Original Article

Compliance With Guidelines for Patients With Bladder Cancer

Variation in the Delivery of Care

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BACKGROUND: Clinical practice guidelines for the management of patients with bladder cancer encompass strategies that minimize morbidity and improve survival. In the current study, the authors sought to characterize practice patterns in patients with high-grade non–muscle-invasive bladder cancer in relation to established guidelines. **METHODS:** Surveillance, Epidemiology and End Results (SEER)-Medicare–linked data were used to identify subjects diagnosed with high-grade non–muscle-invasive bladder cancer between 1992 and 2002 who survived at least 2 years without undergoing definitive treatment (n = 4545). The authors used mixed-effects modeling to estimate the association and partitioned variation of patient sociodemographic, tumor, and provider characteristics with compliance measures. **RESULTS:** Of the 4545 subjects analyzed, only 1 received all the recommended measures. Approximately 42% of physicians have not performed at least 1 cystoscopy, 1 cytology, and 1 instillation of immunotherapy for a single patient nested within their practice during the initial 2-year period after diagnosis. After 1997, only use of radiographic imaging (odds ratio [OR], 1.19; 95% confidence interval [95% CI], 1.03-1.37) and instillation of immunotherapy (OR, 1.67; 95% CI, 1.39-2.01) were found to be significantly increased. Surgeon-attributable variation for individual guideline measures (cystoscopy, 25%; cytology, 59%; radiographic imaging, 10%; intravesical chemotherapy, 45%; and intravesical immunotherapy, 26%) contributes to this low compliance rate. **CONCLUSIONS:** There is marked underuse of guideline-recommended care in this potentially curable cohort. Unexplained provider-level factors significantly contribute to this low compliance rate. Future studies that identify barriers and modulators of provider-level adoption of guidelines are critical to improving care for patients with bladder cancer. *Cancer* **2011;000:000–000.**

KEYWORDS: high grade non-muscle-invasive bladder cancer, guideline adherence, quality of care, variation in care.

Although bladder cancer is not routinely referred to as a chronic condition, it shares many properties with other medical ailments. First, it is the fifth most frequent malignancy (with an estimated 70,980 new cases diagnosed in 2009), and accounts for 7% of all incident cancer cases.[1] Second, bladder cancer requires close surveillance because of its high recurrence and progression rates (50%-70%), with their attendant morbidity.[2] Third, it is costly; due to the prolonged natural history of non-muscle-invasive bladder cancer (535,000 bladder cancer survivors) and the invasive nature of follow-up and treatment strategies, it remains the most expensive malignancy to treat on a per-patient basis ($96,000–$187,000).[3] To address these concerns, best-practice guidelines (such as those set forth by the National Comprehensive Cancer

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We acknowledge the efforts of the Applied Research Program at the National Cancer Institute; the Office of Research, Development, and Information at the Centers for Medicare and Medicaid Services; Information Management Services Inc; and the Surveillance, Epidemiology, and End Results (SEER) program tumor registries in the creation of the SEER-Medicare database.

This study used the linked SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors. Dr. Chamie had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

DOI: 10.1002/cncr.26198, **Received:** February 16, 2011; **Revised:** March 22, 2011; **Accepted:** March 24, 2011, **Published online** in Wiley Online Library (wileyonlinelibrary.com)

Network [NCCN] in 1998, the American Urological Association [AUA] in 1999, and the European Association of Urology [EAU] in 2002) were established in an attempt to the minimize the morbidity and mortality associated with the recurrence and progression of non-muscle-invasive bladder cancer.

Despite the infusion of surveillance and treatment strategies into many areas of education, specialty certification, and reimbursement models, practice patterns do not appear to reflect the ubiquitous adoption of these guidelines. In an analysis of a single quality-of-care measure (endoscopic surveillance), Schrag et al, using a relaxed definition of endoscopic surveillance (once every 6 months instead of once every 3 months), discovered that only 40% of patients underwent the recommended number of procedures.[4] Using MEDSTAT claims data, Madeb et al discovered that of 14,677 subjects with non–muscle-invasive bladder cancer who underwent resection of their bladder tumor, only 49 (0.3%) received perioperative instillation of chemotherapy.[5] Moreover, established clinical practice guidelines incorporate a comprehensive surveillance and treatment schedule and not just a single quality-of-care measure.[6,7] Because of the invasive nature of the surveillance and treatment strategies, nonadherence with clinical practice guidelines may be attributed to patient factors such as advanced age or pre-existing comorbid conditions. In the context of low compliance, we sought to characterize practice patterns on a population level using claims data.

MATERIALS AND METHODS

Data Source

We used the Surveillance, Epidemiology and End Results (SEER)-Medicare–linked database of the National Cancer Institute (NCI), which contains clinical, demographic, and medical claims data for individuals aged $\geq$ 65 years, to identify bladder cancer patients who were diagnosed between 1992 and 2002. SEER data are summarized in the Patient Entitlement and Diagnosis Summary File (PEDSF) and contain demographics (age, gender, race/ethnicity, marital status, and county-level socioeconomic information), tumor characteristics (histology, grade, and TNM and American Joint Committee on Cancer summary stage), and follow-up information (vital status, cause of death, and time to death from date of diagnosis). The PEDSF was linked with 100% of the Medicare claims from the inpatient, outpatient, and national claims history files and was restricted to subjects who had Medicare fee-for-service coverage and for whom Medicare Parts A and B claims data were available for 12 months prior and 24 months after the diagnosis of bladder cancer.[8]

Study Population

The cohort was comprised of patients aged $\geq$ 66 years with an incident diagnosis of high-grade (poor or undifferentiated tumor), urothelial (histology codes 8120 or 8130), non–muscle-invasive (Ta, Tis, or T1) bladder cancer (International Classification of Diseases, Ninth Revision [ICD-9] codes 188.0–188.9 and 233.7) who were diagnosed between January 1, 1992 and December 31, 2002, and for whom claims data were available through December 31, 2004. Although beneficiaries are eligible for Medicare coverage at age 65 years, we limited our cohort to those aged $\geq$ 66 years to allow at least 1 year of eligibility in Medicare before the date of bladder cancer diagnosis to ascertain comorbidity data. We restricted our analysis to those patients who survived at least 2 years and did not undergo definitive treatment (radical cystectomy, radiation therapy, or systemic chemotherapy) during that timeframe. Receipt of definitive treatment was derived from the PEDSF as well as ICD-9 and Healthcare Common Procedure Coding System (HCPCS) codes from the Medicare claims record.

Quality-of-Care Measures

Although there are slight variations between the clinical practice guidelines from the NCCN, AUA, and EAU, we amalgamated the 3 published guidelines to generate compliance measures a priori. The general consensus from these guidelines is that because patients with high-grade non–muscle-invasive bladder cancer have high rates of disease recurrence and progression, they should undergo frequent surveillance (to detect recurrence and progression) and be treated with intravesical agents (to minimize recurrence and progression). Frequent lower urinary tract surveillance is specified as cystoscopy and urine cytology every 3 months for the first 2 years after diagnosis. Upper tract imaging surveillance should be performed at the time of diagnosis and at least every 2 years thereafter. Treatment strategies include instillation of perioperative mitomycin C (ie, an intravesical chemotherapeutic) after any transurethral urethral resection of the bladder tumor (TURBT) and an induction course of immunotherapy, Bacillus Calmette-Guérin (BCG), postoperatively. Translated into claims data, we anticipated that patients with high-grade non–muscle-invasive bladder cancer should undergo at least 8 cystoscopies, 8 cytologies, 2 upper tract imaging studies, 1 instillation of perioperative mitomycin C, and 6 instillations of BCG (or another agent) after the diagnostic TURBT was performed. We relaxed the definition to count as compliant the use of BCG anytime during the first 2 years provided the first instillation occurred within 90 days of diagnosis (to distinguish providers who instilled BCG based on the initial diagnosis [the "preventers,"] from those who used it in response to recurrences [the "reactors"]). We also relaxed the definition of perioperative mitomycin C to include a claim for instillation of any chemotherapeutic within 3 days of TURBT. Although recent guidelines have highlighted compelling evidence of the utility of repeat TURBT in patients with T1 disease, more frequent imaging of the upper tract, and maintenance BCG (an induction course plus 3 weekly instillations at 3, 6, 9, 12, 18, 24, 30, and 36 months after diagnosis), we used an a fortiori argument with less stringent requirements and an exhaustive set of ICD-9 and HCPCS codes from the Medicare claims record to posit that if noncompliance with our measures were found to be high, then the noncompliance rate with more stringent criteria would be far greater.

Study Variables

From the PEDSF, we determined patient age (ages 66-69 years, 70-74 years, 75-79 years, and $\geq$ 80 years), gender, race/ethnicity (white, black, Hispanic, and other), marital status (married or other), tumor grade (poor or undifferentiated tumor), T classification (Ta, Tis, and T1), and year of diagnosis (categorical: 1992-1997 and 1998-2002). We imputed subject socioeconomic status by using 2000 US Census data in the PEDSF to derive quartiles of ZIP code-level median household income (<$35,000, $35,000-$45,000, $45,000-$55,000, and >$55,000) and percentage of residents aged $\geq$ 25 years with at least 4 years of college education (categorical: < 15%, 15%-25%, 25%-35%, and > 35%).[9] We used the Klabunde et al modification of the Charlson comorbidity index to quantify the severity of pre-existing comorbidities (0, 1, 2, and $\geq$ 3).[10,11] For each patient, we noted the provider and institution at which the initial bladder cancer was diagnosed using the Unique Physician Identifier Number (UPIN) and the corresponding Medicare provider number, respectively. The Medicare provider number was linked with the American Medical Association Masterfile to derive institution type (medical school affiliation as well as NCI designation as a comprehensive cancer center). We discovered that only 4 patients (0.1%) were diagnosed at an NCI-designated cancer center without a medical school affiliation, and these patients were subsequently included with those diagnosed at an NCI-designated cancer center with a medical school affiliation. Institution type was therefore stratified into 1) academic cancer center (NCI-designated cancer center with a medical school affiliation); 2) academic non-cancer center (not NCI-designated as a cancer center but with a medical school affiliation); 3) nonacademic, non-cancer center (not NCI-designated as a cancer center and no medical school affiliation); and 4) unknown. Cumulative volumes for the surgeon (using UPIN) and hospital (using the Medicare provider number) were calculated after adjusting for the inclusion of new providers and the 4 new SEER registries in 2000. Caseload for endoscopic resections was stratified into low, medium, and high for each surgeon (low indicates < 4; medium, 4-11; and high, $\geq$ 12) and hospital (low indicates < 11; medium, 11-25; and high, > 25). We generated a region variable (West, Midwest, South, and Northeast) from the SEER registry.

Statistical Analysis

We report differences in the means and percentages compliant with the quality-of-care measures using the 2-sample Student *t* test and chi-square test, respectively. This was performed on a patient and provider level. The provider-level compliance rate was defined as adherence with the measure(s) of interest on at least 1 patient nested within that provider's practice. This method of quantifying compliance was used to counter the argument that because of the invasive and frequent nature of the surveillance and treatment strategies, patients with bladder cancer are noncompliant. Hence, a physician only needs to deliver care that is consistent with a corresponding measure just once to be categorized as compliant.

Because receipt of services may be clustered on the treating physician, we generated mixed-effects logistic regression models for each primary outcome (receipt of individual measures) to account for both the fixed and random effects associated with compliance with the quality-of-care measures. For our mixed-effects models, we defined the following individual outcome measures: 1) $\geq$ 8 cystoscopies, 2) $\geq$8 cytologies, 3) $\geq$2 imaging studies, 4) perioperative instillation of mitomycin C, and 5) $\geq$6 instillations of BCG postoperatively. Each model included patient age, gender, race, marital status, Charlson comorbidity score, education, household income, region, year of diagnosis, tumor grade and stage, institution type, and hospital and surgeon volume as fixed terms, whereas each UPIN was appended to the random effects part of the mixed-effects model.

Table 1. Cohort Characteristics (*n*=4545)

Variable	No.	%
Age group, y		
66-69	649	14.3%
70-74	1189	26.2%
75-79	1175	25.8%
≥80	1532	33.7%
Gender		
Male	3497	76.9%
Female	1048	23.1%
Race		
White	4151	91.3%
Black	109	2.4%
Hispanic	122	2.7%
Other	163	3.6%
Marital		
Not married	1588	34.9%
Married	2957	65.1%
Charlson score		
0	3181	70.0%
1	932	20.5%
2	303	6.7%
≥3	129	2.8%
ZIP code education		
<15%	958	21.1%
15-25%	1171	25.8%
25%-35%	938	20.6%
>35%	1478	32.5%
ZIP code income		
<$35,000	751	16.5%
$35,000-$45,000	1094	24.1%
$45,000-$55,000	1171	25.7%
>$55,000	1530	33.7%
Region		
West	2329	51.2%
Midwest	897	19.7%
South	420	9.2%
Northeast	899	19.8%
Year		
1992-1997	1698	37.4%
1998-2002	2847	62.6%
Surgeon volume		
Low (<4)	718	15.8%
Medium (4-11)	2373	52.2%
High (>11)	1454	32.0%
Hospital volume		
Low (<11)	1487	32.7%
Medium (11-25)	1533	33.7%
High (>25)	1525	33.6%
Institution type		
Nonacademic non-cancer center	3217	70.8%
Academic non-cancer center	979	21.5%
Academic cancer center	85	1.9%
Unknown	264	5.8%
Grade		
Poorly differentiated	3622	79.7%
Undifferentiated	923	20.3%
T classification		
Ta	1727	38.0%
Tis	458	10.1%
T1	2360	51.9%

Partitioning of variance was conducted using the following equation: $\frac{\sigma_F^2}{\sigma_F^2+\tau_0^2+\sigma_R^2}$ in which σ_F^2 is defined as the variance of the fixed term (covariate or group of covariates) derived from the latent-variable approach; τ_0^2 is defined as the intercept (level 2) variance; and σ_R^2 is defined as the level 1 residual variance ($\pi^2/3$ in our logistic model). Groups of patient- and provider-level variables were included as fixed effects for each outcome measure. We stratified these groups as the following: 1) sociodemographic (patient age, race/ethnicity, gender, education, and income), 2) severity of illness (tumor grade and stage and Charlson comorbidity score), 3) provider characteristics (hospital and surgeon volume and institution type and region), and 4) year of diagnosis. The surgeon-attributable residual intraclass correlation coefficient (ICC), representing unexplained provider-level variance, was estimated from the full model of each outcome measure. Unexplained surgeon factors were derived from the ICC of the unconditional or null model of each outcome measure. To test the robustness of these findings, the proportions of attributable variance were recomputed only for providers caring for > 3 patients. Sensitivity analysis using year of diagnosis was performed for the mixed-effects model. Although the estimates and the odds ratios changed slightly, there was no change in which the variables were significant. In addition, we used year of diagnosis as a continuous variable when partitioning variance, to augment explained variance. We conducted all analyses with STATA software (version 11.1; StataCorp, College Station, Tex). All statistical tests were 2-tailed, and the probability of a type I error was set at $< .05$. The institutional review board at the University of California at Los Angeles approved the study protocol.

RESULTS

We identified 4545 subjects who were nested within 1536 provider practices and 667 institutions nationally. The plurality were octogenarian, male, white, married, and without any comorbid conditions, and were diagnosed with a poorly differentiated T1 tumor. The majority were diagnosed in the West, by a medium-volume surgeon (a provider who diagnosed 4-11 bladder cancer patients within an 11-year period) in a nonacademic, non-cancer center and after 1997. The distribution of the cohort is depicted in Table 1.

Univariate analysis (Table 2) demonstrated that with the exception of receipt of an induction course of

Table 2. Patient and Provider Compliance (On at Least 1 Occasion) Stratified by Year the NCCN Guidelines for Non-Muscle-Invasive Bladder Cancer Were Established

	No. of Subjects Compliant (%)			No. of Providers Compliant with ≥1 Patient (%)		
Quality-of-Care Measures	**1992-1997 (*n*=1698)**	**1998-2002 (*n*=2847)**	***P***	**1992-1997 (*n*=725)**	**1998-2002 (*n*=1272)**	***P***
≥8 cystoscopies	93 (4.6%)	131 (4.7%)	.89	70 (9.7%)	126 (9.9%)	.86
≥8 cytologies	98 (5.5%)	143 (4.6%)	.19	**80 (11.0%)**	**106 (8.3%)**	**.04**
≥2 upper tract imaging studies	801 (47.2%)	1446 (50.8%)	.18	491 (67.7%)	909 (71.5%)	.08
Perioperative mitomycin C	48 (2.8%)	92 (3.2%)	.44	43 (5.9%)	73 (5.7%)	.86
≥6 instillations of BCG, first dose within 90 d	**349 (20.5%)**	**824 (28.9%)**	**<.001**	**240 (33.1%)**	**564 (44.3%)**	**<.001**

Abbreviations: BCG, Bacillus Calmette-Guérin; NCCN, National Comprehensive Cancer Network.

Table 3. Progressive Relaxation of Guidelines Depicting the No. of Subjects in Receipt of Compliant Care and the No. of Providers Who Delivered Compliant Care to ≥1 Patient

	Subjects (*n*=4545)	**Providers (*n*=1536)**
Compliance Criteria	**No. (%)**	**No. (%)**
≥8 cystoscopies and ≥8 cytologies and ≥6 BCG	19 (0.4%)	16 (1.0%)
≥8 cystoscopies and ≥8 cytologies and ≥1 BCG	23 (0.5%)	22 (1.4%)
≥8 cystoscopies and ≥4 cytologies and ≥6 BCG	42 (0.9%)	40 (2.6%)
≥4 cystoscopies and ≥4 cytologies and ≥6 BCG	597 (13.1%)	398 (25.9%)
≥4 cystoscopies and ≥4 cytologies and ≥1 BCG	799 (17.6%)	479 (31.2%)
≥4 cystoscopies and ≥1 cytology and ≥1 BCG	1527 (33.6%)	823 (53.6%)
≥1 cystoscopy and ≥1 cytology and ≥1 BCG	1703 (37.5%)	891 (58.0%)
≥1 cystoscopy and ≥1 BCG	2437 (53.6%)	1148 (74.7%)
≥1 cystoscopy	4373 (96.2%)	1510 (98.3%)

Abbreviation: BCG, Bacillus Calmette-Guérin.

BCG (20.5%-28.9%; $P < .001$), the percentage of subjects in receipt of compliant care did not significantly increase after publication of clinical practice guidelines. This finding was further echoed on provider-level compliance. With the exception of an induction course of BCG (33.1%-44.3%; $P < .001$), there was no statistically significant increase noted in provider compliance. In fact, the number of providers who had used ≥8 cytologies decreased (11.0% to 8.3%; $P = .04$).

With regard to comprehensive care, of the 4545 subjects who survived and did not undergo definitive treatment during the initial 2 years after diagnosis, only 1 case was compliant with all the quality-of-care measures. As shown in Table 3, relaxing the definition so as not to necessarily require upper tract imaging or perioperative mitomycin C, yet to mandate ≥ 8 cystoscopies, ≥ 8 cytologies, and an induction course of BCG, yielded 19 cases (0.4%). In fact, nearly two-thirds of the cohort did not have receipt of at least ≥ 1 cystoscopy, ≥ 1 cytology, and a single instillation of intravesical BCG (62.5%). We then repeated the analysis by determining the number of providers who were compliant with a corresponding quality-of-care measure on at least 1 patient. We found that 99% of providers did not provide ≥ 8 cystoscopies, ≥ 8 cytologies, and ≥ 6 instillations of BCG within a 2-year period of time after diagnosis to a single patient. In addition, 42% of providers have not performed at least 1 cystoscopy, 1 cytology, and 1 instillation of immunotherapy for a single patient nested within their practice during the initial 2-year period after diagnosis.

Table 4 presents a multivariate, mixed-effects logistic regression model assessing receipt for each outcome measure (cystoscopy, cytology, imaging, mitomycin C, and BCG instillation). For cystoscopy, female gender and academic affiliation were found to be independent predictors of higher odds of compliance. For cytology, octogenarians had lower odds, whereas education (> 35% of adults with a 4-year college education), region (Midwest), academic affiliation, and T classification (Tis) were all found to be associated with higher odds of compliance. For imaging studies, octogenarians and increasing surgeon volume (medium and high) were found to be

Table 4. Mixed-Effects Model Predicting Compliance With Individual Measures

Variables	≥8 Cystoscopies OR (95% CI)	≥8 Cytologies OR (95% CI)	≥2 Imaging Studies OR (95% CI)	≥1 Perioperative Mitomycin C OR (95% CI)	≥6 Postoperative BCG OR (95% CI)
Age group, y					
66-69	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
70-74	1.39 (0.86-2.25)	0.94 (0.56-1.56)	1.02 (0.83-1.26)	1.35 (0.72-2.50)	0.94 (0.73-1.21)
75-79	1.04 (0.63-1.72)	0.78 (0.45-1.33)	0.97 (0.79-1.20)	0.78 (0.40-1.53)	0.78 (0.60-0.99)[a]
≥80	0.89 (0.54-1.45)	0.39 (0.23-0.68)[a]	0.77 (0.63-0.94)[a]	1.25 (0.67-2.33)	0.52 (0.40-0.67)[a]
Gender					
Male	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Female	1.48 (1.03-2.11)[a]				
	1.11 (0.70-1.75)	0.94 (0.80-1.11)	0.98 (0.58-1.65)	1.00 (0.81-1.23)	
Race					
White	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Black	0.62 (0.18-2.16)	1.58 (0.57-4.36)	0.91 (0.60-1.40)	0.24 (0.03-2.08)	0.40 (0.21-0.77)[a]
Hispanic	0.95 (0.35-2.55)	0.58 (0.15-2.20)	1.15 (0.77-1.72)	0.53 (0.11-2.49)	0.81 (0.48-1.37)
Other	1.08 (0.49-2.38)	0.44 (0.11-1.71)	1.16 (0.81-1.67)	2.78 (1.18-6.56)[a]	1.06 (0.67-1.68)
Marital status					
Not married	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Married	1.07 (0.76-1.50)				
	1.37 (0.91-2.08)	0.99 (0.86-1.15)	1.30 (0.82-2.05)	1.22 (1.02-1.47)[a]	
Charlson score					
0	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
1	0.85 (0.59-1.24)	0.87 (0.56-1.37)	1.19 (1.02-1.40)[a]	1.14 (0.71-1.83)	0.99 (0.81-1.21)
2	0.48 (0.23-1.03)	0.84 (0.40-1.74)	1.41 (1.09-1.82)[a]	1.42 (0.69-2.92)	1.03 (0.75-1.42)
≥3	0.15 (0.02-1.10)	1.40 (0.51-3.88)	1.39 (0.94-2.05)	1.62 (0.56-4.67)	0.74 (0.45-1.21)
ZIP code education					
<15%	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
15%-25%	1.24 (0.74-2.07)	1.23 (0.68-2.21)	1.13 (0.92-1.38)	1.45 (0.77-2.71)	1.03 (0.79-1.34)
25%-35%	1.15 (0.64-2.07)	1.19 (0.58-2.45)	0.99 (0.78-1.25)	1.42 (0.68-2.96)	0.99 (0.72-1.34)
>35%	1.45 (0.79-2.67)	2.64 (1.27-5.50)[a]	0.94 (0.73-1.21)	0.67 (0.29-1.55)	1.21 (0.87-1.68)
ZIP code income					
<$35,000	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
$35,000-$45,000	1.00 (0.57-1.75)	0.81 (0.42-1.56)	0.80 (0.64-1.01)	0.72 (0.37-1.43)	0.83 (0.62-1.10)
$45,000-$55,000	1.06 (0.59-1.90)	0.82 (0.41-1.67)	1.02 (0.80-1.29)	0.89 (0.43-1.83)	0.87 (0.64-1.18)
>$55,000	1.09 (0.57-2.06)	0.54 (0.24-1.18)	1.24 (0.95-1.62)	1.16 (0.51-2.61)	0.93 (0.66-1.31)
Region					
West	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Midwest	0.87 (0.52-1.46)	2.60 (1.31-5.16)[a]	1.84 (1.47-2.30)[a]	1.09 (0.55-2.16)	0.79 (0.57-1.09)
South	0.65 (0.33-1.30)	1.31 (0.57-2.98)	1.69 (1.31-2.19)[a]	1.03 (0.44-2.40)	1.60 (1.15-2.22)[a]
Northeast	1.32 (0.85-2.05)	1.81 (0.94-3.47)	1.19 (0.97-1.46)	0.42 (0.20-0.89)[a]	1.48 (1.12-1.95)[a]
Year					
1992-1997	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
1998-2002	1.02 (0.73-1.42)	0.72 (0.48-1.08)	1.19 (1.03-1.37)[a]	1.17 (0.75-1.83)	1.67 (1.39-2.01)[a]
Surgeon volume					
Low (<4)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Medium (4-11)	1.00 (0.64-1.57)	0.98 (0.55-1.74)	0.82 (0.67-0.99)[a]	2.65 (1.24-5.65)[a]	0.83 (0.65-1.07)
High (≥12)	0.97 (0.57-1.65)	0.85 (0.42-1.71)	0.73 (0.58-0.92)[a]	2.95 (1.23-7.04)[a]	0.86 (0.63-1.18)
Hospital volume					
Low (<11)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Medium (11-25)	0.81 (0.52-1.25)	1.00 (0.57-1.75)	1.11 (0.92-1.33)	1.09 (0.59-2.01)	1.00 (0.79-1.28)
High (>25)	0.81 (0.50-1.31)	0.82 (0.44-1.56)	1.11 (0.89-1.37)	1.23 (0.61-2.48)	1.14 (0.86-1.51)

(Continued)

Table 4. (Continued)

Variables	≥8 Cystoscopies OR (95% CI)	≥8 Cytologies OR (95% CI)	≥2 Imaging Studies OR (95% CI)	≥1 Perioperative Mitomycin C OR (95% CI)	≥6 Postoperative BCG OR (95% CI)
Institution type					
Non-academic non-cancer center	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Academic non-cancer center	1.68 (1.11-2.54)[a]	3.27 (1.88-5.70)[a]	1.05 (0.87-1.28)	1.16 (0.62-2.15)	0.96 (0.74-1.25)
Academic cancer center	1.80 (0.67-4.85)	7.81 (2.60-23.53)[a]	0.91 (0.55-1.49)	2.28 (0.51-10.18)	0.65 (0.33-1.29)
Unknown	1.66 (0.90-3.06)	1.28 (0.52-3.13)	1.03 (0.76-1.39)	1.99 (0.84-4.75)	0.87 (0.59-1.28)
Grade					
Poorly differentiated	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Undifferentiated	1.32 (0.92-1.89)	1.31 (0.83-2.06)	1.12 (0.95-1.32)	0.96 (0.58-1.57)	1.49 (1.22-1.82)[a]
T classification					
Ta	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Tis	1.36 (0.83-2.23)	2.50 (1.41-4.43)[a]	1.18 (0.94-1.49)	0.55 (0.23-1.35)	1.86 (1.39-2.48)[a]
T1	0.93 (0.67-1.28)	0.94 (0.63-1.41)	1.18 (1.03-1.36)[a]	1.26 (0.83-1.91)	2.03 (1.70-2.43)[a]

Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio.
[a]Statistically significant difference.

Table 5. Patient, Tumor, and Surgeon Contributions to Variation in Compliance With Established Measures

Partitioning of Variance	≥8 Cystoscopies	≥8 Cytologies	≥2 Imaging Studies	≥1 Perioperative Mitomycin C	≥6 Postoperative BCG
Surgeon-attributable variance (null model)	26.6%	58.3%	12.2%	47.7%	26.2%
Unexplained surgeon variance (full model)	25.1%	59.3%	9.9%	45.4%	26.3%
Patient sociodemographic characteristics	2.5%	3.6%	1.0%	4.1%	2.5%
Severity of illness	4.5%	0.3%	0.6%	1.5%	2.9%
Provider characteristics	2.9%	5.4%	1.8%	4.7%	2.1%
Year of diagnosis	3.5%	0.6%	0.3%	2.8%	3.1%

Abbreviation: BCG, Bacillus Calmette-Guérin.

associated with a lower rate of compliance, whereas significant comorbid conditions (Charlson score of 1 or 2), region (Midwest and South), and T classification (T1) were associated with a higher rate of compliance. With regard to perioperative mitomycin C instillation, region (Northeast) was found to be associated with lower rate, whereas race (Asian and other) and increasing surgeon volume (medium and high) were associated with a higher rate of compliance. For BCG, advancing age ($\geq$ 75 years) and black race were associated with lower odds of compliance, whereas marital status, region (South and Northeast), diagnosis after 1997, undifferentiated grade, and T classification (T1) were found to be independently associated with higher odds.

With the exception of radiographic imaging (residual ICC, 10% in the full model), unexplained surgeon-attributable variance significantly contributed to the low compliance rate (Table 5). Unexplained surgeon-attributable factors were greatest for cytology (residual ICC, 59%) and perioperative mitomycin C (residual ICC, 45%). Less than 8% of the variance for cystoscopy, cytology, radiographic imaging, perioperative mitomycin C, and BCG instillation was explained by measured patient-level characteristics.

DISCUSSION

There is a marked underuse of care in patients with high-grade non–muscle-invasive bladder cancer; in the current study, we found a single case of comprehensive compliance in 4545 eligible patients. We had to significantly ease our definition of compliance to at least 1 cystoscopy, 1 cytology, and a single instillation of intravesical BCG to achieve a 37% compliance rate on the patient level and a 58% rate of compliance (for at least 1 patient within a 2-year period) on the provider level. Moreover, a significant percentage of variation in the low compliance rate is attributable to the provider. Unexplained provider-level variation contributed significantly to the low compliance rate noted for cystoscopy (25%), cytology (59%), perioperative intravesical chemotherapy (45%), and postoperative instillation of BCG (26%). As a comparison, the percentage of unexplained provider-level variation that contributed to the underuse of radical cystectomy for muscle-invasive bladder cancer was 31%, whereas underuse of renal-preserving surgery (partial nephrectomy) for kidney cancer was 17%.[12,13] Although some may contend that radical cystectomy and partial nephrectomy are difficult procedures that warrant additional specialty surgical training or hospital resources, one cannot make that same argument for cystoscopy, cytology, perioperative intravesical chemotherapy, or postoperative instillation of BCG. Not only have these quality measures been integrated into the reimbursement models, but these are also office-based procedures, which is the site of most urologic care. In addition, the unexplained provider-attributable variation in the current study was significantly greater than that in the study by Hollingsworth et al, in which it was discovered that 9% of unexplained treatment intensity variance was accounted for by unmeasured provider factors.[14] The differences in explained variation are attributed to differences in the outcome measures; we used receipt of individual services and Hollingsworth et al used cost.[14] Thus, although receipt of cancer-based services may be attributed to unexplained provider-level variation, costs may not differ substantially.

Therefore, why is the inadequacy of compliance with guideline-recommended care so prevalent? Can one attribute this insufficiency to the dearth of evidence-based medicine? Although to our knowledge there has been a paucity of studies assessing surveillance strategies,[15] there is significant evidence of the benefits of BCG[7,16-18] and mitomycin C,[6,19,20] as well as other intravesical chemotherapeutics,[21-26] in minimizing the rate of disease recurrence or progression in patients with non–muscle-invasive bladder cancer. Alternatively, because the guidelines were only published in 1998, the insufficient care noted may have been attributed to preference-sensitive variation in the absence of clinical evidence. However, we encountered sensationalism over innovations, such as robotic technology or intensity-modulated radiation therapy, despite an evidence vacuum.[27,28] In addition, the benefits of BCG were well known before 1992. By limiting our cohort to those patients with high-grade disease, we expected preference-sensitive variation to err on the side of overuse, not gross underuse.

The current study findings are commensurate with others depicting the underuse of effective care in patients with bladder cancer.[4,5,29] Although our findings may appear to be at odds with those of Strope et al, who queried a similar cohort and discovered increased use of services over time,[30] we too reported an increase in the use of services such as intravesical therapy and radiographic imaging. In addition, increased use of BCG and radiographic imaging does not necessarily translate into improved compliance if care is not comprehensive, as evidenced by a decreasing rate of urine cytology with time.

Although the sample size is robust, the current study is not without its limitations. As with any observational study, omitted-variable bias may impact adherence rates with clinical guidelines. Patient preferences for surveillance and treatment strategies may have confounded our findings of significant underuse. The discomfort of endoscopic evaluation every 3 months and its subsequent impact on quality of life as well as the adverse effects of intravesical therapy (primarily lower urinary tract symptoms) may have contributed to noncompliance. Although we were able to exclude individuals who likely developed disease progression and underwent cystectomy, radiotherapy, or systemic chemotherapy, we do not know who withdrew from treatment as a result of side effects. It is not uncommon for BCG therapy to be associated with local and systemic side effects so severe that cessation of intravesical immunotherapy occurs (up to 30% of patients).[31] In the current study cohort, only 16% of subjects received 1 to 5 instillations; therefore, the vast majority (84%) either received $\geq$ 6 additional instillations or never received a single dose. Moreover, relaxing the definition from $\geq$ 6 instillations to $\geq$ 1 instillation(s) was found to have a modest impact on compliance (Table 3; lines 1 to 2 yielding 4 additional patients and lines 4 to 5 yielding an additional 202 patients [4.5%]). This is slight when compared with the transition from $\geq$ 1 cystoscopy and $\geq$ 1 BCG instillation to just $\geq$ 1 cystoscopy (lines 8 to 9 yielding 1936 subjects [42.6%]). That difference notwithstanding, the rate of underuse may be in part attributed to patients terminating therapy early (16% in the current study cohort received 1-5 instillations) or not initiating therapy altogether for fear of treatment toxicities. Another limitation is that the findings of the current study may not be generalizable to those patients who are aged < 65 years or who have alternative forms of insurance coverage. However, 75% of all patients with bladder cancer are aged ≥ 65 years, and the vast majority of the elderly have Medicare benefits.[32,33] Last, although there is Level 1 evidence demonstrating recurrence-free and progression-free survival advantages in patients who received intravesical therapy, the surveillance schedule of cystoscopy and cytology every 3 months and imaging every other year have not been thoroughly tested.

Despite these limitations, the findings of the current study serve to alert patients and providers to the wide gap between guideline-recommended care and routine practice. Although providers may not always be responsible for patient noncompliance, we must remember that the Institute of Medicine report outlining the 6 dimensions of high-quality care (safe, timely, effective, efficient, patient-centered, and equitable) focuses on both technical and interpersonal excellence. Akin to the argument advocating for differential compensation for surgeons who perform technically challenging procedures, so too should physicians be incentivized for establishing a working relationship with their patients with bladder cancer and facilitating compliance with clinically effective surveillance and treatment strategies.

How do we bridge the chasm between clinical practice guidelines and routine care? One approach relies on restructuring payment policies through performance-based incentive programs to explicitly promote improvements in quality of care. Pay-for-performance incentives and accountable care organizations have been integrated into greater than one-half of commercial health plans in the United States and into public health plans.[34] By linking incentives with physician adherence to clinically effective measures, thereby facilitating positive patient outcomes and avoiding complications, we hope to improve the quality of care while containing cost.

The age-old adage that "a chain is only as strong as its weakest link" is fitting in light of the findings of the current study. Although bladder cancer care may not be the weakest link in our health care system, it sheds light on the finding that clinically effective measures are not readily practiced through the mere publication of best-practice guidelines. In the absence of a broad quality improvement initiative, the diffusion of clinically effective care will be slow, and many more unnecessary disease recurrences, procedures, and deaths will be realized. This is an especially critical point because progress in preventing bladder cancer-related mortality lags behind other diseases.[1]

FUNDING SUPPORT

Supported by the American Cancer Society (117496-PF-09-147-01-CPHPS [Principal Investigator: K.C.]), Ruth L. Kirschstein National Research Service Award Extramural (1 F32 CA144461-01 [Principal Investigator: K.C.]), Jonsson Comprehensive Cancer Center Seed Grant (Principal Investigator: M.S.L.), and National Institute of Diabetes and Digestive and Kidney Diseases (N01-DK-1-2460 [Principal Investigator: M.S.L.).

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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