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QUALITY OF CARE IN PATIENTS WITH BLADDER CANCER: A CASE REPORT?

Karim Chamie, MD, MSHS[1,2], **Christopher S. Saigal, MD, MPH**[1,2,3], **Julie Lai, MS**[3], **Jan M. Hanley, MS**[3], **Claude M. Setodji, PhD**[3], **Badrinath R. Konety, MD, MBA**[5], **Mark S. Litwin, MD, MPH**[1,2,3,6], and **the Urologic Diseases in America Project**

[1]Department of Urology, Health Services Research Group, David Geffen School of Medicine at UCLA, Los Angeles, California

[2]Jonsson Comprehensive Cancer Center, David Geffen School of Medicine at UCLA, Los Angeles, California

[3]RAND Corporation, Santa Monica, California

[4]RAND Corporation, Pittsburgh, Pennsylvania

[5]Department of Urology, University of Minnesota, Minneapolis, Minneapolis, Minnesota

[6]Department of Health Services, University of California Los Angeles School of Public Health, Los Angeles, California

Abstract

Background—While there is level I evidence demonstrating superiority of intravesical therapy in in patients with bladder cancer, surveillance strategies are primarily founded on expert opinion. We examined compliance with surveillance and treatment strategies and the pursuant impact on survival in patients with high-grade disease.

Methods—Using linked SEER-Medicare data, we identified subjects with a diagnosis of high-grade non-muscle-invasive disease in 1992–2002 who survived two years and did not undergo definitive treatment during that time. We used non-linear mixed-effects regression analyses to examine compliance with surveillance and treatment strategies. After adjusting for confounders using a propensity-score-weighted approach, we determined whether individual and comprehensive strategies during the initial two years after diagnosis were associated with survival after two years.

Results—Of 4,790 subjects, only one received all the recommended measures. While mean utilization for most measures significantly increased after 1997, only compliance with an induction course of BCG increased (13% to 20%, $p<0.001$). On multivariate analysis, compliance with ≥ 4 cystoscopies, ≥ 4 cytologies and BCG instillation was lower among octogenarians and higher among those with undifferentiated, Tis and T1 tumors, and among those diagnosed after

Corresponding Author: Karim Chamie, UCLA Department of Urology, Health Services Research Group, 924 Westwood Blvd., Suite 1000, Los Angeles, California 90024, Office: (310) 794-2526 Fax: (310) 794-2538, kchamie@mednet.ucla.edu.

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1997. Subjects compliant with these measures had a lower hazard of mortality (HR 0.41; 95% CI 0.18–0.93) than those who received <4 cystoscopies, <4 cytologies and no BCG.

Conclusion—There is a statistically significant survival advantage found among those who received at least half of the recommended care. Improving compliance with these process-of-care measures via systematic quality-improvement initiatives serve as the primary target to meliorate bladder cancer care.

Keywords (MeSH Terms)

Urinary Bladder Neoplasms; Guideline Adherence; Quality of Healthcare; Survival

INTRODUCTION

In response to increased consumer and purchaser interest in ensuring high-quality care, the Agency for Health Care Policy and Research funded development of clinical guidelines for the management of patients with chronic conditions in the early 1990s. While there was growing skepticism regarding the quality of care delivered in America prior to publications by the Institute of Medicine (IOM),[1, 2] it was not until McGlynn *et al* reported that only 55% of adults received the recommended care that the public became aware of the sizable gap between science and routine practice.[3]

While bladder cancer is not routinely referred to as a chronic condition, it shares many similar properties: It is common, necessitates multiple interventions, and costly. To address these concerns, clinical guidelines, like those set forth by the National Comprehensive Cancer Network (NCCN), the American Urological Association (AUA) and the European Association of Urology (EAU), were established in an attempt to the minimize morbidity and mortality associated with recurrence and progression of bladder cancer. The surveillance and treatment strategies embodied within these guidelines have been infused into education, specialty certification and reimbursement models. Despite this infusion, Schrag *et al.*, using a relaxed definition for a single quality-of-care measure—endoscopic evaluation every six months instead of every three months—discovered that 40% patients underwent the recommended number endoscopic procedures.[4] Using MEDSTAT claims data, Madeb *et al.* discovered that out 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] Additionally, Huang *et al*., found that only 42% of patients with high-grade non-muscle-invasive bladder cancer received a single instillation of immune- or chemotherapy. [6]

However, established clinical practice guidelines incorporate a comprehensive surveillance (cystoscopy, urinary cytology, and upper tract imaging) and treatment (perioperative mitomycin C and postoperative Bacillus Calmette-Guérin (BCG)) schedule and not just a single quality-of-care measure.[7, 8] Additionally, the current surveillance strategies were derived from expert opinion and have yet to be associated with improved outcomes. Against this backdrop of low compliance with a single measure and an anticipated lower rate with multiple measures, we examined the overall compliance rate with established-clinical guidelines and its subsequent impact on survival.

METHODS

Data Source

We used the Surveillance, Epidemiology and End Results (SEER)-Medicare-linked database of the National Cancer Institute, which contains data on individuals aged 65 years and older,

to identify bladder cancer patients who were diagnosed in 1992–2002. SEER data are summarized in the Patient Entitlement and Diagnosis Summary File (PEDSF) and contains data on patient demographics, tumor characteristics and follow-up information. The PEDSF was linked with 100% of Medicare claims from 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 to and 24 months after diagnosis of bladder cancer.[9]

Study Population

The cohort consisted of patients at least 66 years of age with an incident diagnosis of high-grade (poorly, undifferentiated) urothelial (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, for whom claims data were available through 2007. While beneficiaries are eligible for Medicare coverage at age 65, we limited our cohort to those 66 or older to allow at least one year of eligibility in Medicare before bladder cancer diagnosis to ascertain comorbidity data. We restricted our analysis to those with known grade, stage and histology and those who survived at least two years without undergoing definitive treatment (cystectomy, radiotherapy or systemic chemotherapy) during that timeframe.

Quality-of-Care Measures

While there are slight variations between NCCN, AUA and EAU, we amalgamated the three published guidelines to generate compliance measures *a priori*. For the first two years after diagnosis, at a minimum, patients should undergo (1) lower urinary tract surveillance with cystoscopy and urine cytology every three months, (2) one upper tract image, (3) instillation of perioperative mitomycin C after transurethral urethral resection of bladder tumor (TURBT), and (4) an induction course of BCG. Translated into claims data, we anticipated that patients should undergo at least eight cystoscopies, eight cytologies, one upper tract image, one instillation of perioperative mitomycin C, and six instillations of BCG after the diagnostic TURBT. We relaxed the definition to count as compliant the use of BCG anytime during the first two years after diagnosis. We also relaxed the definition of perioperative mitomycin C to include a claim for instillation of any chemotherapeutic within three days of TURBT. While recent guidelines highlight compelling evidence for the utility of repeat TURBT in T1 disease, more frequent upper-tract imaging and maintenance BCG (an induction course, plus three 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 *Healthcare Common Procedure Coding Systems (HCPCS)* codes from the Medicare claims record, to posit that if noncompliance with our measures were found to be high, then non-adherence with more stringent criteria would be far higher.

Study Variables

From the PEDSF, we determined patient age (66–69, 70–74, 75–79, ≥ 80), gender, race/ethnicity (White, Black, Hispanic, Other), marital status (married, other), tumor grade (poorly differentiated, undifferentiated), T-stage (Ta, Tis, T1), and year of diagnosis (categorical:1992–1997,1998–2002). We imputed subject socioeconomic status by utilizing 2000 US Census data to derive quartiles of ZIP code-level median household income (< $35,000, $35,000–$45,000, $45,001–$55,000, >$55,000) and percent of residents ≥ 25 years of age with at least four years of college education (categorical: <15.0%, 15.0%–25.0%, 25.1%–35.0%, >35.0%).[10] We used the Klabunde *et al* modification of the Charlson Comorbidity index to quantify severity of preexisting comorbidities (0, 1, 2, ≥ 3).[11, 12] For each patient, we noted the provider and institution where the initial bladder cancer was diagnosed utilizing the Unique Physician Identifier Number (UPIN) and the corresponding

institution (Medicare provider number). The Medicare provider number was linked with the American Medical Association Masterfile to derive institution type—medical school affiliation (academic) as well as NCI designation as a Comprehensive Cancer Center (cancer center). Institution type was stratified into academic cancer center, non-academic cancer center, academic non-cancer center, non-academic non-cancer center and unknown. We discovered that only four patients were diagnosed at an NCI designated cancer center without medical school affiliation. Hence, they were included with those diagnosed at an academic cancer center. Cumulative volumes for surgeon and hospital were calculated after adjusting for inclusion of new providers and four new SEER registries in 2000. Caseload for transurethral resections was stratified into low, medium and high for each surgeon (<4, 4–11, ≥ 12) and hospital (≤10, 11–25, >25). We generated a region variable (West, Midwest, South, Northeast) from the SEER registry.

Statistical Analysis

We report differences in means and proportions in compliance using two-sample *t* test and Chi-square analyses. Since receipt of services and attendant compliance with quality-of-care measures may be clustered on the provider, we generated a mixed-effects logistic model to account for both fixed (covariates) and physician-level random effects. A post-estimation function from the mixed-effects model was utilized to generate propensity scores and inverse probability of treatment weights to adjust for measured variable bias. This propensity score model adjusted for patient age, gender, race/ethnicity, marital status, ZIP code-level income and education, comorbidity, tumor grade and stage, hospital type, and surgeon and hospital volume. We then examined the relative survival difference using competing-risks regression analysis stratified by individual and comprehensive quality-of-care measures. For individual measures, five separate mixed-effects, post-estimation propensity score analyses and competing-risks regression analyses were performed for cystoscopy (≥4 vs <4), cytology (≥4 vs <4), upper tract imaging (≥1 vs 0), perioperative instillation of intravesical mitomycin C (≥1 vs 0) and instillation of BCG within 90 days of diagnosis (≥1 instillation within 90 days vs ≥ 1 instillation after 90 days or no instillation). Similarly, six separate mixed-effects, post-estimation propensity score analyses and competing-risks regression analyses were performed to measure the association between compliance with comprehensive measures and survival: 1) <4 cystoscopy, <4 cytology and no BCG (referent); 2) <4 cystoscopy, <4 cytology and 1st instillation of BCG after 90 days; 3) <4 cystoscopy, <4 cytology and 1st instillation of BCG within 90 days; 4) ≥ 4 cystoscopy, ≥ 4 cytology and no BCG; 5) ≥ 4 cystoscopy, ≥ 4 cytology and 1st instillation of BCG after 90 days; and 6) ≥ 4 cystoscopy, ≥ 4 cytology and 1st instillation of BCG within 90 days. The most intense strategy that was clinically meaningful and statistically feasible was receipt of ≥ 4 cystoscopies, ≥ 4 cytologies and an induction course of BCG with the 1st instillation within 90 days. While this combined measure is not entirely comprehensive, it serves as essential minimum requirement urologists should follow—without dispute of overutilization—and based on the low compliance rate, would overcome computational limitations from rare events. The instillation within 90 days helped distinguish providers who instilled BCG based on the initial diagnosis (“preventers”) from those who utilized it in response to recurrences (“reactors”).

We utilized a maximum likelihood, competing-risks regression model as described by Fine and Gray. [13] Competing-risks regression analysis was performed to characterize the risks of bladder cancer-specific mortality across intensity of surveillance and treatment. We defined failure as bladder cancer mortality and the competing event as non-bladder cancer mortality. Estimates are reported as sub-hazard ratios (HR) with corresponding 95% confidence intervals. Additionally, since patients treated by the same provider may have similar outcomes, we accounted for this potential clustering by utilizing the Huber/White/sandwich

variance estimator to the competing-risks regression analysis to yield more conservative confidence intervals. While competing-risks regression analysis does not have a goodness-of-fit statistic, we utilized the Cox model as a proxy. We confirmed non-violation of the proportional hazards assumption using "log-log" plots and adequate model fit using Hosmer and Lemeshow analysis.[14]. We conducted all analyses with STATA software (College Station, Texas). All statistical tests were two-tailed, and the probability of a type I error was set at 0.05. The institutional review board at UCLA approved the study protocol.

RESULTS

We identified 4,790 subjects and the plurality was octogenarian, male, white, married and without any comorbid conditions. The majority was diagnosed in 1998–2002 with a poorly differentiated T1 tumor by a medium-volume surgeon at a non-academic non-cancer center (Table 1).

On univariate analysis, while the mean utilization of cystoscopy, upper-tract imaging, and intravesical instillation of BCG significantly increased after the establishment of established-clinical guidelines, the proportion compliant with each measure did not significantly increase after 1997, with the exception of receipt of an induction course of BCG (13.0% to 19.7%, p <0.001) (Table 2).

With regard to comprehensive care, out of the 4,790 subjects, only one case was compliant with all the quality-of-care measures (Table 3); hence the title of this report. Relaxing the definition to mandate ≥ 8 cystoscopies, ≥ 8 cytologies and an induction course of BCG, yields 21 cases fulfilling this requirement (0.4%). In fact, over 65% did not have receipt of at least ≥ 1 cystoscopy, ≥ 1 cytology and a single instillation of intravesical BCG.

Table 4 presents a mixed-effects model assessing receipt of ≥ 4 cystoscopies, ≥ 4 cytologies and an induction course of BCG with the first dose within 90 days of diagnosis. A higher odds of compliance with the aforementioned measures was found among subjects diagnosed with an undifferentiated grade (OR 1.74; 95% CI 1.30–2.32), Tis (OR 2.12; 95% CI 1.41–3.20) T1 (OR 1.56; 95% CI 1.19–2.04) tumor and diagnosed after 1997 (OR 1.55; 95% CI 1.17–2.05) and lower odds among octogenarians (OR 0.44; 95% CI 0.30–0.66). When year of diagnosis was represented as a continuous variable, we discovered a 10% increase in odds of compliance with time (OR 1.10; 95% CI 1.05–1.15). A post-estimation prediction of compliance over time was performed and at the current rate of progress, we would predict 25% compliance by 2024.

With regard to individual measures, a statistically significant lower hazard of mortality was discovered among subjects with receipt of ≥ 4 cystoscopies (HR 0.61; 95% CI 0.47–0.79), ≥ 4 cytologies (HR 0.55; 95% CI 0.39–0.80) and instillation of BCG within 90 days of diagnosis (HR 0.71; 95% CI 0.51–0.98). Upper tract imaging (HR 1.14; 95% CI 0.77–1.73) and instillation of perioperative mitomycin C (HR 0.74; 95% CI 0.34–1.65) were not associated with a survival advantage (Table 5). With regard to comprehensive measures, only those who had ≥ 4 cystoscopies, ≥ 4 cytologies and initiation of BCG within 90 days of diagnosis was associated with a statistically significant lower hazard for mortality than those who underwent <4 cystoscopies, <4 cytologies and no instillation of BCG (HR 0.41; 95% CI 0.18–0.93). There was a trend towards statistical significance among men who underwent ≥ 4 cystoscopies, ≥ 4 cytologies and initiation of BCG after 90 days of diagnosis (HR 0.43; 95% CI 0.16–1.16). Less frequent surveillance or delayed initiation (or no use) of BCG was not associated with a lower hazard for mortality (Table 6).

DISCUSSION

We discovered a single case of comprehensive compliance out of 4,790 eligible patients. We did not anticipate that the considerable discordance between established guidelines and routine practice would yield a single case to report. Moreover, those who received at minimum ≥ 4 cystoscopies, ≥ 4 cytologies and initiation of BCG within 90 days of diagnosis had improved survival when compared with those who did not.

Factors that may explain the inadequacy of compliance with guideline-recommended care include: 1) the dearth of evidence-based medicine for surveillance strategies, 2) the surveillance and treatment strategies are too stringent, 3) patient preferences and treatment-related toxicities, 4) publication of practice guidelines after 1997, and 5) meta-analyses documenting the benefits of perioperative chemotherapy in 2004. With regard to the first three factors, a surveillance schedule that is too stringent with the attendant patient discomfort that is based on expert opinion will undoubtedly yield low compliance. In the absence of validation of surveillance strategies, we anticipate that compliance will remain low. Our study is especially timely, since it is among the first in bladder cancer to examine the relationship between process-of-care surveillance measures and an outcome that matters to cancer patients—survival. We hope our findings demonstrating a process-outcomes link will improve utilization of surveillance and treatment services. With regard to point 4, although the guidelines were first published in 1997, by limiting our cohort to those with high-risk disease, we expected preference-sensitive variation in this high-risk group to err on overutilization, not underutilization. Moreover, the benefits of BCG were well known prior to 1992. In fact, Southwest Oncology Group 8795 was closed prematurely in 1991 after accruing half of the projected number of subjects (349 in lieu of 720) as evidenced by the superiority of BCG over mitomycin C in recurrence-free survival (let alone placebo). With regard to the point 5—meta-analysis demonstrating an advantage of a single perioperative intravesical dose of chemotherapy was first reported in 2004—multiple studies published in the 1980s and 1990s demonstrated the benefits of perioperative intravesical chemotherapy. [7, 15–21] Some contend that with time, compliance with practice guidelines will be sufficient. Notwithstanding the statistically significant increase of compliance with at ≥ 4 cystoscopies, ≥ 4 cytologies and an induction course of BCG, we anticipate only 25% compliance by the year 2024. This anticipated 25% rate of compliance with recommended care (in 2024) is congruent with the deficit seen in patients with atrial fibrillation and hip fractures in 2003.[3] Not coincidentally, atrial fibrillation and hip fractures have since been prioritized in the Initial National Priorities for Comparative Effectiveness Research.[22]

Our findings are commensurate with others depicting the underutilization of effective care in patients with bladder cancer, spanning extent of disease, from the underuse of definitive treatment and neoadjuvant chemotherapy for patients with at least stage II disease, 37% and 1%, respectively,[23] to endoscopic surveillance and perioperative instillation of mitomycin in patients with non-muscle-invasive disease, 40% and 0.3%, respectively.[4–6] Our findings may appear at odds with those of Strope *et al.*, who have queried a similar cohort and discovered increased utilization of intravesical therapy and physician office visits.[24] While office visits was not a process metric in our analysis, our findings echoed theirs with regard to intravesical therapy (post-operative immunotherapy). Moreover, while we also demonstrate increased mean utilization of most services over time we note that the compliance rate did not increase; hence the increased utilization may be as a result of non-coordinated care. With regard to treatment intensity and survival, our findings are at odds with 1) Hollingsworth *et al.*, who demonstrated that while increasing treatment intensity was associated with major interventions (radical cystectomy, radiotherapy, and systemic chemotherapy), it was not significantly associated with median cancer-specific survival (albeit there was a trend with p=0.07); [25] and 2) the Hollenbeck *et al.* analysis that

demonstrated that increasing treatment intensity was actually associated with a significantly higher hazard for cause-specific mortality (HR 1.43). [26] In fact, based on Hollingsworth *et al.* analysis, if provider treatment intensity was modified to reflect the 25th percentile, the authors anticipate Medicare savings of $18.7 million without detriment to oncologic outcomes. Our analysis differed from the Michigan's group in that we excluded individuals who 1) underwent definitive treatment (cystectomy, radiotherapy or systemic chemotherapy) within the initial two-year period, or 2) did not survive during the initial two years, since a significant proportion of individuals with non-muscle-invasive bladder cancer on the initial transurethral resection may have been understaged. Therefore, this may in part explain why in their analyses, they discovered that the upper quartile of treatment intensity may not benefit from more services, [25, 26] since more intense surveillance and intravesical treatment strategies are unlikely to rescue a patient who has progressed to myoinvasion.[27–30]

While our sample size is large, our study has methodological limitations. As with any observational study, omitted-variable bias may impact adherence rates with established-clinical guidelines and the propensity score model. Patient preferences for surveillance and treatment strategies may have also confounded our findings of significant non-compliance. While the discomfort associated with endoscopic evaluation and intravesical therapy, may have contributed to noncompliance, we attempted to minimize confounding by limiting our cohort to those with high-grade tumors—a disease state that warrants higher intensity of surveillance and treatment—and to those who survived at least two years without undergoing definitive treatment (thus excluding those with competing causes of death and those who were understaged and quickly progressed). Last, while the surveillance strategies were statistically significant predictors of lower mortality, they may be a proxy for improved access to care. However, in the absence of an association between education and median income with the quality measures, this is not likely to be a significant cause.

Despite these limitations, our findings serve to alert patients and providers to the wide gap between guideline-recommended care and routine practice. So, 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 alternative payment models (e.g., PROMETHIUS® and accountable care organizations) have been integrated into most commercial and public health plans (e.g., the Centers for Medicare & Medicaid Services sponsors the Hospital Quality Improvement Demonstration Project).[31] By linking incentives with physician adherence to clinically effective measures, facilitating positive patient outcomes and avoiding complications, we hope to bend the arc of the care trajectory for bladder cancer by implementing adequate cystoscopies and cytologies and initiation of BCG. These measures are feasible and effective in minimizing the morbidity and mortality associated with bladder cancer. Alternative strategies such as clinical reminders, electronic health records and development of scorecards not tied to financial incentives, may improve quality of care without the unintended consequences—gaming the system for financial incentives, stifling innovation and hindering development of creative solutions to improving quality and the potential to paradoxically penalize providers caring for underserved, non-compliant patients who are at high risk for progression.

Irrespective of the approach, in the absence of a broad quality-improvement initiative, the diffusion of clinically effective care will be slow, and many more unnecessary recurrences, procedures and deaths will be realized. This is an especially critical point since progress in preventing bladder cancer-related mortality lags behind other diseases—a 5% relative reduction in mortality rate over the last 15 years.[32] This contribution is slight when one considers that bladder cancer is the fifth most common cancer contrasts starkly with

prostate, breast, lung and colon cancers where we have seen greater reductions in mortality during the same period.[33]

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Table 1

Cohort characteristics

Variables	Number	%
Age-group		
66–69	701	14.6%
70–74	1246	26.0%
75–79	1230	25.7%
≥80	1613	33.7%
Gender		
Male	3695	77.1%
Female	1095	22.9%
Race		
White	4377	91.4%
Black	115	2.4%
Hispanic	126	2.6%
Other	172	3.6%
Marital		
Married	3107	64.9%
Other	1683	35.1%
Charlson Score		
0	3354	70.0%
1	984	20.5%
2	315	6.6%
≥3	137	2.9%
% Of Subjects in ZIP code ≥ 25 years of age with ≥ 4 years of college education		
<15%	1009	21.1%
15–25%	1231	25.7%
25% 35%	992	20.7%
>35%	1558	32.5%

Variables	Number	%
Median ZIP code household income		
<$35,000	801	16.7%
$35,000–$45,000	1146	23.9%
$45,000–$55,000	1232	25.7%
>$55,000	1611	33.6%
Region		
West	2448	51.1%
Midwest	951	19.9%
South	448	9.4%
Northeast	943	19.7%
Year		
1992–1997	1809	37.8%
1998–2002	2981	62.3%
Surgeon Volume		
Low (<4)	963	20.1%
Medium (4–11)	2373	49.5%
High (≥12)	1454	30.4%
Hospital Volume		
Low (≤10)	1563	32.6%
Medium (11–25)	1613	33.7%
High (>25)	1614	33.7%
Institution Type		
Non-Academic Non-Cancer Center	3362	70.2%
Academic Non-Cancer Center	1042	21.8%
Academic Cancer Center	96	2.0%
Unknown	290	6.0%
Grade		

Variables	Number	%
Poorly Differentiated	3814	79.6%
Undifferentiated	976	20.4%
Stage		
Ta	1822	38.0%
Tis	488	10.2%
T1	2480	51.8%

Table 2

Overall and compliant use of services stratified by year the NCCN guidelines for non-muscle-invasive bladder cancer were established.

	Mean (SD)			Number Compliant (%)		
Quality-of-Care Measures	**1992–1997**	**1998–2002**	**p-value**	**1992–1997**	**1998–2002**	**p-value**
Cystoscopy	4.73 (2.07)	4.86 (2.02)	0.04	84 (4.6%)	143 (4.8%)	0.81
Cytology	2.26 (2.75)	2.24 (2.65)	0.80	98 (5.4%)	143 (4.8%)	0.34
Upper tract imaging	1.81 (1.50)	1.97 (1.64)	<0.001	1582 (87.4%)	2610 (87.5%)	0.92
Mitomycin C	1.63 (3.50)	1.08 (3.00)	<0.001	50 (2.8%)	95 (3.2%)	0.41
BCG	3.76 (5.16)	4.89 (5.38)	<0.001	235 (13.0%)	586 (19.7%)	<0.001

Table 3

Number compliant with progressive relaxation of guidelines

Compliance criteria	N	%
≥8 Cystoscopies and ≥ 8 cytologies and ≥ 6 instillations of BCG	21	0.4%
≥8 Cystoscopies and ≥ 8 cytologies and ≥ 1 instillation of BCG	26	0.5%
≥4 Cystoscopies and ≥ 4 cytologies and ≥ 6 instillations of BCG	631	13.2%
≥4 Cystoscopies and ≥ 4 cytologies and ≥ 1 instillation of BCG	846	17.7%
≥4 Cystoscopies and ≥ 1 cytology and ≥ 1 instillation of BCG	1603	33.5%
≥1 Cystoscopy and ≥ 1 cytology and ≥ 1 instillation of BCG	1790	37.4%
≥1 Cystoscopy and ≥ 1 instillation of BCG	2558	53.4%
≥1 Cystoscopy	4602	96.1%

Table 4

Mixed-effects model predicting compliance with ≥4 cystoscopy, ≥4 cytology and ≥6 instillations of BCG with the 1st instillation within 90 days of diagnosis.

Variables	Odds Ratio	95% CI
Age-group		
66–69 (referent)	1.00	…
70–74	1.34	(0.93–1.94)
75–79	0.92	(0.63–1.34)
≥80	0.44	(0.30–0.66)
Gender		
Male (referent)	1.00	…
Female	1.24	(0.91–1.68)
Race		
White (referent)	1.00	…
Black	0.57	(0.23–1.45)
Hispanic	0.73	(0.33–1.61)
Other	0.34	(0.14–0.85)
Marital		
Married (referent)	1.00	…
Other	0.82	(0.62–1.08)
Charlson Score		
0 (referent)	1.00	…
1	1.16	(0.87–1.55)
2	1.04	(0.63–1.70)
≥3	0.64	(0.29–1.41)
% Of Subjects in ZIP code ≥ 25 years of age with ≥ 4 years of college education		
<15% (referent)	1.00	…
15–25%	0.95	(0.63–1.43)
25%–35%	0.97	(0.60–1.56)
>35%	1.08	(0.66–1.79)
Median ZIP code household income		
<$35,000 (referent)	1.00	…
$35,000–$45,000	0.82	(0.52–1.30)
$45,000–$55,000	1.03	(0.64–1.66)
>$55,000	1.15	(0.68–1.95)
Region		
West (referent)	1.00	…
Midwest	1.28	(0.81–2.02)

Variables	Odds Ratio	95% CI
South	0.87	(0.52–1.47)
Northeast	1.13	(0.75–1.71)
Year		
1992–1997 (referent)	1.00	…
1998–2002	1.55	(1.17–2.05)
Surgeon Volume		
Low (<4) (referent)	1.00	…
Medium (4–11)	0.93	(0.64–1.36)
High (≥12)	0.78	(0.49–1.24)
Hospital Volume		
Low (≤10) (referent)	1.00	…
Medium (11–25)	0.94	(0.65–1.35)
High (>25)	1.06	(0.70–1.61)
Institution Type		
Non-Academic Non-Cancer Center (referent)	1.00	…
Academic Non-Cancer Center	1.39	(0.95–2.03)
Academic Cancer Center	2.04	(0.87–4.79)
Unknown	0.78	(0.43–1.44)
Grade		
Poorly Differentiated (referent)	1.00	…
Undifferentiated	1.74	(1.30–2.32)
Stage		
Ta (referent)	1.00	…
Tis	2.12	(1.41–3.20)
T1	1.56	(1.19–2.04)

Table 5

Propensity score-adjusted competing-risks regression analysis measuring the association between individual compliance measures and survival.

Variable	HR	95% CI
Cystoscopy		
<4 Cystoscopies (referent)	1.00	…
≥4 Cystoscopies	0.61	(0.47–0.79)
Cytology		
<4 Cytologies (referent)	1.00	…
≥4 Cytologies	0.55	(0.39–0.80)
Upper Tract Imaging		
No upper tract image (referent)	1.00	…
≥1 Upper tract image	1.15	(0.77–1.73)
Perioperative Instillation of Mitomycin C		
No instillation of mitomycin C after any TURBT (referent)	1.00	…
At least one instillation of mitomycin C after any TURBT	0.74	(0.34–1.65)
Postoperative Instillation of BCG		
No instillations, or ≥ 1 instillation with 1st dose after 90 days (referent)	1.00	…
≥1 instillation with 1st dose within 90 days	0.71	(0.51–0.98)

Table 6

Propensity score-adjusted competing-risks regression analysis measuring the association between comprehensive compliance measures and survival.

Surveillance and Treatment Strategy	HR	95% CI
<4 cystoscopy, <4 cytology and no BCG (referent)	1.00	***
<4 cystoscopy, <4 cytology and 1st instillation of BCG after 90 days	1.62	0.67–3.94
<4 cystoscopy, <4 cytology and 1st instillation of BCG within 90 days	0.88	0.36–2.11
≥4 cystoscopy, ≥ 4 cytology and no BCG	1.11	0.34–3.60
≥4 cystoscopy, ≥ 4 cytology and 1st instillation of BCG after 90 days	0.43	0.16–1.16
≥4 cystoscopy, ≥ 4 cytology and 1st instillation of BCG within 90 days	0.41	0.18–0.93