

Definition of BCG Failure in Non-Muscle Invasive Bladder Cancer in Major Urological Guidelines

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ABSTRACT

Bladder cancer (BC) is the fifth most commonly diagnosed cancer in the nation. Radical cystectomy (RC) is the most effective treatment for locally advanced bladder cancer and is a formidable operation. The perioperative mortality in high-volume centers ranges from 0.7 to 5.6%. Thus, when faced with this diagnosis, there is a desire to pursue a bladder-preserving strategy and avoid RC. One treatment for HG Ta/T1 and carcinoma in situ (CIS) is intravesical bacillus Calmette-Guérin (BCG) therapy. Many studies have confirmed its value in reducing tumor recurrence following transurethral resection of bladder tumors (TURBT). After reviewing the various guidelines, we summarize our recommendations for defining BCG failure.

INTRODUCTION

Bladder cancer (BC) is the fifth most commonly diagnosed cancer in the nation. It is estimated that 70 980 men and women will be diagnosed with BC, and 14 330 patients will die of this disease in the United States in 2009. As of January 1, 2004, approximately 51 1790 individuals in the US have bladder cancer [1,2].

According to the International Society of Urological Pathology (ISUP)/World Health Organization (WHO), BC is graded as high or low grade [3]. A classic report by Jordan et al. [4] examined the progression and disease-specific survival in low- and high-grade transitional-cell cancer (TCC). The progression and disease-specific survival rates for low-grade tumors were 7.7 and

3.3%, respectively. The progression and disease-specific survival rates for high-grade tumors were 62 and 59%, respectively. For patients with high-grade (HG) BC, the prognosis was poor, even if invasion (lamina propria/muscular wall) was not observed in the initial biopsy. Most of the BC deaths (84%) occurred in the first 5 years after diagnosis. Thus, individuals who have high-grade bladder cancer are at a significant risk, whereas those with low grade are unlikely to die of this cancer.

Radical cystectomy (RC) is the most effective treatment for locally advanced bladder cancer and is a formidable operation [5]. The perioperative mortality in high-volume centers ranges from 0.7 to 5.6% [6]. Thus, when faced with this diagnosis, there is a desire to pursue a bladder-preserving strategy and avoid

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RC. One of those treatments for HG Ta/T1 and carcinoma in situ (CIS) is intravesical bacillus Calmette-Guérin (BCG) therapy.

Since its introduction in 1976 by Morales, intravesical BCG has played an important role in the management of high-grade, non-muscle-invasive bladder cancer (NMIBC). Many studies have confirmed its value in reducing tumor recurrence following transurethral resection of bladder tumors (TURBT). Following endoscopic resection for HG Ta tumors, followed by BCG, the recurrence and progression rates are 47 and 25%, respectively [7]. For HG T1 bladder cancer (tumor invasion of lamina propria), the recurrence and progression rates are 42 and 23%, respectively, with a 14% delayed cystectomy rate [8]. In CIS (flat, high-grade, non-invasive cancer), the 5- and 10-year recurrence-free rates are 63 and 54%. The 5- and 10-year progression-free rates are 79 and 77%, with a 90 and 86% disease-specific survival at 5 and 10 years, respectively [9].

Following initial transurethral resection, patients with high-grade NMIBC are increasingly offered a second transurethral resection to eradicate residual tumors and confirm the tumor stage and grade. This is performed within 4 weeks of the initial diagnosis. Residual cancer is detected in up to 33% of patients [10]. Under staging of NMIBC at an initial diagnosis, especially when no muscle is present in the specimen, is a major problem. Under staging was observed in 78% of patients with clinical T1 tumors, but *muscularis propria* was present in only 34% [11]. A recent report showed that a delay of more than 12 weeks from the time of transurethral resection to radical cystectomy significantly reduced the disease-free survival in muscle-invasive bladder cancer [12].

BCG is commonly given as a 6-week induction course with an evaluation endoscopy 6 weeks later. If the patient has either recurrent or new transitional-cell carcinoma, the patient is often given the option of another 6-week course. Since BCG is perceived as the most effective adjunct to endoscopic tumor resection for CIS and HG Ta/T1 bladder cancer [13], and there is a paucity of options when this has failed, the definition of BCG failure is a most important one. Patients offered RC after multiple courses of BCG failure have a much poorer prognosis [14]. Early RC and orthotopic urinary diversion in high-grade NMIBC cancer is associated with a reasonable quality of life [15]. Herr and Sogani demonstrated that patients who have radical cystectomy offered less than 2 years from the start of BCG therapy had better disease-specific survival than if

performed more than 2 years from the initiation of BCG [16]. Recently, Soloway et al. conducted a retrospective review showing that more than 10% of patients who were initially diagnosed with NMIBC and received BCG had lymph-node metastases at RC. Thus, it is very important to recognize BCG failure [34]. Effective bladder preservation options in the case of BCG failure are limited. They include intravesical BCG with interferon, gemcitabine, and valrubicin [17].

A careful search in the literature identifies a variety of definitions for "BCG failure." The First International Consultation on Bladder Tumors (FICBT) classified BCG failure into 4 types. BCG refractory is when there is failure to achieve a disease-free state within 6 months after initial BCG, with either maintenance or re-treatment at 3 months because of either persistent or rapidly recurrent disease. It also includes any progression in stage or grade by 3 months after the first cycle of BCG (i.e., non-improving or worsening disease, despite BCG). Consequently, if, for example, a patient with HG Ta TCC was given 6 weeks of BCG and the 3-month follow-up endoscopy showed the tumor progressed to T1, this is considered BCG refractory. BCG resistant is when there is recurrence or persistence of disease at 3 months after the induction cycle. It is of lesser degree, stage, or grade, and is no longer present at 6 months from BCG re-treatment with or without TUR (i.e., disease improves and then resolves with further BCG). BCG relapse is defined as a tumor after 6 months of BCG. Relapse is further defined by the time of recurrence: early (within 12 months), intermediate (12 to 24 months), and late (>24 months). BCG intolerant indicates tumor recurrence after less than an adequate course of therapy due to a BCG-related adverse event [18]. We feel the definitions of BCG refractory and BCG resistant are confusing. The dictionary defines refractory as: "Resistant to treatment or cure" [19].

In the online version of the National Cancer Institute (NCI) guidelines on bladder cancer for stage 0 (Ta N0 M0 and CIS N0 M0)/stage I (T1 N0 M0), patients with a T1 tumor at the 3-month evaluation after a 6-week course of BCG, and patients with CIS that persists after a second 6-week BCG course, have a high likelihood of developing muscle-invasive disease and should be considered for cystectomy [20]. The NCI referenced 3 reports in support of its recommendation for RC if there is a T1 tumor at the first 3-month evaluation [21-23]. Two reports favored a second course of BCG [21,22]. In the third report, only 1 course of BCG was tried [23].

Table 1. Various definitions of BCG failure.

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Tumor type	NCI (20)	EAU (24)	FICBT (18)	NCCN (28)
HG Ta/T1	Persistent T1 tumor despite 6-week course of BCG Level of evidence 1ii, Grade Diii[‡]	T2 or higher HG NMIBC at both 3 and 6 months (2 courses of BCG) Worsening disease as increase stage, grade, higher number of recurrences or CIS Level of evidence: 3†	<i>BCG refractory</i> : Increase in tumor stage, grade, or disease extent at 3 months of BCG treatment (either due to persistent or rapidly occurring disease) <i>BCG resistant</i> : Recurrence or persistence of disease at 3 months after the induction cycle. It is of lesser degree, stage, or grade, and is no longer present at 6 months from BCG re-treatment with or without TUR <i>BCG relapsing</i> : Tumor recurs after 6 months of BCG (early <12 months, intermediate 12-24 months, and late >24 months) <i>BCG intolerant</i> : Tumor recurs after less than an adequate course of therapy due to a BCG-related adverse event Grade D*	Persistence of cTa, cT1 No more than 2 cycles of 6 weeks of BCG Category 2A[‡]
Bladder CIS	Persistent CIS despite 2 BCG courses	Persistent CIS despite 2 BCG courses Level of evidence: 3†	Persistent CIS despite 2 BCG courses Level of evidence: 4, Grade C*	Persistent despite 2 BCG courses Category 2A[‡]
Prostatic Urethra CIS	NA	NA	Only in CIS-confined urothelium. Failure if CIS persists despite one 6-week course of BCG Level of evidence: 4, Grade C*	In CIS confined to urothelium, failure if CIS persists despite 1 course. BCG and TURP may be tried only 1 time in tumor involving prostatic ductal acini Category 2A[‡]

NCCN: National Comprehensive Cancer Network; NCI: National Cancer Institute; EAU: European Urological Association; NA: Not available

[‡] 1. Randomized Clinical Controlled Trial; ii. Nonblinded Treatment; D. Indirect surrogates; iii. Progression Free Survival

[†] Level 3: Evidence obtained from well-designed, non-experimental studies, such as comparative studies, correlation studies, and case reports

^{*}Level 4: Expert opinion based on "first principles" or bench research, not on evidence. Grade C: Level 4 evidence, "majority evidence," from level 2 or 3 studies; expert opinion. Grade D: No recommendation possible because of inadequate or conflicting evidence

[‡] Category 2A: Based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate

In the European Association of Urology (EAU) guidelines on NMIBC, treatment with BCG is considered to have failed in the following situations: 1) whenever a muscle-invasive tumor is detected during follow-up, 2) if a high-grade, non-muscle-invasive tumor is present at both 3 and 6 months, or 3) any "worsening" of the disease during BCG treatment, such as a higher number of recurrences, higher T-stage or higher grade, or the appearance of CIS, despite an initial response [24]. The EAU guidelines, in contrast to the NCI guidelines, advises a second course of BCG if HG NMIBC (Ta/T1) is present at the initial 3-month evaluation. The EAU addresses 2 reports demonstrating a 50% complete response with a second course of BCG [25,26].

In the American Urological Association guidelines on NMIBC, there was little pertaining to BCG failure [27]. The AUA guidelines described an index patient (index patient 4) with HG NMIBC (HG Ta/T1 and/or CIS). An initial course of 6-week BCG and maintenance is advised. In the same patient, early radical cystectomy is an option in high-risk disease; e.g., large tumor size, high-grade tumor location in a site poorly accessible to complete resection, diffuse disease, the presence of CIS, infiltration of lymphatic or vascular spaces, and prostatic urethral involvement. If the same patient developed recurrent T1 disease after initial BCG treatment (index patient 5), either another course of 6 weeks of BCG or immediate radical cystectomy is advised. The AUA guidelines based its recommendation for proceeding with radical cystectomy based on a report by Herr and Sogani [16]. In this report, 90 patients had radical cystectomy after BCG failure. Thirty-five patients had RC to control recurrent NMIBC and 55 for muscle-invasive bladder cancer (MIBC). In the NMIBC group, survival was 92 and 56% in patients who had RC earlier than or after 2 years from start of BCG therapy, respectively. In the MIBC group, survival was 41 and 18% in patients who had RC earlier than or after 2 years from the start of BCG therapy. However, the average number of recurrences in the NMIBC group, prior to cystectomy, was 3.7, and the median time to radical cystectomy, in both the early and late groups, was 11 months. It is not clear from the report how many courses of BCG were tried given the median time to RC, and with the average number of recurrences, one would assume that at least 2 courses of BCG were tried in a large percentage of these patients.

The National Comprehensive Cancer Network (NCCN) guidelines [28] have BCG failure definitions that are very similar to FICBT.

Table 1 summarizes the definitions for BCG failure in the NCI, EAU, NCCN, and FICBT guidelines.

In the case of a high-grade T1 tumor, The FICBT guidelines recommend radical cystectomy for BCG refractory. A second course of BCG is indicated only if the patient is unfit or unwilling to have a cystectomy. For BCG-resistant disease, a second course of BCG is a reasonable approach. For the BCG-relapsing patient, early failure while the patient is still on maintenance BCG (<12 months) is managed by a second course of BCG, unless the recurrence is high-grade T1 or CIS. In this case, a cystectomy should be strongly considered. The same applies for late failures after completing BCG maintenance (>12 months). Any T1 tumor should be considered for cystectomy after failure of 2 courses of BCG. A high-grade Ta recurrence is managed by endoscopic resection and a second course of BCG [18]. A report by Lerner et al. [29] assessed the patterns of recurrence and outcome following BCG. Patients with no recurrence following BCG enjoyed a better disease-specific survival. The timing of recurrence (<12 months versus >12 months) did not have an impact on disease-specific mortality or development of muscle invasion. The same group of experts suggested that should the recurrence be high-grade T1, radical cystectomy should be offered if the patient is medically fit. The NCI guidelines [20], as previously mentioned, recommend radical surgery after failure of only 1 course of BCG for a T1 recurrence. The NCCN [28] and EAU [24] guidelines agree that 2 courses of BCG may be tried before proceeding to radical surgery. A report from Memorial Sloan-Kettering Cancer Center emphasized a minimum period of 6 months of BCG (induction or maintenance) to define BCG refractory disease [25].

In the case of bladder CIS, we found that there is an agreement between major guidelines to try 2 courses of BCG before proceeding to radical cystectomy. In a phase III trial from the European Organization for the Research and Treatment of Cancer (EORTC), the response rate to BCG in CIS is 57% with 1 course of BCG, and it increases to 67% with 2 courses [30].

In the case of prostatic urethral (PU) TCC, only the FICBT [18] and NCCN [28] guidelines have a clear definition of BCG failure. In both, BCG is indicated in high-grade, transitional-cell carcinoma confined to the urothelium, and RC is indicated after failure of 1 course of BCG. The NCCN added that 1 course of 6-week BCG following TURP may be tried in urothelial carcinoma involving prostatic ducts. There are not many studies assessing BCG

Table 2. Authors recommendations to define BCG failure.

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Tumor type	Definition
Bladder HG Ta/T1	Progression in stage from Ta to T1 or higher Persistent HG Ta/T1 despite 2 course of BCG* New occurrence of CIS
Bladder carcinoma in situ	Persistent CIS despite 2 BCG courses
Prostatic urethral tumor	Persistent HG, CIS, or ductal TCC after 1 6-week course of BCG

* There is a role to proceed to radical cystectomy with persistent HG T1 disease after 1 course of BCG. Quality-of-life issues related to a radical cystectomy and benefits related to long-term survival to be discussed with the patient.

efficacy in prostatic, urethral, transitional-cell carcinoma. In 1 report, radical cystectomy was advised after the failure of only 1 course of BCG with prostatic-duct involvement [31]. In another report, the overall risk of having radical cystectomy because of persistent or progressive disease in the urethra, despite 1 or 2 courses of BCG, was 33%. Even with a complete response, more than 50% will exhibit recurrence in the prostate or prostate and bladder [32]. An interesting report assessed the long-term outcome of radical cystectomy in patients with 2 courses of BCG failure for bladder TCC, and they had undetected preoperative PU involvement showing an increased risk of under staging and a significantly reduced long-term survival [33]. In urethral TCC, we believe a consensus is needed on the best treatment options. We believe persistence of any HG TCC in the PU after a single course of BCG is an indication for cystectomy.

After reviewing the various guidelines, it appears that for bladder CIS, BCG failure is best defined after a failure of 2 courses of BCG. In prostatic urethral CIS, BCG failure is defined after the failure of 1 course. In T1 or high-grade Ta bladder tumors, recommendations from the FICBT or NCCN guidelines are useful. We summarized our recommendations for defining BCG failure in Table 2.

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