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Association between Metabolic Syndrome and Recurrence of Nonmuscle Invasive Bladder Cancer following bacillus Calmette-Guérin Treatment

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Abstract

Introduction—Intravesical bacillus Calmette-Guérin (BCG) therapy is the gold standard adjuvant treatment for patients with high-grade non-muscle-invasive bladder cancer (NMIBC). Despite the association between metabolic syndrome (MetS) and bladder cancer, the association between MetS and BCG failure is unknown. The objective of this study was to characterize disease recurrence following BCG in patients with and without MetS.

Methods—We retrospectively evaluated the records of patients undergoing TURBT at our institution in 2012–2015 for NMIBC and identified those who received adjuvant BCG therapy. MetS was defined as having three of four components: diabetes mellitus, hyperlipidemia, hypertension, or body mass index (BMI)≥30kg/m^2. The primary outcome was recurrence or progression. Descriptive statistics, chi-squared analysis, Kaplan-Meier survival analysis, and Cox multivariable regression analyses were performed.

Results—High grade was present in 83/90 (92.2%) patients. MetS was present in 27/90 (30%) patients. Median follow-up was 20 months. On Kaplan-Meier analysis, patients with MetS had worse DFS compared with patient without MetS. On multivariable analysis, BMI≥30 kg/m^2 was a significant predictor of recurrence or progression (HR 2.94, 95% CI: 1.43–6.03). Presence of MetS did not significantly affect the type of BCG failure.

Conclusions—The association between MetS and failure to respond to BCG therapy is multifactorial but is in part associated with obesity. Elevated BMI is strongly associated with recurrence or progression. Further studies are warranted to investigate the relationship between increased adiposity and response to BCG, especially as other novel immunotherapeutic agents are likely to enter the NMIBC space.

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Keywords (MeSH Terms)

Calmette-Guérin Bacillus; Metabolic Syndrome; Bladder Cancer; Outcome Assessment; Recurrence

INTRODUCTION

Bladder cancer is the second most commonly diagnosed malignancy of the genitourinary system with an estimated 77,000 new cases diagnosed in 2016, of which 70% are non-muscle invasive (NMIBC).[1,2] Prognosis from this form of the disease is generally excellent.[3] This is in part due to the use of intravesical bacillus Calmette-Guérin (BCG), which has been shown to be effective in eradicating carcinoma in situ (CIS), as well as preventing recurrence and progression of disease following surgical resection of papillary tumors. Regrettably, BCG fails in up to 40% of patients.[2] The etiology of BCG failure is not well understood, and is the subject of continual investigation, as the ability to identify patients in whom BCG will fail would allow for pursuit of an alternative treatment approach. This could minimize potential risks associated with BCG use, prevent delays in utilization of more effective alternative treatments, and help preserve BCG for those who are likely to benefit, particularly important in the setting of worldwide BCG shortages.[4,5]

Recent investigations have demonstrated an association between metabolic syndrome (MetS) and an increased risk of bladder cancer.[6] MetS is an increasingly prevalent, complex disorder characterized by the co-occurrence of several factors, namely insulin resistance as in diabetes mellitus (DM), hyperlipidemia (HLD), hypertension (HTN), and visceral obesity.[7–9] Given that the median age at bladder cancer diagnosis is 73 years, bladder cancer patients are often affected by multiple comorbidities, including MetS.[3,10,11] Despite a growing body of literature suggesting an association between MetS, bladder cancer incidence, and oncological outcomes, none have evaluated the relationship between MetS and BCG failure. Because MetS is known to decrease immune responsiveness by inducing chronic, sub-acute inflammation and coaxing of macrophage differentiation toward an anti-inflammatory M2 phenotype, immunotherapeutic treatments such as BCG that rely on an intact immune system may be less effective in this population.[12,13] It is well known that innate and adaptive immunity deteriorates with age, and immunosuppression diminishes response to BCG therapy.[14,15] Therefore, we hypothesized that BCG therapy may also have diminished efficacy in patients with MetS. In order to test our hypothesis, we compared recurrence following adjuvant BCG therapy in patients with and without MetS.

MATERIALS AND METHODS

Patient Cohort

Patients undergoing endoscopic resection of bladder tumors at our institution between March 2012 and July 2015 were identified from the medical record by Current Procedure Terminology (CPT)-4 codes for transurethral biopsy and resection (52204, 52214, 52224, 52234, 52235, 52240). Pathologic and clinical reports were reviewed, and patients with NMIBC who were treated with intravesical BCG therapy were selected for inclusion.

Generally, BCG was given per the SWOG protocol as an induction course of six-weekly instillations followed by maintenance of three-weekly instillations at 3 and 6 months following induction, and then every 6 months for up to 3 years.[16] We excluded all patients with non-urothelial variant histology. We also excluded patients with a diagnosis of upper tract urothelial carcinoma within one year, metastatic disease, less than three months of follow up, or patients who underwent cystectomy within three months of diagnosis for reasons other than recurrence or progression. Follow up was calculated from the time of the last cystoscopy. Study conduct was approved by the Institutional Review Board at our institution.

Independent variables

Metabolic syndrome was defined as the presence of three or more of the following four conditions: DM, HTN, HLD, or a body mass index (BMI)≥30 kg/m^2. DM, HTN, and HLD were identified as either: 1) an International Classification of Diseases (ICD)-9 diagnosis in the medical record, or 2) documentation of prescribed medications used to treat DM, HTN, or HLD. The BMI cutoff was defined a priori and according to the World Health Organization and National Institute of Health classification of obesity (BMI≥30 kg/m^2). This was also selected to maintain consistency with other studies of MetS and the role of obesity in bladder cancer.[17]

Dependent variables

Our dependent variable of interest was recurrence or progression of disease. Recurrence was defined as the presence of urothelial carcinoma on biopsy or repeat resection. Patients who were found to have a lesion visible on cystoscopy that warranted intervention in the office (e.g. fulguration) were also classified as having disease recurrence. Progression was any increase in grade or stage of disease. Patients with recurrence or progression were classified as BCG failures and categorized into the following groups: refractory (presence of disease following induction but within 6 months of diagnosis), relapsing (recurrence of disease after 6 months), or intolerant (cessation or reduction in dose secondary to symptoms). Patients with persistent suspicious cytology but negative cystoscopy were evaluated at the discretion of the surgeon, generally with bladder biopsies and upper tract imaging. These patients were not considered failures unless a biopsy detected recurrence or a lesion warranted intervention, as above.

Statistical analysis

Comparisons between categorical variables were tested using chi-squared analysis and Fisher’s exact test. Two-sample Student’s t-test was used to test for differences between continuous variables. Differences in disease-free survival (DFS) were analyzed using the Kaplan-Meier method. Cox proportional hazards models were used to estimate hazards ratios for covariates of interest and DFS. Cox-snell residuals were calculated to evaluate the fit of the final model. The hazard function has an approximate exponential distribution and provides evidence that the model fits the data well. All statistical analyses were performed with STATA statistical software version 14 (StataCorp, College Station, TX).

RESULTS

A total of 90 patients underwent TURBT for NMIBC during the study period, received adjuvant BCG therapy, and met all inclusion criteria for analysis. Our cohort was predominantly male (80.0%), with a mean age of 69.7 years (SD=12.2). The primary grade was low grade (LG) and high grade (HG) in 7 (7.8%) and 83 (92.2%) patients, respectively. Stage was Ta without CIS, Ta with CIS, T1 without CIS, T1 with CIS, and CIS alone in 22 (24.4%), 10 (11.1%), 30 (33.3%), 14 (15.6%), and 14 (15.5) of patients, respectively. Multiple tumors were present in 52 (57.8%) patients and 34 (37.8%) patients had a history of recurrent bladder cancer. Overall, MetS was present in 27 (30.0%) patients, with DM, HTN, HLD, and BMI≥30 kg/m^2 found in 17 (18.9%), 50 (55.6%), 57 (63.3%), and 22 (24.7%) of the cohort. Cohort characteristics, stratified by MetS and by recurrence or progression, are summarized in Table 1 and Table 2, respectively.

With a median follow-up time of 20 [Interquartile range (IQR): 8–30] months, a total of 27 (30.0%) patients recurred and 8 (8.9%) patients progressed. The median DFS for the entire cohort was 44 months (95% CI: 38–Not Reached). The median DFS was 45 months and 24 months for patients without and with MetS, respectively. The Kaplan-Meier curve is presented in Figure 1 and demonstrates a significant DFS advantage for patients without MetS compared with patients with MetS (log rank test: p=0.04)

A total of 48 patients underwent induction BCG only and 31 patients received BCG induction and maintenance. One patient underwent induction and maintenance with 1/3 dose BCG secondary to BCG shortage. Six patients underwent induction with BCG+interferon. Only four patients underwent incomplete induction, two of which were secondary to BCG shortages, one secondary to intolerable side effects, and one patient preferred to stop treatments. Of the 37 patients who experienced BCG failure (defined as recurrence, progression, or intolerance of therapy), 19 were refractory, 16 were relapsing, and only 2 were intolerant. Associations between the type of BCG failure and presence of MetS were not significant.

Lastly, we created a multivariable model incorporating variables significant on univariate analysis, and our variable of interest, MetS. In this model MetS was not significant when accounting for other variables (HR1.53 95% CI: 0.71 – 3.29, p=0.28). Given the association between BMI and HTN and recurrence or progression on univariate analysis, however, we decided to perform a post hoc analysis to evaluate each component of MetS. HTN was no longer associated with recurrence or progression. BMI, however, became a strong predictor of BCG failure when analyzed as a binary variable with BMI≥30 kg/m^2 (HR 3.42, 95% CI: 1.55–7.52, p=0.002) and as a continuous variable (HR 1.12, 95% CI: 1.04–1.22, p=0.005) (Table 3). Moreover, if we excluded the two patients who “failed” secondary to intolerance —they had a BMI of 26.4 and 27.4 kg/m^2—the univariate Kaplan Meier survival curves diverge further and the log rank test p-value decreases from 0.04 to 0.019. The association between elevated BMI≥30 kg/m^2 and recurrence or progression is maintained in the multivariable Cox model.

DISCUSSION

There is no current standard therapy for patients in whom BCG therapy fails. Current recommendations include additional intravesical treatments, extirpative surgery, bladder-sparing protocols (maximal resection and chemo-radiation), or clinical trials. The optimal treatment pathways have been heavily debated.[18] However, there continues to be an extensive divergence in the aggressive treatment of patients with bladder cancer.[19] Therefore, determining clinically useful predictors of response to BCG may help aid decisions to choose a definitive treatment and set appropriate expectations.

Our hypothesis that MetS is associated with BCG efficacy was predicated on several large studies suggesting an association between MetS and bladder cancer pathogenesis. Haggestrom et al., demonstrated in a prospective cohort of 580,000 patients that MetS was significantly associated with an increased risk of bladder cancer in men.[20] A meta-analysis by Esposito et al., confirmed that men with MetS were significantly more likely to be diagnosed with bladder cancer.[6] Although the mechanisms that link MetS and cancer risk are not fully understood, it is well established that MetS induces a chronic, low-grade inflammatory state with changes found in both immune and non-immune cells.[12] MetS decreases cellular immunity by limiting chemotaxis, phagocytosis, and killing of polymorphonuclear cells and monocytes/macrophages, resulting in decrease immune responsiveness.[21] Conversely, the requirements for effective immunotherapeutic treatments, such as BCG therapy, necessitate a competent host immune system. The anti-tumor effect of BCG is multifaceted, and includes a component of direct cytotoxicity, recruitment of other immune cell subsets into the tumor microenvironment, and stimulation of cytokine and chemokine secretion.[13] Thus, a state of decrease immune responsiveness, such as that induced by MetS, may result in diminished BCG efficacy.

We hypothesized that patients with MetS would demonstrate worse DFS compared with patients that did not have MetS, or its components. Although significant in a univariate Kaplan-Meier survival analysis, MetS as a predictor of recurrence or progression was not maintained in a multivariable model controlling for other factors. This is potentially secondary to our sample size. However, when evaluating each component of MetS separately in a multivariable model, a BMI≥30 kg/m^2 was significantly associated with recurrence or progression. This association held even when BMI was analyzed as a continuous variable. This finding corroborates two recent studies analyzing the role of obesity in the prognosis of NMIBC. Kluth et al., demonstrated that obesity (also defined as BMI≥30 kg/m^2) was associated with an increased risk of disease recurrence, disease progression, and cancer-specific mortality in a cohort study of 892 patients after adjusting for other factors.[17] Similarly, a study of 726 patients with NMIBC reported that high BMI values at diagnosis were associated with an increased risk of recurrence.[22] The growing body of literature suggesting the negative influence of obesity on genitourinary malignancies and oncologic outcomes has led to speculation regarding the underlying biological mechanisms. One proposed pathogenesis involves excess adipocytes, particularly in visceral adipose tissue, resulting in an overproduction of pro-inflammatory cytokines and macrophage recruitment contributing to a pro-tumorigenic environment.[23] Other models also suggest polymorphisms of adiponectin and its receptor genes.[24] Further studies are required

to better elucidate this relationship, and mechanistic targets for disrupting the obesity-cancer association could be exploited for therapeutic intervention. Finally, we did not find an association between MetS and the type of BCG failure. This was likely secondary to the small sample size of patients who failed BCG within the study period. Larger sample sizes are required to investigate this further.

Our findings should be considered in the context of its limitations. First, this study was performed retrospectively and we were limited by the data available in medical records. Secondly, while we collected and reported data on BCG failure types, these definitions are inconsistently defined in the literature and may not represent unique clinical states.[2] Additionally, our patient cohort was managed with a variety of surveillance protocols and an institutional pathway could have enhanced consistency of follow up and the identification of failures. MetS was defined simply as present or absent and no degree of severity was utilized in our analysis (e.g. HgbA1C or serum cholesterol levels), with the exception of BMI. Finally, BMI has been replaced by abdominal circumference in the definition of MetS, a change that underscores the importance of visceral adiposity in the pathophysiology.[25] Unfortunately, abdominal circumference was unable to be obtained from the medical records in this retrospective study. Several studies cited herein have also used BMI in the definition of MetS as a substitute for abdominal circumference, as this is not generally obtained during routine office visits.[17,20,22]

Despite these limitations, our study addresses a concern that may become more important as patients with NMIBC become older with more comorbidities (including MetS), also as BCG continues to be in short supply outside clinical trials and require sparing and rationed use. There are several practical applications for this data. First, this study better informs the urologist managing high-risk NMIBC with BCG regarding the potentially decreased responsiveness of patients with elevated BMI to BCG treatments. Secondly, similar to the smoking cessation counseling opportunities that come with a bladder cancer diagnosis, treatment of patients with BCG who have an elevated BMI can be an opportunity to counsel patients to engage in healthy lifestyle choices that could potentially reduce the chances of BCG failure and certainly improve cardiovascular health.[26] Third, patients with decreased immune responsiveness to BCG, potentially in patients with multiple risk factors including elevated BMI, may be better served with intravesical cytotoxic agents (e.g. gemcitabine or MMC) in lieu of a second induction course of BCG, and clinical studies could be planned to evaluate this hypothesis. This is especially important in the era of upcoming global BCG shortage.[4] Moreover, these results address a concept within the expanding field of immunotherapy for urothelial carcinoma, specifically regarding the effect of the host immune status on the efficacy of immunotherapy. Recently approved novel immunomodulators, such as anti-programmed cell death ligand-1, rest heavily on the function of the host's immune system. Further research is needed to determine whether these therapies are similarly effective in patients unable to mount a vigorous immune response. Finally, our results highlight the need for predictive models to help identify patients who will fail BCG therapy and therefore warrant more aggressive upfront treatment.

CONCLUSIONS

We found that MetS is not significantly associated with risk of NMIBC recurrence or progression following treatment with BCG. An elevated BMI, however, is strongly associated with risk of recurrence or progression in our cohort. Patients receiving immunotherapy who have elevated BMI may be counseled regarding the possibility of an increased risk of recurrence or progression. The effect of host immune status on newer, more targeted immunomodulators, is unknown and of interest.

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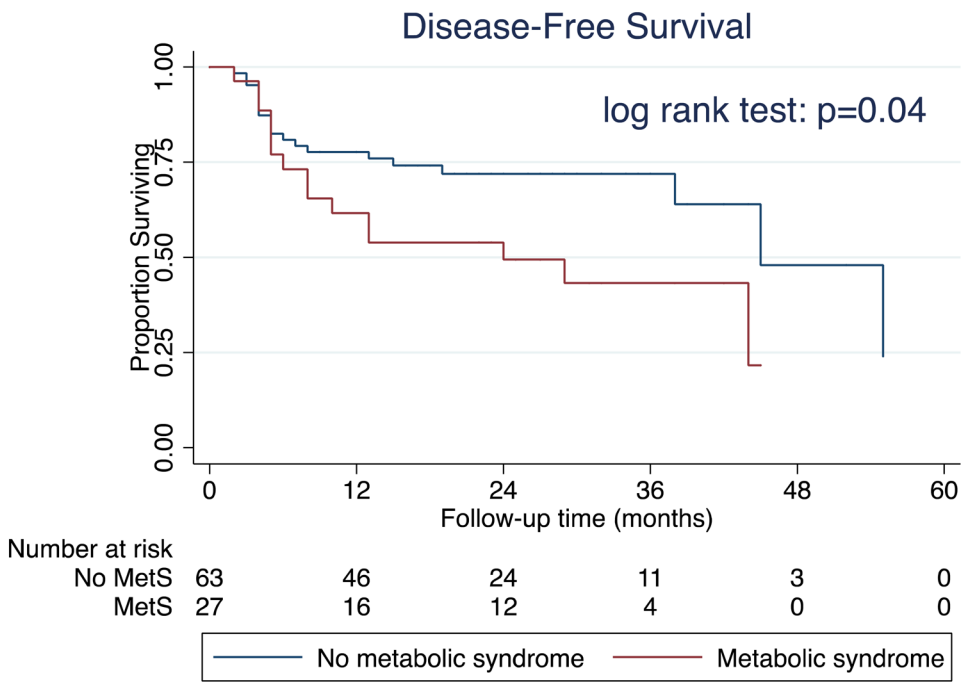

Figure 1.
Kaplan-Meier survival curve stratified by presence of metabolic syndrome. MetS, metabolic syndrome.

Table 1

Cohort characteristics stratified by presence of metabolic syndrome.

Variable	With MetS (n = 27)	Without MetS (n = 63)	p-value
Age, mean (SD)	74.7 (10.4)	67.6 (12.4)	<0.01
Gender, n (%)			0.57*
Male	23 (85.2)	49 (77.8)	
Female	4 (14.8)	14 (22.2)	
Grade, n (%)			
HG	25 (92.6)	58 (92.1)	1.00*
LG	2 (7.4)	5 (7.9)	
Stage, n (%)			
Ta without CIS	6 (22.2)	16 (25.4)	0.67*
Ta with CIS	4 (14.8)	6 (9.5)	
T1 without CIS	7 (25.9)	23 (36.5)	
T1 with CIS	4 (14.8)	10 (15.9)	
CIS	6 (22.2)	8 (12.7)	
Tumor size, n (%)			0.70*
<0.5cm	13 (48.2)	26 (41.3)	
0.5–2.0cm	2 (7.4)	3 (4.8)	
2.0–5.0cm	3 (11.1)	13 (20.6)	
>5.0cm	9 (33.3)	21 (33.3)	
Multiple tumors, n (%)	20 (74.1)	32 (50.8)	0.04
Recurrent disease, n (%)	13 (48.2)	21 (33.3)	0.18
Follow-up time, mean (SD)	19.5 (14.0)	21.2 (14.0)	0.30
MetS components, n (%)			
DM	15 (55.6)	2 (3.2)	<0.01*
HTN	23 (85.2)	27 (42.9)	<0.01
HLD	27 (100.0)	30 (47.6)	<0.01
BMI≥30	19 (70.4)	4 (6.4)	<0.01*
BMI, mean (SD)	31.0 (5.6)	25.7 (3.4)	<0.01+

MetS, metabolic syndrome. SD, standard deviation. CIS, carcinoma in situ. HG, high grade. LG, low grade. DM, diabetes mellitus. HTN, hypertension. HLD, hyperlipidemia. BMI, body mass index.

*, Fisher's exact test.

+, Student's t-test.

Table 2

Cohort characteristics stratified by recurrence or progression.

Variable	Recurrence or Progression (n=35)	No Recurrence or Progression (n=55)	p-value
Age, mean (SD)	70.6 (9.8)	69.1 (13.6)	0.59
Gender, n (%)			0.03 *
Male	32 (91.4)	40 (72.7)	
Female	3 (8.6)	15 (27.3)	
Primary grade, n (%)			
HG	34 (97.1)	49 (89.1)	0.24 *
LG	1 (2.9)	6 (10.9)	
Stage, n (%)			
Ta without CIS	7 (20.0)	15 (27.3)	0.10 *
Ta with CIS	1 (2.9)	9 (16.4)	
T1 without CIS	12 (34.3)	18 (32.7)	
T1 with CIS	6 (17.1)	8 (14.6)	
CIS	9 (25.7)	5 (9.1)	
Tumor size			0.99 *
<0.5cm	16 (45.7)	23 (41.8)	
0.5–2.0cm	2 (5.7)	3 (5.5)	
2.0–5.0cm	6 (17.1)	10 (18.2)	
>5.0cm	11 (31.4)	19 (34.5)	
Multiple tumors, n (%)	24 (68.6)	28 (50.9)	0.10
Recurrent disease, n (%)	16 (45.7)	18 (32.7)	0.22
MetS, n (%)	15 (42.9)	12 (21.8)	0.03
MetS components, n (%)			
DM	8 (22.9)	9 (16.4)	0.44
HTN	25 (71.4)	25 (45.5)	0.02
HLD	23 (65.7)	34 (61.8)	0.71
BMI≥30	17 (48.6)	6 (10.9)	<0.01
BMI, mean (SD)	29.7	25.7	<0.01 +

MetS, metabolic syndrome. SD, standard deviation. CIS, carcinoma in situ. HG, high grade. LG, low grade. DM, diabetes mellitus. HTN, hypertension. HLD, hyperlipidemia. BMI, body mass index.

*, Fisher's exact test.

+, Student's t-test.

Table 3

Cox multivariable model for recurrence or progression with MetS stratified into components.

Variable	Hazard Ratio	95% Confidence Interval	p-value
Age (per year)	1.00	0.97–1.04	0.84
Gender			
Female	Reference		
Male	1.78	0.51–6.20	0.37
Grade			
LG	Reference		
HG	2.35	0.27–20.5	0.44
Stage			
Ta without CIS	Reference		
Ta with CIS	0.24	0.03–2.09	0.20
T1 without CIS	1.20	0.43–3.29	0.73
T1 with CIS	1.70	0.52–5.54	0.38
CIS	1.18	0.41–3.39	0.76
Components of MetS			
DM	1.09	0.46–2.59	0.84
HTN	2.15	0.89–5.15	0.09
HLD	0.61	0.27–1.37	0.23
BMI≥30	3.42	1.55–7.52	0.002

LG, low grade. HG, high grade. CIS, carcinoma in situ. MetS, metabolic syndrome. DM, diabetes mellitus. HTN, hypertension. HLD, hyperlipidemia. BMI, body mass index.