Published in final edited form as:

J Urol. 2008 August ; 180(2): 520–524. doi:10.1016/j.juro.2008.04.016.

Predictors of Intravesical Therapy Use in Non-Muscle Invasive Bladder Cancer: Results from the Surveillance, Epidemiology, And End-Results Program's 2003 Patterns of Care Project

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Abstract

Introduction—In response to variations in cancer care, organizations have developed clinical guidelines. In the case of non-muscle invasive bladder cancer (also known as superficial bladder cancer), two similar sets of guidelines were released in the late 1990's that provide care recommendations. The purpose of this study was to examine patterns of intravesical therapy utilization in non-muscle invasive bladder cancer in 2003, to determine if disparities in the quality of cancer care remained.

Methods—Data from the Surveillance, Epidemiology, and End-Results (SEER) Program's 2003 bladder cancer patterns of care project were used. Subjects newly diagnosed with non-muscle invasive bladder cancer in 2003 were included. Clinical and sociodemographic data were obtained from the SEER program and detailed medical record review. Statistical analyses were performed to identify independent predictors of intravesical therapy use in the entire cohort and in a subset of high-risk patients.

Results—685 patients were included in the study. 216 (31.5%) patients received intravesical therapy. In addition to higher tumor stage and grade, intravesical therapy use was independently associated with race/ethnicity and geographic region. In the subset of 350 high-risk patients, 42% received intravesical therapy. Stage, grade, race/ethnicity and geographic region were independently associated with intravesical therapy use in this sub-cohort.

Conclusions—These data suggest there is underutilization of intravesical therapy, even in patients with high-risk non-muscle invasive bladder cancer, and disparities in the quality of care exist. Barriers to utilization of this cancer treatment must be identified, particularly in higher-risk individuals, and providers must become more aware of existing clinical guidelines.

Keywords

non-muscle invasive bladder cancer; intravesical therapy; disparities; quality of care; clinical guidelines

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Introduction

Geographic and ethnic variation in patterns of care has been noted for several common malignancies, including colon,¹ breast,² and prostate cancer.³ These disparities may arise from a lack of sound clinical evidence or consensus regarding how best to treat patients, as opposed to true regional or ethnic differences in quality of care.⁴ It has also been suggested that, in settings where clinical evidence exists, clinical guidelines may reduce these variations.⁵ Non-muscle invasive bladder cancer (also known as superficial bladder cancer) is a common malignancy for which clinical guidelines have been published.^{6, 7} These guidelines include specific recommendations regarding the appropriate use of intravesical agents, including bacilli Calmette-Guerin (BCG), mitomycin C, thiotepa, doxorubicin and interferon.

Complete transurethral resection of visible tumor burden is the current standard of care for patients with non-muscle invasive transitional cell carcinoma (TCC) of the bladder.⁸ However, except in cases with low-grade Ta tumors, treatment with transurethral resection alone is associated with a 60–80% chance of bladder recurrence within 5 years.⁹ Adjuvant intravesical instillation (either immunotherapeutic or chemotherapeutic agents) can reduce disease recurrence. First, introduced in 1976,¹⁰ the immunotherapeutic agent BCG has demonstrated proven efficacy in preventing disease recurrence. Chemotherapeutic agents such as mitomycin and doxorubicin are also effective in this setting, although equivalence to BCG has not been demonstrated.¹¹ Adjuvant intravesical therapy is also utilized in the setting of carcinoma-in-situ (CIS), where resection and fulguration are often inadequate to eradicate this diffuse form of cancer. BCG employed for CIS has a response rate of approximately 70%, and chemotherapeutic agents approximately 50%.¹² A meta-analysis regarding the use of adjuvant intravesical therapy was performed by the American Urological Association Bladder Cancer Guidelines Panel in 1999. The resulting clinical guidelines recommend adjuvant intravesical therapy for patients with high grade Ta disease, with T1 disease, and those with CIS disease.⁶ The National Comprehensive Cancer Network (NCCN) released clinical guidelines in 1998 that made similar recommendations.⁷

The purpose of this study was to examine patterns of intravesical therapy use in patients with non-muscle invasive bladder cancer. Although clinical guidelines on this topic were published by the American Urological Association (AUA) in 1999,⁶ we hypothesized that there would be significant geographic and racial variation in intravesical therapy use, representing true disparities in the quality of care as opposed to clinical uncertainty. Data from the National Cancer Institute's Surveillance, Epidemiology, and End-Results (SEER) 2003 Bladder Cancer Patterns of Care project were used to ensure that there was adequate time for the provider community to assimilate the 1999 AUA guidelines into clinical practice. As non-muscle invasive bladder cancer is primarily managed by urologists¹³ and the AUA is the primary professional organization for American urologists, we expected that the majority of practicing urologists would be aware of the recommendations of the 1999 guideline panel by 2003.

Methods

The SEER program regularly obtains data on all new cases of cancer diagnosed within defined geographic regions. Information is gathered on diagnosis, tumor characteristics, demographics, primary treatment, and survival status. To survey evolving patterns of care associated with specific cancers at the time of initial diagnosis, the National Cancer Institute (NCI) periodically conducts patterns of care (POC) projects, which supplement the annual SEER database by collecting additional detailed sociodemographic and clinical data (such as co-morbid conditions and adjuvant treatments) not otherwise captured in the SEER program.

The geographically-defined SEER registries provide the patient pool from which the POC projects sample their subjects.

Data from the most recent NCI bladder cancer POC project were used. To be included, subjects had to meet the following two criteria: 1) a first-time diagnosis of bladder cancer between January 1 and December 31, 2003 and; 2) bladder cancer must have been the first cancer diagnosed in this patient. Subjects were enrolled from the following SEER registries: New Jersey, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, Louisiana, San Jose/Monterey, San Francisco/Oakland, Los Angeles, and the remainder of California excluding SF/SJM/LA. We deliberately used an accepted sampling strategy that was designed to assemble a study cohort representative of the general population of bladder cancer patients in the United States. Initially, each participating SEER registry randomly sampled approximately 10% of bladder cancer cases from the pool of eligible patients. To ensure adequate representation, minority ethnic/racial groups were intentionally over-sampled. In other words, given the possibility that a 10% random sampling might result in few or no minority subjects (because in some registries, the proportion of minority subjects with bladder cancer was near or less than 10%), we intentionally over-sampled these patients. This approach, however, would result in a non-representative sample. Therefore, the final cohort was weighted to reflect the true ethnic and racial distribution of bladder cancer in the U.S. population during statistical analyses. This ensured that sample included adequate data from minorities, but was still reflective of the distribution of minorities in the general population. For the current study of intravesical therapy use in non-muscle invasive disease, all patients with non-transitional cell histology, synchronous upper tract disease, metastatic disease, and muscle-invasive disease were excluded, leaving 685 patients for inclusion in the study. For each subject, clinical and sociodemographic data were obtained from the SEER program and from detailed medical record review. Intravesical therapy use was defined as the receipt of any of the following intravesical agents, either in the peri- or post-operative period: BCG, 5-fluorouracil, bropirimine, DFMO (eflornithine), doxorubicin (adriamycin), gemcitabine, interferon, mitomycin C or thiotepa.

To measure the association between clinical/socio-demographic information and treatment with intravesical therapy, univariate regression was performed. A total of 12 sociodemographic and histopathologic variables were selected for evaluation. They included: tumor stage, tumor grade, tumor multifocality, comorbidities, age, gender, race, marital status, income level, insurance status, academic/teaching hospital status and geographic region. Variables significantly associated with intravesical therapy on univariate analysis were then included into a multivariate model. In addition, variables not significantly associated with intravesical therapy on univariate analysis, but thought to be plausible influencing factors, were arbitrarily forced into the multivariate model. The results of the multivariate analysis were reported as odds ratios. Subset analyses were then performed on a high-risk population defined by a risk stratification schema previously outlined by the 1999 AUA guidelines panel,⁶ as the guidelines recommend intravesical therapy in this population. This high-risk group included patients with grade 3 (G3) Ta disease, T1 disease, and/or CIS. Statistical analysis for this subset was carried out in identical fashion as the entire cohort. All statistical analyses were performed using the Survey Data Analysis (SUDAAN) statistical computer package and were weighted to reflect the source population from which the cases were sampled.

Results

A total of 685 patients with non-muscle invasive TCC of the bladder were included in the study. 216 (31.5%) patients received adjuvant intravesical therapy. Table 1 shows the baseline characteristics of the study population. On univariate analysis, intravesical therapy

utilization significantly varied with tumor stage and grade (see table 1). None of the other 10 variables were significantly associated with receipt of intravesical therapy. A logistic regression model was then created using 9 of the 12 variables (see table 2). This multivariate analysis revealed a significant association between higher tumor stage and grade and receipt of intravesical therapy. Specifically, patients with pT1 disease (odds ratio (OR)=3.32), CIS disease in the presence of Ta or T1 disease (OR=9.19) and grade III/IV disease (OR=3.69) were more likely to receive intravesical therapy. Importantly, no difference was seen between subjects with isolated CIS and Ta disease. Significant differences in intravesical therapy utilization were also noted between subgroups within the categories of race/ethnicity and geographic region. Specifically, patients from the Midwest were more likely to receive intravesical therapy than those from Los Angeles (OR=4.03) and patients of racial or ethnic groups other than white, black or Hispanic (likely consisting of Asian patients primarily) were more likely to receive intravesical therapy than white patients (OR=2.89).

To investigate patterns of intravesical therapy utilization specifically in those patients that who should be receiving it, according to the 1999 AUA and the 1998 National Comprehensive Cancer Network (NCCN)^{6, 7}, we examined intravesical therapy use in a higher-risk population that included all patients with non-muscle-invasive disease except those with Ta G1-2 disease. Three-hundred sixty-two higher-risk patients were identified. Twelve of these patients underwent immediate cystectomy without any intravesical therapy and were therefore excluded from analysis. This left 350 (52%) high-risk patients who likely would be considered appropriate candidates for intravesical therapy according to both sets of guidelines. However, only 147 (42%) received some form of intravesical therapy.

On multivariate logistic regression, stage, grade, race/ethnicity, and geographic region were independently associated with receipt of intravesical therapy in the high-risk group. (Table 3) In this select group of high-risk patients, stage and grade remained important predictors. Those with T1 disease (OR=14.24, 95% C.I.: 3.15–64.36) and those with Ta/T1 and concomitant CIS (OR=63.32, 95% CI: 10.36–390.85) received intravesical therapy at a significantly higher rate than those with Ta disease. Higher utilization rates were observed with grade 2 and grade 3/4 disease compared to grade 1 disease (OR=17.81, 95% CI: 1.63 – 194.15; and and OR=76.75, 95% CI: 7.64 – 770.78, respectively). Similar to the findings for the overall cohort, significant differences between groups in the categories of race/ethnicity and geographic region were observed in this higher-risk population. Patients in the “other” racial/ethnic group were more likely to have received intravesical therapy than white patients. (OR: 3.40, 95% CI: 1.27–9.09). Usage was significantly higher in the Midwest (OR: 10.74, 95% CI: 2.16–53.34) compared with the reference region of Los Angeles.

Discussion

Data from the 2003 NCI bladder cancer POC study indicate that intravesical therapy use is strongly associated with tumor stage and grade in all patients with non-muscle invasive TCC. This is in accordance with previously published clinical guidelines.^{6, 7} However, contrary to the guideline recommendations, we found that patients with isolated carcinoma-in-situ did not have higher rates of utilization compared to those with Ta disease. This may be partly attributable to the small sample size of this subset of patients; among the 685 patients included in the study, only 51 patients had isolated carcinoma-in-situ. Regardless, this finding represents a significant departure from standards of care recommended by commonly available guidelines.

Geographic variation in intravesical therapy use was also noted in this analysis. Geographic locale has been reported to be associated with differences in patterns of care for numerous other cancers.¹⁴ The reasons for this regional variation are unclear. Physical distance to

treatment centers¹⁵ and medical liability laws¹⁶ have been suggested as possible mechanisms by which geography influences treatment. In addition, lack of conclusive clinical evidence has also been cited as a possible explanation.⁴ In the case of intravesical therapy, however, there is good clinical evidence and clear guidelines and recommendations, ergo, one would expect less geographic variation. This, however, is not the case, underscoring the potential limitations of national clinical care guidelines in influencing regional practice patterns.

Results from this NCI bladder cancer POC study also indicate that race/ethnicity is independently associated with intravesical therapy; specifically, those in the “other” SEER racial/ethnic category (consisting mainly of Asians) had higher utilization rates than white patients. Racial/ethnic disparities in treatment have been reported in the past for lung, colorectal, and prostate cancer.^{14, 17, 18} With regard to bladder cancer, Konety and Joslyn¹⁹ reported that black patients were more likely to undergo radiation therapy than white patients. The current study also seems to indicate more aggressive bladder cancer treatment in racial/ethnic minority groups. Further studies are needed to confirm and better explain these observations.

Overall, data from the NCI bladder cancer POC study suggest that intravesical therapy is generally under-utilized. This is underscored by the dismal 42% application rate in the higher-risk group, for which there is general consensus that intravesical therapy is appropriate.^{6, 7} Given the relative ease and safety with which intravesical therapy can be administered, these results are concerning. Furthermore, it is worrisome that only 31% of patients with carcinoma-in-situ (in absence of concomitant papillary lesions) received intravesical treatment. Carcinoma in situ of the bladder treated by TUR alone is associated with a 60–80% progression rate to invasive disease within 5 years.¹¹ Intravesical BCG has clearly been shown to delay both recurrence and progression in this setting.¹² The reasons for the low intravesical therapy application rate for those with carcinoma-in-situ remain unclear.

As with all observational cohort analyses, the NCI bladder cancer POC study has limitations. Relevant to the current study, the reported data did not differentiate between one-dose peri-operative intravesical therapy and adjuvant intravesical therapy. However, this limitation likely would conservatively bias the study, as patients who receive only a peri-operative dose of intravesical therapy would be considered to have received adjuvant treatment. This implies that the underutilization of adjuvant intravesical therapy may be even greater than noted here. In addition, sample size concerns precluded us from looking at individual intravesical therapy agent use. However, previously published guidelines have not provided definitive recommendations for one agent over another and, therefore, this should not significantly impact the validity of our findings.

Conclusions

The NCI bladder cancer POC study documents that there is general underutilization of adjuvant intravesical therapy in non-muscle invasive bladder cancer. While use of intravesical therapy is appropriately driven by pathological factors such as grade and stage, there is also evidence for subtle racial/ethnic disparity and geographical variation in its application. Taken together, this study indicates that, while those with high stage and with high grade disease are more likely to receive intravesical therapy than those with lower risk disease, many patients who would benefit from this treatment still do not receive it. Further efforts should be made to identify barriers to application of this therapy particular in the higher-risk population.

Acknowledgments

Source of Funding: Dr. Huang was supported by the Ferdinand C. Valentine Fellowship for Laboratory or Clinical Research in Urology of The New York Academy of Medicine. The National Cancer Institute Bladder Cancer Patterns of Care study is funded through the following NCI contracts: N01-PC-35133, N01-PC-35135, N01-PC-35136, N01-PC-35137, N01-PC-35138, N01-PC-35139, N01-PC-35141, N01-PC-35142, N01-PC-35143, N01-PC-35145, N02-PC-15105, N02-PC-15106, N02-PC-15107

The authors would like to acknowledge the contributions of the participating SEER registries and staffs. Without their dedicated efforts this research could not be conducted.

Key of Definitions for Abbreviations

SEER	Surveillance, Epidemiology, and End-Results
BCG	Bacilli Calmette-Guerin
TCC	transitional cell carcinoma
CIS	carcinoma-in-situ
NCCN	National Comprehensive Cancer Network
AUA	American Urological Association
NCI	National Cancer Institute
POC	Patterns of Care

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Table 1

Patient clinical and demographic characteristics for patients in the POC study with non-muscle invasive disease (n=685). Percentages may not add up to 100% due to rounding.

Characteristic	Count (unweighted %)	Weighted percentage (%)	Proportion Receiving Intravesical Therapy (weighted %)	Univariate OR for use of intravesical therapy (95%CI)	p value
Age					
<60	181 (26%)	25%	27%	referent	
60-69	175 (26%)	27%	42%	1.95 (0.74-5.14)	.18
70-79	213 (31%)	32%	37%	1.58 (0.67-3.76)	.30
80+	116 (17%)	16%	18%	0.59 (0.22-1.64)	.31
Gender					
Female	279 (41%)	23%	29%	referent	
Male	406 (59%)	77%	34%	1.25 (0.67-2.32)	.49
Race/Ethnicity					
White	258 (38%)	87%	33%	referent	
Black	141 (21%)	4%	29%	0.83 (0.44-1.54)	.55
Hispanic	156 (23%)	5%	26%	0.71 (0.39-1.31)	.28
Other	130 (19%)	4%	46%	1.75 (0.93-3.28)	.08
Marital Status					
Not currently married	294 (43%)	33%	27%	referent	
Married	391 (57%)	67%	35%	1.48 (0.76-2.91)	.25
Geographic Regions					
Los Angeles	117 (17%)	11%	19%	referent	
Northeast (CT, NJ)	109 (16%)	21%	36%	2.50 (0.74-8.52)	.14
Midwest (Detroit, Iowa)	74 (11%)	11%	37%	2.63 (0.76-9.05)	.13
South (Atlanta, Louisiana)	100 (15%)	10%	33%	2.16 (0.63-7.43)	.22
West (Hawaii, Seattle, Utah)	125 (18%)	13%	33%	2.15 (0.67-6.94)	.20
CA other than LA	160 (23%)	34%	33%	2.15 (0.55-8.43)	.27
Income					

Characteristic	Count (unweighted %)	Weighted percentage (%)	Proportion Receiving Intravesical Therapy (weighted %)	Univariate OR for use of intravesical therapy (95%CI)	p value
<20,000	79 (12%)	5%	30%	referent	
20–50,000	245 (36%)	30%	33%	1.16 (0.27–4.91)	.84
50,001–75,000	247 (36%)	43%	34%	1.20 (0.29–4.97)	.81
>75,000	114 (17%)	22%	29%	0.96 (0.24–3.82)	.96
Health Insurance					
Yes	657 (97%)	98%	33%	referent	
No	21 (3%)	2%	20%	0.52 (0.10–2.71)	.44
Teaching Hospital					
No	353 (52%)	60%	34%	referent	
Yes	330 (48%)	40%	31%	0.86 (0.43–1.73)	.68
Comorbidity					
0	171 (25%)	23%	32%	referent	
1–2	221 (32%)	32%	40%	1.40 (0.53–3.74)	.50
3+	293 (43%)	45%	28%	0.82 (0.37–1.80)	.62
Tumor Stage					
Ta	288 (42%)	46%	16%	referent	
T1	189 (28%)	28%	44%	4.11 (1.56–10.79)	.004
CIS Only	51 (7%)	7%	31%	2.37 (0.72–7.85)	.16
Ta/T1 + Cis	157 (23%)	19%	55%	6.39 (2.49–16.43)	<.001
Grade					
I	124 (19%)	13%	23%	referent	
II	286 (44%)	51%	24%	1.05 (0.35–3.16)	.93
III/IV	246 (38%)	37%	47%	2.98 (1.06–8.39)	.04
Multifocal Disease					
No	514 (77%)	79%	31%	referent	
Yes	156 (23%)	21%	38%	1.36 (0.63–2.95)	.44

Table 2

Results of multivariate logistic regression analysis for receipt of intravesical therapy for all patients in POC study with non-muscle invasive disease (n=685)

Characteristic	Multivariate Adjusted OR (95%CI)	p value
Tumor stage		
Ta	referent	
T1	3.32 (1.35–8.20)	.009
Ta/T1+CIS	9.19 (3.35–25.20)	<.001
CIS only	0.77 (0.17–3.56)	.74
Grade		
I	referent	
II	1.46 (0.41–5.24)	.56
III/IV	3.69 (1.17–11.64)	.03
Multifocality		
No	referent	
Yes	0.96 (0.42–2.18)	.92
Age		
<60	referent	
60–69	2.35 (0.87–6.34)	.09
70–79	1.50 (0.64–3.51)	.35
80+	0.58 (0.21–1.63)	.30
Comorbidities		
0	referent	
1–2	1.12 (0.29–4.29)	.87
3+	0.59 (0.17–2.04)	.40
Gender		
Female	referent	
Male	1.20 (0.57–2.53)	.63
Race/Ethnicity		
White	referent	
Black	0.72 (0.35–1.50)	.38
Hispanic	0.80 (0.34–1.89)	.61
Other	2.89 (1.35–6.19)	.006
Geographic Region		
Los Angeles	referent	
other CA	2.06 (0.57–7.40)	.27
Northeast	2.37 (0.69–8.10)	.17
Midwest	4.03 (1.08–15.03)	.04
South	3.14 (0.84–11.75)	.09

Characteristic	Multivariate Adjusted OR (95%CI)	p value
West excluding CA	2.35 (0.79–7.06)	.13
Marital Status		
Non-Married	referent	
Married	1.73 (0.87–3.44)	.12

Table 3

Results of Multivariate Analysis for Receipt of Intravesical Therapy for High-Risk Patients with Non-Muscle Invasive Disease (n=350)

Characteristic	Proportion Receiving Intravesical therapy (weighted %)	Adjusted Odds Ratio (95%CI)	p value
Tumor stage			
Ta	15%	referent	
T1	45%	14.24 (3.15–64.36)	<.001
Ta/T1+CIS	72%	63.62(10.36–390.85)	<.001
CISonly	32%	4.90 (0.67–36.16)	.12
Grade			
I	2%	referent	
II	22%	17.81 (1.63–194.15)	.02
III/IV	47%	76.75 (7.64–770.78)	<.001
Multifocality			
No	37%	referent	
Yes	49%	1.58 (0.55–4.57)	.39
Age			
<60	32%	referent	
60–69	52%	2.87 (0.88–9.41)	.08
70–79	48%	1.64 (0.52–5.21)	.40
80+	23%	0.63 (0.15–2.66)	.53
Comorbidities			
0	37%	referent	
1–2	47%	2.80 (0.90–8.70)	.08
3+	38%	1.47 (0.45–4.83)	.52
Gender			
Female	35%	referent	
Male	42%	1.60 (0.50–5.13)	.43
Race/Ethnicity			
White	40%	referent	
Black	47%	0.95 (0.31–2.90)	.93
Hispanic	33%	0.94 (0.30–2.95)	.92
Other	60%	3.40 (1.27–9.09)	.01
Geographic Region			
Los Angeles	33%	referent	
other CA	37%	1.55 (0.31–7.67)	.59
Northeast	41%	1.49 (0.34–6.47)	.60
Midwest	60%	10.74 (2.16–53.34)	.004
South	40%	2.23 (0.26–19.13)	.46

Characteristic	Proportion Receiving Intravesical therapy (weighted %)	Adjusted Odds Ratio (95%CI)	p value
West excluding CA	41%	3.39 (0.72–15.95)	.12
Marital Status			
Non-Married	36%	referent	
Married	43%	1.67 (0.59–4.77)	.34