disease [80]. These are just a few examples that highlight just how important critical interpretation of studies is for the practicing urologist.

Table 3
Multivariate analysis of variable evaluated as part of the National Phase II BCG/IFN Trial with associated hazard ratios (HR) to evaluate the degree of influence of each variable

Variable	*p* Value	HR
Age (Categorical variable by decade, >80 years old)	0.0225	1.564[a]
Gender	0.645	1.065
Stage (T1 vs. Ta)	0.0165	1.424
Grade (high vs. low)	0.706	1.036
Tumor size (<1 vs.>5 cm)	0.0186	1.595
Prior intravesical chemotherapy	0.529	1.098
Prior BCG (≥2 vs.≤1 vs. none)	0.0002	1.556
No. TURBTs	0.6103	1.088
BCG failure pattern[b]	0.1721	0.895
BCG maintenance	0.0674	1.326
BCG Strain (TICE vs. Connaught)	0.122	1.243
Multifocality (>5 vs. 2–5 vs. solitary)	<0.0002	1.336
Primary vs recurrent disease	0.2326	1.153

[a]Adjusted hazard ratio (HR) for gender, stage, grade, tumor size, prior BCG and chemotherapy, BCG failure pattern, BCG maintenance, and primary vs recurrent disease. [b]Analyzed as a continuous variable (naïve vs. refractory vs. <6 months vs. 6–12 months vs. 12–24 months vs. >24 months). Adapted from Joudi et al. [46] and Joudi et al. [47].

CONCLUSIONS

Thus, what truly constitutes BCG unresponsive disease? A number of key variables have been identified with varying degrees of influence (Table 3). Based upon the above data, we believe that the following features represent patients unlikely to benefit from further BCG therapy: (1) patients with recurrent T1HG disease within 6 months after at least one course of BCG or patients who have failed 2 courses of BCG with either (2) persistent or recurrent pure papillary (Ta) disease within 6 months or (3) persistent or recurrent CIS within 12 months. Further investigation into the efficacy of repeat BCG administration in patients with T1HG, CIS, and other known variables (i.e., age, tumor multiplicity, tumor size) is warranted.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to report.

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