Title

Association Between Number of Endoscopic Resections and Utilization of Bacillus Calmette-Guérin Therapy for Patients With High-Grade, Non–Muscle-Invasive Bladder Cancer

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ASSOCIATION BETWEEN NUMBER OF ENDOSCOPIC RESECTIONS AND UTILIZATION OF BACILLUS CALMETTE-GUERIN THERAPY FOR PATIENTS WITH HIGH-GRADE, NON-MUSCLE INVASIVE BLADDER CANCER

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Abstract

Background—Bacillus Calmette-guerin (BCG) is the gold standard treatment for patients with high-grade, non-muscle-invasive bladder cancer (NMIBC). We previously described non-compliance with guidelines for BCG use in patients with high-risk disease. In the current study we sought to characterize how the number of endoscopic resections of bladder tumors affects BCG utilization using population-level data.

Methods—We queried a SEER-Medicare linked database to evaluate claims records of 4,776 patients diagnosed with high-grade NMIBC between 1992 and 2002 and followed until 2007, who survived for at least two years and did not undergo definitive treatment with cystectomy, radiotherapy, or systemic chemotherapy. We stratified patients based on the number of endoscopic resections of bladder tumors. We used chi-squared analysis to compare number of resections to

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CONFLICTS OF INTEREST

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BCG utilization and multinomial logistic regression analysis to quantify BCG utilization by patient and tumor characteristics.

Results—Utilization of BCG increases with increasing endoscopic resections from 40% at diagnosis to 72% after six resections. The cumulative rate of at least an induction course of BCG plateaus after three resections. Lower BCG utilization was associated with advanced age (≥80 years), while increased utilization was associated with being married, higher stage (Tis and T1) and grade (undifferentiated), and increasing endoscopic resections.

Conclusions—A significant fraction of patients with NMIBC do not receive induction BCG despite proven benefit in minimizing recurrences. Most patients receive BCG only after multiple endoscopic resections. Strategies focused on earlier adoption of BCG to prevent recurrences instead of reacting to recurrences may limit progression and improve survival.

MICRO-ABSTRACT

Bacillus Calmette-Guérin (BCG) is an effective yet underutilized treatment for high-grade, non-muscle invasive bladder cancer. We evaluated the patterns of BCG utilization with respect to number of endoscopic resections in a SEER-Medicare linked database and found that BCG adoption is slow and incomplete. Methods to improve compliance with this therapy are warranted.

MeSH Terms

Urinary Bladder Neoplasms; Calmette-Guerin Bacillus; Recurrence; Quality of Healthcare; Guideline Adherence

INTRODUCTION

High-grade urothelial cell carcinoma accounts for approximately 25% of newly diagnosed non-muscle invasive bladder cancer (NMIBC).[1] Within the first two years approximately 61% will have at least one recurrence, and only 15% of these patients will proceed with aggressive treatment (i.e. cystectomy, radiotherapy, or chemotherapy) after the first recurrence.[2,3] Several studies have demonstrated that patients with high-grade NMIBC who opt for more aggressive treatment, for example cystectomy, do so early usually after the first recurrence.[3] Consequently, a significant fraction of patients with recurrent, high-grade NMIBC are managed primarily with endoscopic and intravesical treatments.

Intravesical bacillus Calmette-Guerin (BCG) following transurethral resection of bladder tumor (TURBT) has been shown in multiple studies to reduce recurrence and progression in patients with high-grade NMIBC.[4,5] Furthermore, maintenance BCG therapy has been shown to decrease recurrence in patients with NMIBC.[6] Unfortunately, adherence rates to standardized surveillance and treatment protocols for this disease are suboptimal.[7,8] For example, less than half of patients in the landmark Southwest Oncology Group Trial 8507 completed three cycles of maintenance BCG and only 16% of completed the full seven cycles.[9] Despite data demonstrating increasing rates of BCG utilization, fewer than 30% of patients with high-grade NMIBC receive a full course of induction.[7]

Utilization patterns of BCG on a population level as they relate to disease recurrences have not been described. The aim of our study was to further evaluate non-compliance with BCG by examining the association between number of endoscopic resections and BCG utilization. We speculated that upfront BCG therapy is under-utilized and is instead utilized as a reaction to recurrence. Therefore we hypothesized that the initiation of BCG would increase with the number of endoscopic resections, and that the number of patients completing maintenance therapy would be few.

METHODS

Data Source

We used the linked Surveillance, Epidemiology, and End Results (SEER)-Medicare database of the National Cancer Institute to acquire information on patients diagnosed with bladder cancer between 1992 and 2002 and followed until 2007. We restricted inclusion to those with Medicare Fee-For-Service coverage with complete data for Medicare Parts A and B for at least 12 months preceding bladder cancer diagnosis.

Study Population

Patients eligible for the study were 66 years or older to allow for at least one year of eligibility in Medicare before their diagnosis of bladder cancer to ascertain comorbidity data. As we have previously defined, eligible patients must have had an incident diagnosis of non-metastatic (N0M0), high-grade (poorly or undifferentiated) urothelial cell (histology codes 8120, 8130), non-muscle invasive (Ta, Tis, T1) bladder cancer (International Classification of Diseases, Ninth Revision *(ICD-9)* 188.0–188.9, 233.7) diagnosed between January 1, 1992 and December 31, 2002.[2] We also limited our cohort to patients who survived at least two years without undergoing definitive treatment (cystectomy, radiation, systemic chemotherapy).

Induction BCG was defined as six weekly instillations. Maintenance was defined as three weekly instillations at 3, 6, 12, 18, and 24 months. Based on these recommended protocols we classified BCG utilization into the following groups: no BCG (0 instillations during the entire followup period), partial induction (1–5 instillations), full induction (6 instillations), induction and ≤1 year of maintenance (7–15 instillations), induction and ≤2 years of maintenance (16–21 instillations), and induction and >2 years of maintenance (≥22 instillations).

Study Variables

We determined patient age, gender, race/ethnicity, marital status, tumor grade, and T-stage using the Patient Entitlement and Diagnosis Summary File (PEDSF). Using 2000 US Census data we determined levels of median house hold income and percent of residents 25 years or older with at least four years of college education. Similarly, using the Unique Physician Identifier Number, we were able to determine treatment center Region and Institution type.

Statistical Analysis

Bivariable analysis comparing utilization of BCG to the number of endoscopic resections (i.e., TURBTs and bladder biopsies) was performed using a chi-squared analysis. To quantify the association between utilization of BCG (partial, induction, or induction followed by maintenance) and our study variables we used a multivariate, multinomial logistic regression analysis. We report the relative risk ratio and corresponding confidence interval (CI).

The Institutional Review Board at the University of California, Los Angeles, exempted our study from review. All analyses were conduced using STATA software 13.1 (StataCorp, College Station, TX). Statistical tests were all 2-tailed with probability of type I error set at 0.05.

RESULTS

Cohort characteristics for the 4,776 patients meeting inclusion criteria are described in Table 1. A total of 1,590 (33.2%) underwent 1 resection, 1,128 (23.6%) underwent 2 resections, 742 (15.5%) underwent 3 resections, 470 (9.8%) underwent 4 resections, 330 (6.9%) underwent 5 resections, 191 (3.9%) underwent 6 resections, and 325 (6.8%) underwent 7 resections.

BCG utilization was stratified by number of resections in Table 2. Of the 1,590 patients who underwent a single resection, 59.6% did not receive any BCG therapy, 25.8% received partial induction, 7.1% received full induction courses, and 7.5% received treatment beyond induction. The percent of patients receiving at least partial BCG increased as the number of resections increased (chi squared analysis, $p<0.05$).

Figure 1 demonstrates cumulative BCG utilization. Cumulative use increased from 11% after the first resection to 20% after the third resection. An additional fourth and fifth resection only yielded a 2% increase in cumulative BCG utilization. After the fifth resection, we found no increase in BCG utilization.

In Table 3, the relative risk ratio (RRR) for partial BCG, induction BCG, and induction followed by maintenance BCG (compared with no BCG as a referent) is defined for several variables. We found that those with advanced age and female gender were less likely to receive BCG therapy. Those ≥80 years of age were less likely to receive partial (RRR 0.60 [95% CI 0.49–0.75]), induction (RRR 0.61 [95% CI 0.42–0.90]), and induction plus maintenance (0.61 [95% CI 0.46–0.83]) BCG therapy. Women were also less likely to receive induction followed by maintenance BCG (RRR 0.79 [95% CI 0.62–1.00]). Conversely, patients of other race or with more aggressive tumors and increasing number of resections were more likely to receive BCG therapy. Patients of other race were significantly more likely to receive partial induction (RRR 1.58 [95% CI 1.08–2.31]), full induction (RRR: 2.16 [95% CI 1.16–4.01]), as well as induction plus maintenance BCG (RRR 1.68 [95% CI 1.02–2.75]) compared with White patients. Patients treated in the South or Northeast had a higher risk of receiving induction BCG (South RRR 1.85 [95% CI 1.19–2.87], Northeast RRR 2.24 [95% CI 1.60–3.12]) and induction plus maintenance BCG

(South RRR 1.68 [95% CI 1.22–2.31], Northeast RRR 1.58 [95% CI 1.22–2.04]) compared with the patients treated in the West. Patients diagnosed with undifferentiated tumors were more likely to be treated with partial BCG (RRR 1.62 [95% CI 1.36–1.93]) and induction plus maintenance BCG (RRR 1.62 [95% CI 1.29–2.03]) compared with poorly differentiated tumors. Patients diagnosed with T1 tumors were more likely to receive partial BCG (RRR1.38 [95% CI 1.19–1.60]), full induction BCG (RRR 1.57 [95% CI 1.20–2.05]), and induction followed by maintenance BCG (RRR 1.69 [95% CI 1.38–2.06]) when compared with patients diagnosed with Ta tumors. Patients having undergone ≥1 resections were more likely to receive partial BCG (RRR 1.28 [95% CI 1.23-1.33]) and induction followed by maintenance BCG (RRR 1.43 [95% CI 1.37–1.51]) compared with patients who underwent only one resection.

DISCUSSION

High-grade NMIBC poses a treatment dilemma given that recurrence is common and only a small fraction of patients undergo definitive therapy with cystectomy, radiation, or systemic chemotherapy.[3] Consequently, many patients with disease recurrence are treated with endoscopic and intravesical therapy. We sought to evaluate the relationship between number of endoscopic resections and BCG use to understand how compliance and utilization may be optimized. Our study has five principal findings: 1) only 40% of patients received any BCG following a single resection; 2) over 60% of those who did receive BCG following first resection had an incomplete induction course (<6 instillations); 3) BCG use increases with multiple resections; 4) chronological age but not medical comorbidities were associated with less BCG use; and 5) patients diagnosed and treated at academic medical centers were no more likely to receive BCG therapy. These observations demonstrate that there is substantial opportunity to improve the rate of BCG induction and maintenance, especially in the current era of limited access to BCG.

There is widespread consensus that induction BCG is standard adjuvant treatment for high-risk, NMIBC.[10] In a poll by Nielsen *et al*, 99% of urologists reported using induction therapy (including mitomycin C) following a diagnosis of high-grade disease, most commonly with BCG.[11] However, in our study, only 40% of patients received any BCG therapy following a single resection. This result is similar to data published previously. For example, Patschan *et al* analyzed a Swedish cohort of patients with T1 disease and found that only 24% received BCG.[12] Utilizing SEER-Medicare data, Spencer *et al* found that only 39% of patients with Tis or T1 disease and only 29% of patients with high-grade received any BCG.[13] Differences in reported rates of BCG use may stem from the varying definitions of low, intermediate, and high-risk subgroups of NMIBC. Based on guidelines by the National Comprehensive Cancer Network and the American Urological Association, all patients with high-grade disease are at high risk of recurrence and progression, and therefore warrant BCG therapy.[14,15] While our data may not have captured some patients with low-grade yet high-risk disease (e.g. multiple tumors, multiple recurrences), all patients in our cohort were high-grade and should have received BCG based on commonly used guidelines.

Our second major finding is that the majority of BCG courses in our cohort is incomplete. By stratifying BCG use into number of instillations, we were able to analyze utilization

more critically than many of the previously cited population-based studies. More than 60% of patients in our cohort who received BCG following the first resection received less than the standard induction. While no data exists to suggest a shorter induction course, we do know that six instillations is sufficient to develop a delayed hypersensitivity reaction and has been shown to be efficacious in randomized trials.[16–18] Furthermore, the protective effects of BCG wane with time and require periodic maintenance instillations to induce durability.[19] Unfortunately, in our cohort less than 1% of patients received induction therapy followed by more than two years of maintenance therapy. It is possible that some of the failure to receive BCG therapy is secondary to intolerance. We did not analyze rates of intolerance, however Van der Meijden *et al* demonstrated that side effects contributed to 12–15% of BCG failures.[20] Furthermore, we did not identify patients in our cohort that were started on novel regimens, such as that proposed by Oddens *et al* who showed non-inferior recurrence rates with one year of maintenance therapy in intermediate risk patients.[21] Patients on these regimens may have artificially skewed our cohort to appear less compliant.

We also demonstrated that BCG is being used despite multiple endoscopic resections. We found that use of BCG (induction alone or induction followed by maintenance) occurs in approximately 11% of our cohort after the first resection and takes three subsequent resections before cumulative use plateaus near 22%. While adjuvant BCG is known to limit recurrence and progression, there is also data to suggest that repeated BCG instillations in the face of persistent recurrences is associated with worse outcomes. Catalona *et al* demonstrated that each intravesical treatment increases the risk of metastasis, likely secondary to delayed definitive treatment.[22] Lambert *et al* also suggested that increasing intravesical therapy use is associated with poorer outcomes compared with those who underwent early cystectomy.[23] Identification of patients who will fail BCG early is critical as Herr and Sogani have demonstrated that delaying radical cystectomy for high-risk NMIBC by longer than two years leads to worse diseasespecific survival.[24] Ideally, all patients with high-grade NMIBC should be treated with early and complete BCG therapy. Early BCG failure may then trigger a discussion regarding potential definitive therapy.

It is known that older patients with more significant medical comorbidities do not respond to or tolerate BCG as well as younger, healthy patients.[25,26] Our data support the observation that older patients (>80 years) are less likely to receive BCG therapy. However, our analysis revealed that patients with greater comorbidities, as defined by the Charlson comorbidity scoring system, were *no* less likely to receive BCG. Thus, we have observed that age but not potential comorbidity status affects the decision to initiate BCG. In practice we should consider that elderly patients with no medical comorbidities might respond to and benefit from intravesical BCG therapy.

Finally, we expected to find that academic medical centers would be more likely to treat patients with BCG therapy. However, we were not able to confirm this hypothesis with our data. It is possible that patients referred to academic medical centers required second-line intravesical therapy secondary to BCG failure or intolerance.[27] Incorporation of these patients into our cohort would artificially skew our results to non-compliance. Another potential confounder is that patients treated at academic medical centers may have been

more likely to be enrolled in clinical trials that forego BCG therapy, although fewer of these trials existed at the time.

Our findings must be considered in the context of several limitations. First, this is a retrospective study that uses only Medicare patients greater than 66 years of age, and some patients diagnosed with bladder cancer are younger than the age captured by our data. Second, our choice of endoscopic resection as a marker of recurrence could not capture untreated recurrences, which may be substantial in this elderly population. Finally, we did not analyze alternative intravesical therapies or treatments being offered as second line or salvage options.

Nevertheless, our data add to the current literature that demonstrates low levels of adherence to NMIBC treatment protocols by suggesting that the timing of BCG is often delayed and reactionary—current use is *too little and too late* to maximally affect recurrence and progression rates. Limiting recurrences may curb the substantial economic costs associated with chronic surveillance and multiple treatment cycles in NMIBC.[28] Finally, in light of the recent worldwide shortage of BCG, we must strive to optimize utilization of this limited resource.[29] Early and more complete utilization of BCG to limit recurrences, as opposed to reacting to them, may ultimately decrease progression and improve survival.

CONCLUSIONS

Despite significant evidence for use of BCG in an adjuvant setting to prevent recurrences, utilization of BCG in NMIBC has not yet been optimized. We show that despite multiple endoscopic resections, the cumulative adoption of BCG is incomplete, slow, and reactionary. To improve rates of progression and overall survival for patients with NMIBC we should strive for earlier and more complete utilization of this proven therapy.

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CLINICAL PRACTICE POINTS

- BCG is the gold standard treatment for high-grade, non-muscle invasive bladder cancer yet compliance with this therapy is poor.
- We used a SEER-Medicare linked database to analyze BCG utilization with respect to number of endoscopic resections of bladder tumors.
- We found that BCG utilization was low, even for patients who underwent multiple endoscopic resections of high-grade disease.
- We found that increasing number of endoscopic resections was associated with increased utilization of BCG up to three resections, at which point utilization plateaued.
- We conclude that BCG utilization is incomplete reactionary and should be used upfront to prevent recurrences rather than react to them.

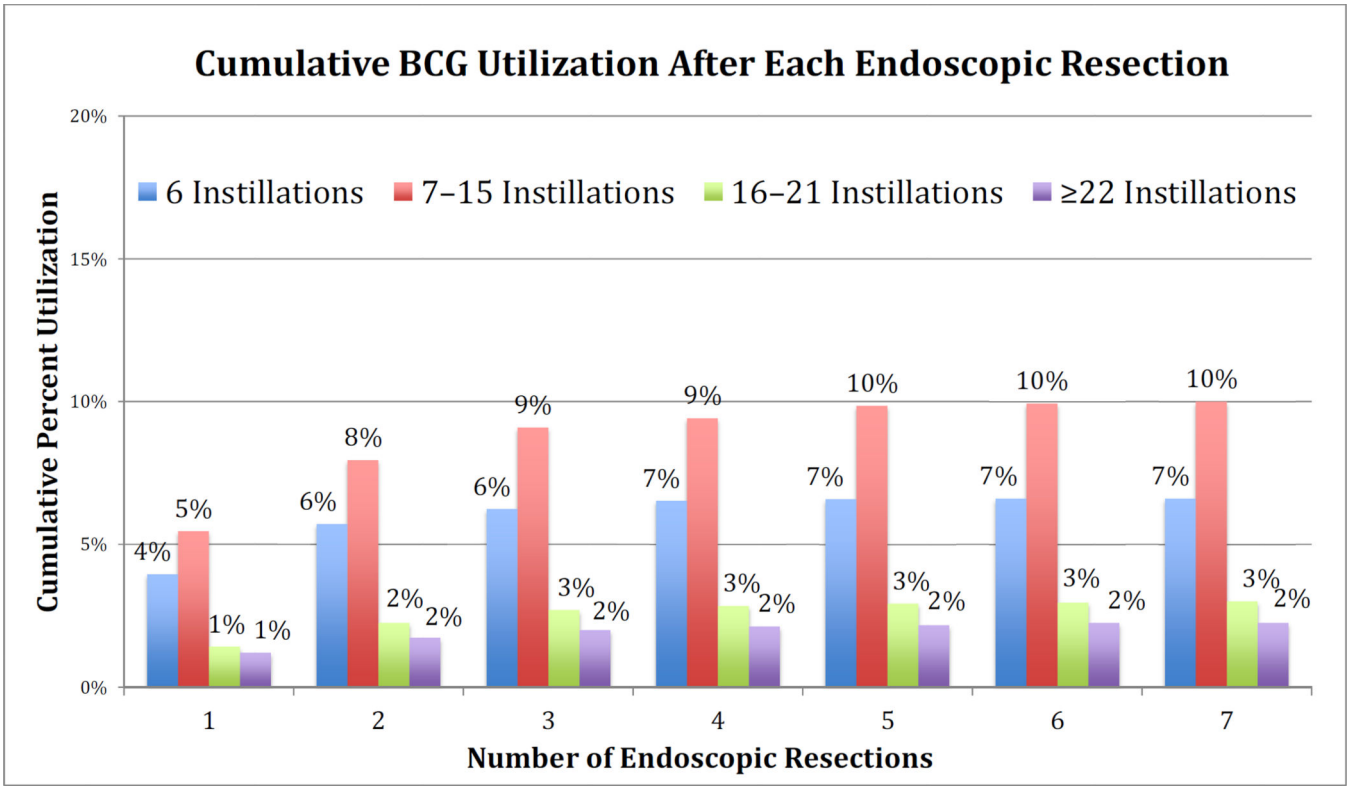

Figure 1.

Cumulative Utilization of BCG after each endoscopic resection. We found that with increasing resections, the percentage of patients receiving at least an induction course increases from 11% to 22%. Similarly, the number of patients receiving more than 15 instillations (more than one year of maintenance therapy) also increased from 2% to 5% with increasing recurrences.

Table 1

Cohort characteristics (*N*=4776)

Variables	Distribution	%
Age group		
66–69	699	14.6%
70–74	1245	26.1%
75–79	1222	25.6%
≥80	1610	33.7%
Gender		
Male	3686	77.2%
Female	1090	22.8%
Race/Ethnicity		
White	4364	91.4 %
Black	115	2.4%
Hispanic	126	2.6%
Other	171	3.6%
Marital status		
Other	1675	35.1 %
Married	3101	64.9%
Charlson Score		
0	3345	70.0%
1	980	20.5%
2	315	6.6%
≥3	136	2.9%
% with ≥4 years of college		
<15%	1004	21.0 %
15–25%	1227	25.7%
25%–35%	991	20.8%
>35%	1554	32.5%
Median household income		
<$35,000	800	16.8%
$35,000–$45,000	1141	23.9%
$45,000–$55,000	1229	25.7%
>$55,000	1606	33.6%
Region		
West	2442	51.1%
Midwest	946	19.8%
South	447	9.4%
Northeast	941	19.7%
Institution Type		
Non-academic	3350	74.8%
Academic	1127	25.2%

Variables	Distribution	%
Grade		
Poorly differentiated	3802	79.6%
Undifferentiated	974	20.4%
Stage		
Ta	1819	38.1 %
Tis	485	10.1%
T1	2472	51.8%

Table 2

Utilization of BCG stratified by the number endoscopic resections (Chi Square Analysis: p<0.01)

Number of Resections	No BCG	1–5 Instillations	6 Instillations	7–15 Instillations	16–21 Instillations	≥22 Instillations
1	947 (60%)	411 (26%)	112 (7%)	96 (6%)	13 (<1%)	*(<%)
2	517 (46%)	368 (33%)	89 (8%)	120 (11%)	19 (2%)	15 (1%)
3	275 (37%)	279 (38%)	43 (6%)	87 (12%)	42 (6%)	16 (2%)
4	171 (36%)	188 (40%)	30 (6%)	53 (11%)	19 (4%)	*(<3%)
5	90 (27%)	125 (38%)	20 (6%)	56 (17%)	19 (6%)	20 (6%)
6	54 (28%)	84 (44%)	*(<6%)	18 (9%)	13 (7%)	12 (6%)
7	91 (28%)	130 (40%)	12 (4%)	48 (15%)	19 (6%)	25 (8%)

* For these variables, results for n<11 were not reportable because of confidentiality issues.

Table 3

Multinomial logistic regression analysis of Utilization of BCG (baseline is no BCG)

Variables	Partial BCG RRR (95% CI)	Induction BCG RRR (95% CI)	Induction and Maintenance RRR (95% CI)
Age group (referent=66–69)			
70–74	0.83 (0.66–1.04)	0.77 (0.52–1.15)	1.00 (0.74–1.34)
75–79	0.79 (0.63–1.00) *	0.93 (0.63–1.37)	1.07 (0.79–1.44)
≥80	0.60 (0.49–0.75) **	0.61 (0.42–0.90) *	0.61 (0.46–0.83) **
Gender (referent=Male)			
Female	0.98 (0.82–1.18)	1.21 (0.89–1.64)	0.79 (0.62–1.00) *
Race/Ethnicity (referent=White)			
Black	0.94 (0.59–1.49)	1.18 (0.54–2.58)	0.75 (0.40–1.41)
Hispanic	0.74 (0.47–1.15)	1.10 (0.53–2.27)	0.54 (0.28–1.07)
Other	1.58 (1.08–2.31) *	2.16 (1.16–4.01) *	1.68 (1.02–2.75) *
Marital Status (referent=Not Married)			
Married	1.29 (1.10–1.52) **	1.53 (1.14–2.04) **	1.17 (0.95–1.44)
Charlson Score (referent=0)			
1	1.18 (0.99–1.40)	0.88 (0.64–1.22)	0.85 (0.67–1.08)
2	1.02 (0.77–1.35)	1.00 (0.62–1.61)	0.92 (0.64–1.34)
≥3	1.16 (0.77–1.76)	0.54 (0.21–1.38)	0.93 (0.54–1.62)
% with ≥4 years of college education (referent=<15%)			
15–25%	1.00 (0.81–1.25)	1.06 (0.71–1.57)	1.06 (0.79–1.42)
25%–35%	1.13 (0.88–1.46)	1.05 (0.66–1.66)	1.33 (0.96–1.86)
>35%	1.37 (1.05–1.79) *	0.95 (0.58–1.56)	1.34 (0.94–1.91)
Median household income (referent=<$35,000)			
$35,000–$45,000	0.82 (0.65–1.04)	0.93 (0.60–1.44)	0.80 (0.59–1.10)
$45,000–$55,000	0.85 (0.66–1.10)	0.97 (0.61–1.55)	0.73 (0.52–1.01)
>$55,000	0.79 (0.59–1.04)	1.45 (0.87–2.42)	0.81 (0.56–1.17)
Region (referent=West)			
Midwest	0.64 (0.53–0.79) **	1.10 (0.77–1.57)	0.80 (0.61–1.04)
South	1.28 (0.99–1.65)	1.85 (1.19–2.87) *	1.68 (1.22–2.31) **
Northeast	1.15 (0.94–1.42)	2.24 (1.60–3.12) **	1.58 (1.22–2.04) **
Institution Type (referent=Non-Academic)			
Academic	0.96 (0.81–1.14)	0.83 (0.61–1.13)	0.97 (0.78–1.21)
Grade (referent= Poorly differentiated)			
Undifferentiated	1.62 (1.36–1.93) **	1.11 (0.80–1.54)	1.62 (1.29–2.03) **
Stage (referent=Ta)			
Tis	1.34 (1.05–1.71) *	1.33 (0.86–2.05)	1.37 (0.98–1.89)

Variables	Partial BCG RRR (95% CI)	Induction BCG RRR (95% CI)	Induction and Maintenance RRR (95% CI)
T1	1.38 (1.19–1.60) **	1.57 (1.20–2.05) **	1.69 (1.38–2.06) **
Number of endoscopic resections (referent=1)			
≥1	1.28 (1.23–1.33) **	1.06 (0.98–1.14)	1.44 (1.37–1.51) **

RRR= Relative Risk Ratio

* = p<0.05

** = p<0.01

Baseline Cohort= Patients who did not receive any BCG therapy