Care Quality and Variability in the Use of Intravesical Therapy for Initial Treatment of Nonmuscle Invasive Bladder Cancer Within a Large, Diverse Integrated Delivery System

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OBJECTIVES To examine treatment variability, disparities, and quality among newly diagnosed nonmuscle invasive bladder cancer (NMIBC) patients, and to identify factors associated with treatment use in a large, diverse integrated delivery system.

METHODS Retrospective cohort study of 5386 NMIBC patients diagnosed between January 2001 and June 2015 within Kaiser Permanente Southern California. Electronic health data were used to identify treatment outcomes and patient, provider, and tumor characteristics. Outcomes were use of (1) postoperative intravesical chemotherapy, (2) induction Bacille Calmette-Guérin (BCG) immunotherapy, and (3) any intravesical therapy. Multivariable odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using generalized linear mixed models with a binary outcome and urologist as a random effect.

RESULTS From 2001 to 2015, 41% of newly diagnosed NMIBC patients were treated with intravesical therapy. Postoperative chemotherapy use increased significantly over this period (OR per-year = 1.16, 95% CI: 1.07-1.25). BCG use was strongly associated with tumor characteristics: patients with high-grade or carcinoma in situ tumors were more likely to receive BCG (OR = 10.10, 95% CI: 8.39-12.16). Few treatment differences were found by sex or race/ethnicity, but were observed by age. Wide treatment variability across urologists was observed, with some urologists never using intravesical therapy as part of initial treatment while others almost always used it. Differences across urologists accounted for more variability in postoperative chemotherapy (intraclass correlation coefficient = 0.52) than BCG immunotherapy (intraclass correlation coefficient = 0.11) use.

CONCLUSION Substantial variability in initial treatment of NMIBC was observed across urologists, accounting for tumor, patient, and provider characteristics. Results suggest a considerable opportunity for quality improvement programs to reduce unwanted treatment variability and improve care for patients. UROLOGY 131: 93−103, 2019.

Treatment recommendations for nonmuscle invasive bladder cancer (NMIBC) have remained largely the same for the past several decades, with broad consensus across professional societies.[1-4] Agreement regarding treatment guidance has not translated into clinical practice, however. While recommendations suggest that most NMIBC patients should be treated with some type of intravesical therapy, studies report low treatment levels, leading to calls to improve treatment practices.[5-12]

Intravesical postoperative chemotherapy or Bacillus Calmette-Guérin (BCG) immunotherapy may be administered following a tumor resection to prevent recurrence or progression.[13-22] Because tumor recurrence and progression can trigger a cascade of treatments and surveillance,

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reducing them may improve patient outcomes, reduce the burden of care on patients and their families, and decrease costs to healthcare systems. Disparities in use of these treatments may contribute to outcomes disparities. Studies have found that disparities in bladder cancer survival have been observed by race/ethnicity even among early-stage bladder cancer patients.[23]

Quality metrics have been proposed as one way to increase guideline-consistent treatment.[12] The proposed metrics and quality improvement goals they set may benefit from updated information on care quality, as treatment use may have increased in recent years.

Our study describes the initial treatment of NMIBC among a contemporary cohort of 5386 patients, including variability across providers and over time, using data from a large, diverse integrated delivery system. We assessed the frequency of use of any intravesical therapy, postoperative intravesical chemotherapy, and induction immunotherapy. We also evaluated the relationship between treatment use and patient, tumor, and provider characteristics.

MATERIALS AND METHODS

Setting

Kaiser Permanente Southern California (KPSC) is an integrated delivery system serving >4.5 million members, equivalent to >1% of the US population.[24] Members are broadly representative of the diverse underlying population.[25] KPSC's cancer registry, which follows SEER guidelines, includes cancer cases diagnosed from 1988 forward. In 2006, KPSC adopted an electronic health record; prior to 2006, clinical and administrative data were stored in other electronic data systems. Approximately 100 full-time urologists provide care within KPSC, including both urologic oncologists and noncancer specialists who trained in different medical schools and residency and fellowship programs over a wide range of years.

Study Population

KPSC cancer registry data were used to identify members of age ≥21 years who were diagnosed with NMIBC between January 2001 and June 2015. Patients were excluded if they had a cancer diagnosis in the previous 5 years other than nonmelanoma skin cancer or experienced any of the following within 3 months of diagnosis: radical cystectomy/urinary diversion (RC/UD) surgery, infusion chemotherapy, hospice care, or mortality.

Outcomes

Initial treatment of NMIBC was captured by three outcome variables: use of (1) postoperative intravesical chemotherapy (typically mitomycin C (MMC)), instilled the same day or day after tumor resection, (2) induction BCG immunotherapy (any use within 92 days of resection), or (3) any intravesical therapy within 92 days of resection. Tumor resections included transurethral resection of bladder tumors and cystoscopies with bladder biopsies. Outcomes and procedures were captured using pharmacy data, procedure codes, and other data (see online supplement).

Exposures

Because a primary study goal was to assess treatment disparities over patient groups and time, the main exposure variables were: sex (female, male), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian, other/unknown), age (<50, 50-59, 60-69, 70-79, and ≥80 years), and year of diagnosis.

Covariates

Several tumor, patient, and urologist characteristics were considered as covariates: stage, grade, histology, high-risk tumors (defined as high-grade or carcinoma in situ tumors), Charlson Comorbidity Index, kidney disease, diabetes, smoking, body mass index (BMI), whether the urologist was an oncology specialist, urologist's years at KPSC, and urologist's bladder cancer experience (based on number of RC/UD surgeries performed in the year prior to diagnosis). Due to the focus on disparities, we also included contextual variables: healthcare insurance type, length of health plan membership before diagnosis, healthcare utilization in the year before diagnosis, neighborhood education level, and neighborhood household income level. We did not restrict eligibility based on prediagnosis membership given our interest in disparities, since insurance might be related to socioeconomic status or patient demographics. However, 93% of patients were members ≥1 year before diagnosis.

American Joint Committee on Cancer staging was used. (For NMIBC tumors, American Joint Committee on Cancer stage, and T stage are equivalent, although this is not true for muscle-invasive bladder cancer.) Tumor variables were primarily based on cancer registry data and supplemented by study chart reviews. Urologist was assigned based on tumor resection or diagnosis if there was no coded tumor resection.

Statistical Analyses

Bivariate analyses were used to examine the relationship between each treatment outcome and exposure variables or covariates. For categorical exposures and covariates, the χ^2 test or Fisher's exact test for sparse data was used to test associations with treatment outcomes; for continuous variables, the Wilcoxon rank sum test was used.

Multivariable models included the exposure variables along with variables significant at $P \leq .20$ in bivariate analyses. Multivariable odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using generalized linear mixed models with a binary outcome (treatment vs no treatment) and urologist as a random effect. All analyses used 2-sided *P* values calculated by an F test (type III fixed effects). The intraclass correlation coefficient (ICC) was calculated to examine correlations within urologist.[26] Higher ICC values indicate that more of the unexplained treatment variability was due to the urologist. Analysis of deviance was tabulated to assess the unique contribution of the individual urologist.[27] In secondary analyses, medical center was used as the random effect instead of urologist. Analyses were conducted using SAS Enterprise Guide version 7.13 and SAS version 9.4.

Missing data were greatest for BMI (n = 1934) and smoking (n = 664), primarily reflecting study year; after 2008, missing data were rare (n = 1 for BMI, n = 3 for smoking). Other variables with missing data were: tumor grade (n = 241), neighborhood education (n = 137), neighborhood household income (n = 150), oncology specialist (n = 23), urologist's years at KPSC (n = 112), and urologist's bladder cancer experience (n = 34). We used complete case data for analysis with the exception of BMI, for which we used a missing category.

Primary analyses included all NMIBC patients, a small proportion (6%) of whom did not have a coded tumor resection from 7 days before to 60 days after diagnosis but who were presumably eligible for a tumor resection and adjuvant therapy.

In sensitivity analyses, we restricted models to patients with a tumor resection. We conducted chart reviews of 50 randomly selected patients without a coded tumor resection to generate insights into potential misclassification. Additionally, we performed sensitivity analyses among patients diagnosed in 2008-2015 for 2 reasons. First, treatment patterns in recent years may be most relevant for setting quality goals. Second, data were most complete following adoption of the electronic health record, allowing assessment of the robustness of study findings. Because we were unable to ask about patient-physician treatment decision-making in this retrospective study, we reviewed a random sample of 45 patient charts to assess why intravesical therapy was not used.

The KPSC IRB approved this study.

RESULTS

From January 2001 to June 2015, 6237 patients were newly diagnosed with NMIBC. Patients were excluded if they had a cancer diagnosis in the previous 5 years other than nonmelanoma skin cancer (n = 579), were <21 years old at diagnosis (n = 1), were not health plan members at diagnosis (n = 41), or had RC/UD surgery, started infusion chemotherapy, entered hospice care, or died within 3 months of diagnosis (n = 230). After exclusions, 5386 patients remained (Table 1).

Intravesical therapy was used as part of initial treatment among 41% of newly diagnosed NMIBC patients (2183 of 5386). Postoperative chemotherapy was used among 17% of these patients (936 of 5386), and induction BCG among 22% (1210 of 5386). Some patients were treated with both postoperative chemotherapy and induction BCG (6%), and a small number of patients (7%) were treated using other induction therapies (eg, induction MMC).

Multivariable results are presented for use of any intravesical therapy (Table 2), postoperative chemotherapy (Table 2), and induction BCG immunotherapy (Table 2). Selected results are discussed below.

Treatment by Sex, Race/Ethnicity, and Age

Patient sex was not associated with use of any intravesical therapy (OR = 1.00 for female vs male, 95% CI: 0.84-1.18), postoperative chemotherapy (OR = 0.89, 95% CI: 0.71-1.13), or induction BCG (OR = 1.16, 95% CI: 0.94-1.44).

Race/ethnicity was not associated with use of any intravesical therapy (P = .44) or induction BCG (P = .46). Race/ethnicity was associated with postoperative chemotherapy use (P = .04). Asian patients were less likely to be treated with postoperative chemotherapy than non-Hispanic white patients (OR = 0.50, 95% CI: 0.30-0.82).

Age was associated with use of any intravesical therapy (P < .0001). Patients ≥80 were less likely to receive intravesical therapy than patients age 60-69 (OR = 0.70, 95% CI: 0.57-0.87). Age was not associated with postoperative chemotherapy (P = .57) but was associated with BCG use (P = .01), with patients ≥80 less likely to receive BCG than patients age 60-69 (OR = 0.67, 95% CI: 0.50-0.89).

Treatment Over Time and Overall

Treatment use increased significantly over time for any intravesical therapy (OR per-year = 1.03, 95% CI: 1.003-1.07) and postoperative chemotherapy (OR per-year = 1.16, 95% CI: 1.07-1.25), but not for BCG (P = 0.11). Among more recent years (2008-2015),

Table 1. Characteristics of 5386 newly diagnosed nonmuscle invasive bladder cancer patients by treatment status

Characteristic	Any Intravesical Therapy*		
	No (n = 3203)	Yes (n = 2183)	*P* value
	N (%)	N (%)	
Age at diagnosis (years)			0.001
<50	200 (6)	91 (4)	
50-59	419 (13)	291 (13)	
60-69	872 (27)	612 (28)	
70-79	993 (31)	748 (34)	
≥80	719 (22)	441 (20)	
Sex			0.10
Male	2506 (78)	1749 (80)	
Female	697 (22)	434 (20)	
Race/Ethnicity			0.06
Non-Hispanic White	2372 (74)	1565 (72)	
Non-Hispanic Black	210 (7)	160 (7)	
Hispanic	411 (13)	322 (15)	
Asian	164 (5)	117 (5)	
Other or Unknown	46 (1)	19 (1)	
Stage at diagnosis			<0.0001
0a	2206 (69)	1043 (48)	
0is	219 (7)	207 (9)	
1	778 (24)	933 (43)	
Grade at diagnosis			<0.0001
Low	1200 (39)	535 (26)	
Intermediate	1046 (34)	405 (19)	
High	816 (27)	1143 (55)	
High grade or CIS tumor			<0.0001
No	2200 (69)	890 (41)	
Yes	1003 (31)	1293 (59)	

Continued

Table 1. Continued

Characteristic	Any Intravesical Therapy*		*P* value
	No (n = 3203)	Yes (n = 2183)	
Histology			0.05
Urothelial	3136 (98)	2153 (99)	
Other or unknown	67 (2)	30 (1)	
Charlson Comorbidity Index†			<0.0001
0	1492 (47)	885 (41)	
1	681 (21)	458 (21)	
≥2	1030 (32)	840 (38)	
Ever smoked			0.24
No	804 (30)	602 (29)	
Yes	1835 (70)	1481 (71)	
Health insurance type at diagnosis			0.43
Medicare or Medicaid	1997 (62)	1384 (63)	
Commercial or other	1206 (38)	799 (37)	
Years of health plan enrollment prior to diagnosis			0.02
0-6	945 (30)	564 (26)	
7-15	773 (24)	536 (25)	
16-27	768 (24)	546 (25)	
≥28	717 (22)	537 (25)	
Neighborhood education			0.90
≤High school	1519 (49)	1053 (49)	
Some college or associate's degree	671 (22)	452 (21)	
Bachelor's degree or graduate school	927 (30)	627 (29)	
Neighborhood household income			0.03
<$30,000	858 (28)	621 (29)	
$30,000- $49,999	134 (4)	66 (3)	
$50,000- $74,999	87 (3)	44 (2)	
≥$75,000	2032 (65)	1394 (66)	
Oncology specialist			<0.0001
No	2922 (92)	1878 (86)	
Yes	264 (8)	299 (14)	
Urologist: years at KP at the time of diagnosis			0.67
Mean (SD)	13.5 (8.8)	13.7 (9.0)	
Median (IQR)	12 (7-19)	12 (7-19)	
Urologist: bladder cancer experience in year prior to patient's diagnosis‡			0.27
Mean (SD)	26 (14)	27 (16)	
Median (IQR)	25 (17-34)	24 (17-32)	
Urologist: bladder cancer experience with RC/UD in year prior to patient's diagnosis§			<0.0001
Mean (SD)	1.4 (2.7)	1.2 (3.0)	
Median (IQR)	1 (0-2)	0 (0-1)	

CIS, carcinoma in situ; IQR, interquartile range; RC, radical cystectomy; SD, standard deviation; UD, urinary diversion. Percents and p-values were calculated ignoring missing data, unless missing/unknown data were shown in the table.
* Any intravesical therapy includes postoperative chemotherapy, induction chemotherapy, or induction BCG immunotherapy.
† Assessed in the year prior to the bladder cancer diagnosis.
‡ Experience was defined as the total number of bladder cancer-related surgeries (ie, tumor resection or radical cystectomy/urinary diversion).
§ Experience was defined as the total number of radical cystectomy/urinary diversion surgeries.

any intravesical therapy was used as part of initial treatment for NMIBC among 56% of patients (1674 of 2988), postoperative chemotherapy among 28% (823 of 2988), and induction BCG among 35% (1054 of 2988). BCG was used among 57% (812 of 1422) of patients with high-risk tumors. BCG use among patients with high-risk tumors declined nonsignificantly ($P = 0.29$) from 2008 (61%) to 2015 (56%).

BCG use was strongly associated with tumor characteristics, particularly high-risk tumors (OR = 10.10, 95% CI: 8.39-12.16). In analyses using stage and grade instead of high-risk tumors, patients with high-grade (OR = 12.08, 95% CI: 9.46-15.43) and intermediate-grade (OR = 2.70, 95% CI: 2.01-3.62) tumors were more likely to receive BCG than patients with low-grade tumors. Stage 1 tumors were associated with increased odds of BCG use compared with 0a tumors (OR = 2.18, 95% CI: 1.78-2.67), while treatment of 0is and 0a tumors did not differ (OR = 1.25, 95% CI: 0.85-1.86). Having a high-risk tumor was not associated with postoperative chemotherapy use ($P = 0.33$) but was associated with any intravesical therapy use (OR = 4.31, 95% CI: 3.73-4.98).

Healthcare insurance type, neighborhood household income, and neighborhood education level were not associated with treatment.

Variability by Urologist and Medical Center

Substantial variability in treatment practices was observed across urologists (Fig. 1). Urologists with ≥10 newly diagnosed NMIBC patients used intravesical therapy for initial treatment in 0%-93% of their patients. They used postoperative chemotherapy to treat

Table 2. Multivariable odds ratios* for use of any intravesical therapy†, postoperative chemotherapy, and induction BCG immunotherapy among 5386 nonmuscle invasive bladder cancer patients

	Any Intravesical Therapy†		Postoperative Chemotherapy		BCG Immunotherapy	
Characteristic	OR	95% CI	OR	95% CI	OR	95% CI
Age at diagnosis (years)						
<50	0.72	0.51 - 1.02	0.82	0.52 - 1.32	0.80	0.51 - 1.25
50-59	0.98	0.78 - 1.24	1.00	0.72 - 1.37	0.82	0.60 - 1.13
60-69	Referent		Referent		Referent	
70-79	1.10	0.92 - 1.32	0.95	0.72 - 1.24	0.99	0.77 - 1.28
≥80	0.70	0.57 - 0.87	0.80	0.59 - 1.09	0.67	0.50 - 0.89
Sex						
Male	Referent		Referent		Referent	
Female	1.00	0.84 - 1.18	0.89	0.71 - 1.13	1.16	0.94 - 1.44
Race/Ethnicity						
Non-Hispanic White	Referent		Referent		Referent	
Non-Hispanic Black	1.10	0.83 - 1.46	1.10	0.76 - 1.61	0.92	0.64 - 1.31
Hispanic	1.00	0.82 - 1.23	0.92	0.69 - 1.21	0.97	0.76 - 1.24
Asian	0.83	0.61 - 1.14	0.50	0.30 - 0.82	0.78	0.54 - 1.13
Other or Unknown	0.60	0.29 - 1.24	0.42	0.14 - 1.31	0.49	0.18 - 1.32
Year of diagnosis (ordinal)	1.03	1.003 - 1.07	1.16	1.07 - 1.25	0.97	0.94 - 1.01
High grade or CIS tumor	4.31	3.73 - 4.98	0.91	0.75 - 1.10	10.10	8.39 - 12.16
Histology						
Urothelial	Referent		Referent			
Other or unknown	0.47	0.28 - 0.79	0.44	0.19 - 1.03		
Charlson Comorbidity Index‡						
0	Referent		Referent		Referent	
1	0.92	0.76 - 1.11	1.02	0.78 - 1.32	0.78	0.61 - 1.00
≥2	0.92	0.75 - 1.13	1.03	0.75 - 1.40	0.80	0.61 - 1.05
Kidney disease†	0.82	0.66 - 1.03	0.95	0.71 - 1.27	0.76	0.58 - 0.98
Diabetes†			0.75	0.58 - 0.97	1.31	1.04 - 1.65
Body mass index (kg/m^2)‡						
<25	Referent		Referent		Referent	
25-29	1.16	0.96 - 1.41	1.13	0.89 - 1.43	1.22	0.99 - 1.51
≥30	1.12	0.91 - 1.38	1.38	1.06 - 1.80	1.07	0.85 - 1.36
Missing	0.17	0.12 - 0.22	0.15	0.09 - 0.26	0.005	0.002 - 0.01
Health insurance type						
Medicare or Medicaid			Referent		Referent	
Commercial or other			1.09	0.83 - 1.43	0.99	0.77 - 1.28
Utilization visits in year prior to diagnosis						
0-7			Referent			
8-12			0.91	0.70 - 1.19		
13-20			0.95	0.72 - 1.25		
≥21			0.77	0.57 - 1.04		
Years health plan enrollment prior to diagnosis						
0-6	Referent				Referent	
7-15	1.12	0.92 - 1.36			1.05	0.82 - 1.35
16-27	1.18	0.97 - 1.44			1.05	0.82 - 1.36
≥28	1.12	0.91 - 1.38			1.15	0.89 - 1.49
Neighborhood household income						
<$30,000	Referent		Referent		Referent	
$30,000-$49,999	0.80	0.55 - 1.18	1.33	0.79 - 2.25	1.07	0.64 - 1.78
$50,000-$74,999	1.03	0.65 - 1.65	0.83	0.40 - 1.73	0.93	0.48 - 1.82
≥$75,000	0.96	0.82 - 1.13	1.21	0.98 - 1.50	0.99	0.81 - 1.21
Oncology specialist	1.59	0.92 - 2.74	1.13	0.47 - 2.74	1.43	0.82 - 2.49
Urologist: Years at KP (continuous)			0.99	0.96 - 1.02	1.01	1.00 - 1.03
Urologist: Bladder cancer experience, RC/UD (ordinal)	0.97	0.93 - 1.02	0.96	0.89 - 1.03	0.95	0.90 - 1.01

BMI, body mass index; CI, confidence interval; CIS, carcinoma in situ; OR, odds ratio; RC/UD, radical cystectomy/urinary diversion.
* Covariates were selected based on bivariate analyses with each treatment variable ($P \leq .20$). A high-risk tumor variable (high-grade or CIS) was used as a covariate in the primary models, and stage and grade were used in sensitivity analyses, due to the overlap between these variables.
† Any intravesical therapy includes post-operative chemotherapy, induction chemotherapy, or induction BCG immunotherapy.
‡ The Charlson Comorbidity Index and kidney disease were assessed in the year prior to the bladder cancer diagnosis, while BMI was assessed in the year prior to or 30 days after bladder cancer diagnosis.

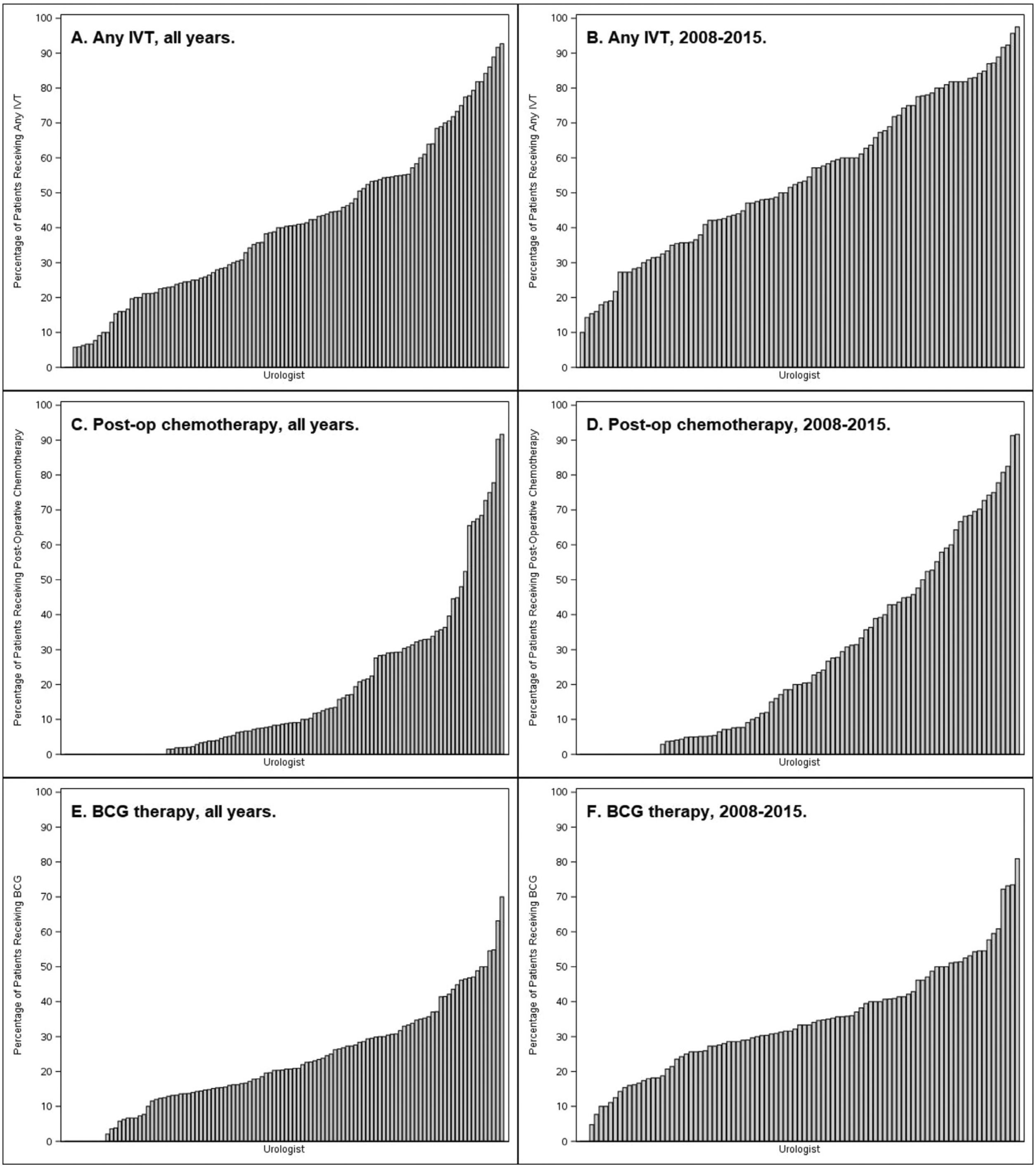

Figure 1. Variability across urologists in the use of any intravesical therapy,* postoperative intravesical chemotherapy, and induction BCG immunotherapy as part of initial treatment for non-muscle invasive bladder cancer.

BCG, Bacillus Calmette-Guérin; IVT, intravesical therapy

*Any intravesical therapy includes postoperative chemotherapy, induction chemotherapy, and induction BCG immunotherapy.

The x-axis shows urologist, sorted in order of those using a treatment least to those using it most. The y-axis shows the percent of each urologist's patients receiving a given treatment (any intravesical therapy, postoperative chemotherapy, or BCG immunotherapy) as part of their initial treatment for NMIBC. The figures on the left side show treatment practices across all study years; the figures on the right side show treatment practices in more recent years (2008-2015).

from 0% to 92% of their patients, and BCG to treat from 0% to 70% of their patients. Most urologists saw a mix of lower- and higher-risk NMIBC patients. For the majority of urologists, high-risk patients comprised between 30% and 55% of their NMIBC patients. Both urologic oncologists and noncancer specialists treated NMIBC patients, reflecting the diversity of providers treating NMIBC in our community-based delivery system.

Treatment variability across urologists persisted when analyses were restricted to recent years and stratified by whether patients had high-risk tumors or not (Fig. 2). Urologists with ≥10 patients with high-risk tumors used intravesical therapy for initial treatment in 32%-100% of their high-risk patients. They used postoperative chemotherapy to treat from 0% to 90% of their high-risk patients, and BCG to treat 0%-93%. Urologists with ≥10 patients with low-risk tumors used intravesical therapy

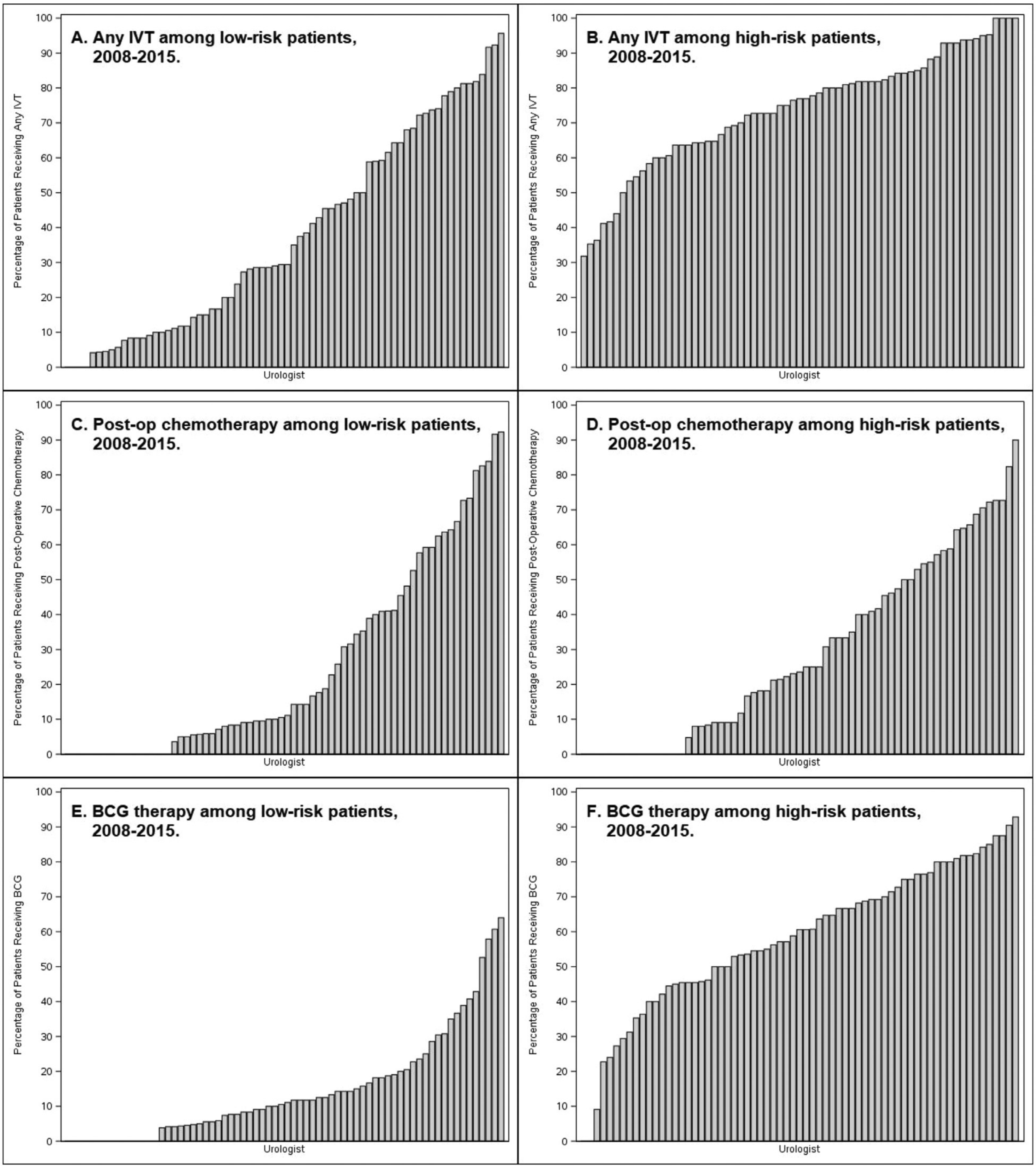

Figure 2. Variability by tumor risk across urologists in the use of any intravesical therapy,* postoperative intravesical chemotherapy, and induction BCG immunotherapy as part of initial treatment for nonmuscle invasive bladder cancer.

BCG, Bacillus Calmette-Guérin; IVT, intravesical therapy

*Any intravesical therapy includes postoperative chemotherapy, induction chemotherapy, and induction BCG immunotherapy.

The x-axis shows urologist, sorted in order of those using a treatment least to those using it most. The y-axis shows the percent of each urologist's patients receiving a given treatment (any intravesical therapy, postoperative chemotherapy, or BCG immunotherapy) as part of their initial treatment for NMIBC in 2008-2015. The figures on the right side show treatment practices among high-risk patients, defined as patients with high-grade tumors or carcinoma in situ. The figures on the left side show treatment for low-risk patients.

for initial treatment in 0%-96% of their low-risk patients. They used postoperative chemotherapy to treat from 0% to 96% of their low-risk patients, and BCG to treat 0%-64%.

Treatment variability was more strongly related to the individual urologist for postoperative chemotherapy than for any intravesical therapy or induction BCG use. For postoperative chemotherapy, the ICC for the random effect of urologist was 0.52. Analysis of deviance indicated that 45% of the model's explanatory power was due to the addition of the random effect of urologist. For any intravesical therapy use, the ICC for urologist was 0.15. Analysis of deviance indicated that 25% of the model's explanatory power was due to urologist. For induction BCG use, the ICC for urologist was 0.11. Analysis of deviance indicated that 8% of the model's explanatory power was due to urologist.

Medical center explained less treatment variability than urologist. When medical center was used as the random effect instead of urologist, the ICC was 0.06 for any intravesical therapy use, 0.07 for postoperative chemotherapy use, and 0.01 for induction BCG use.

Chart Review on a Sample of Patients

Reliance on coded data may involve some misclassification in any setting. Among 50 randomly sampled patients without an identified tumor resection, our reviews found that 38% of patients had a tumor resection that was uncoded. Additionally, 50% had a tumor resection beyond 60-days postdiagnosis (used in our study to distinguish diagnostic and surveillance procedures). Sensitivity analyses restricting to patients with a coded tumor resection, or to 2008-2015, yielded similar results to the primary multivariable analyses.

Reviews of 45 randomly sampled patient charts to determine why intravesical therapy was not used found that 2% of patients declined treatment and surveillance only was planned for 29%. In 20%, another resection was performed, potentially resulting in intravesical therapy beyond our study time windows, or patients were found to have muscle-invasive bladder cancer. In 11% of charts, intravesical therapy was administered but not captured by coded study data. In the remaining charts, there was not enough information to determine why treatment was not used.

DISCUSSION

In this cohort of 5386 NMIBC patients from a large, diverse integrated delivery system, intravesical therapy was used as part of initial treatment among 56% of patients from 2008 to 2015. Postoperative chemotherapy use increased significantly over time, whereas BCG use did not and was more strongly associated with tumor characteristics. Treatment variability was substantial: some urologists never used intravesical therapy as part of initial treatment for NMIBC, whereas other urologists almost always used it. This was true even restricting to more recent years and stratifying by tumor characteristics and treatment type. The wide spectrum of treatment practices suggests a considerable opportunity for quality improvement programs to reduce unwanted treatment variation.

Treatment use generally did not vary by patient sex or race/ethnicity, and tests for effect modification between treatment and race/ethnicity or sex were null. Treatment varied by age, with older patients less likely to be treated with intravesical therapy than middle-aged patients. Other studies also have reported lower intravesical therapy use among older patients despite its effectiveness.[28,29] Because BCG may not be well-tolerated by older patients, they may choose to undergo surveillance only. Progression is of greater concern among older patients, however, because they are less likely to be good candidates for RC surgery. Studies are needed to explore reasons behind treatment decisions, including patient preferences, and how treatment practices are related to outcomes.

Prior studies reported low and variable use of intravesical therapy,[5-11] and proposed quality metrics[12] have correspondingly set relatively low benchmarks. However, results from our study suggest that current treatment use may be higher than previously reported. Any intravesical therapy use was considered an important outcome from a quality improvement perspective because most NMIBC patients are eligible for either intravesical chemotherapy (lower-risk patients) or induction BCG (higher-risk patients). Thus, the primary focus was on whether any intravesical therapy was used for initial treatment across different patient groups. We plan to examine more nuanced aspects of over- or under-treatment in future studies and explore reasons for treatment changes (eg, in BCG use) further.

The higher estimates of intravesical therapy use in our study (and some other studies) may reflect increases in treatment over time as compared with earlier research. However, it also is possible that the complexity of capturing treatment led to underestimates in some prior reports. We used a multitude of approaches to capture treatment, including targeted chart reviews, and found this increased treatment use estimates. Thus, some prior estimates may have been affected by limitations in available data (eg, access to claims data only) and an inability to explore additional data sources.

Because of our interest in treatment disparities and physician decision-making, we focused on initiation of any intravesical therapy use, as treatment completion may reflect subsequent complications. The urologist characteristics we examined (including age, years within KPSC, oncology specialization, and experience treating bladder cancer) did not explain the wide treatment variability observed. Future studies on providers' beliefs and preferences for treatment — including the relative weight they place on prevention of recurrence vs side effects — are needed to better understand treatment variability. Additionally, we plan to examine disparities in completion of recommended treatments, treatment trajectories, and outcomes in future work. We also plan to extract additional information on tumors that is not available in discretely coded data, such as tumor size and multiplicity, to allow us to further risk-stratify patients.

Our study population included patients with bladder cancer diagnosed >5 years ago, because our clinical collaborators felt they would be treated as new cases; only a small number of patients (n = 99) had a prior bladder cancer diagnosis. Additionally, to account for aggressive treatment of bladder cancer, or other health conditions that might result in bladder cancer not being treated, we excluded patients with early RC/UD, infusion chemotherapy, entry into hospice, or death.

Our study took place within a single entity, and within our equal-access system, we did not observe treatment disparities by sex, insurance type, neighborhood household income, or neighborhood education level. This was true despite the wide variability in treatment practices and the large number of urologists seeing patients across our 15 medical centers. Similar research on surgery for prostate cancer found wide variability in treatment practices within a high-volume academic center.[30] That study also found that the wide treatment variability persisted in analyses stratified on patient characteristics.

Future studies are needed to assess quality, variability, and disparities across healthcare systems and in a wider range of populations. They also are needed to examine other treatments for NMIBC, as we did not study all potential quality indicators. Some prior research suggests that other treatment recommendations, such as restaging transurethral resection of bladder tumors, have been adopted more readily compared with use of intravesical therapy.[5] We plan to examine these and other quality measures in future work.

CONCLUSION

Substantial variability exists in the use of intravesical therapy for initial treatment of NMIBC, even within a single integrated delivery system and accounting for tumor characteristics. Data suggest a considerable opportunity exists for quality improvement programs and metrics to help reduce unwanted variation and improve care for NMIBC patients.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2019.03.035.

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EDITORIAL COMMENT

The authors report on a retrospective cohort study of 5386 patients diagnosed with nonmuscle-invasive bladder cancer (NMIBC) at Kaiser Permanente Southern California between 2001 and 2015. They find that 41% of patients received any intravesical therapy. Use of postoperative intravesical chemotherapy was rarer (given to 17%), but increased over time. There was substantial variation in use of intravesical therapy across urologists. The variation was greatest for use of postoperative intravesical chemotherapy, with 45% of the observed variation explained by the treating urologist.

The findings are important because the use of intravesical chemotherapy is a crucial component of guideline concordant NMIBC care.[1] An immediate postoperative dose of intravesical chemotherapy decreases 5-year recurrence rates by 14% from 59% to 45%.[2] Thus, administration of postoperative intravesical chemotherapy has been suggested as a quality measure.[3]

However, it is hard to know what the "right rate" of intravesical chemotherapy use should be. Clearly, there are contraindications present in some patients that justify non-use. To that end, the authors performed a random chart review among patients who did not receive intravesical therapy and found that in 20% a reresection was performed, providing a good rationale for not giving postoperative chemotherapy. Only 2% of patients declined intravesical therapy. However, in about two thirds of patients, reasons for nonadministration of intravesical therapy were less clear, including plan for surveillance only in 29% and no documented reason in 38%.

While it is somewhat encouraging that use of intravesical therapy increased over the study period, simply relying on natural time trends to improve care is not enough. There clearly is a need to implement more guideline concordant use of postoperative intravesical therapy, illustrated by the fact that some urologists used this therapy almost all of the time while others never used it. First, we will need to gain a thorough understanding of the barriers to guideline concordant NMIBC care, which are likely at the provider––(eg, lack of knowledge, worry about side-effects, and habit) and the hospital-level (eg, ease of writing the chemotherapy order, availability of trained nurses to administer drug in the recovery room). To that end, mixed-methods studies guided by implementation science frameworks provide a rigorous way to assess existing challenges to guideline concordant care.[4] Once known, these challenges can be addressed by systematically developing implementation strategies to improve care.[5]

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AUTHOR REPLY

We agree that the wide variability in postoperative chemotherapy use observed in our study underscores the need to increase guideline-consistent care for nonmuscle invasive bladder cancer. The physician factors we examined – including physician age, years employed at our institution, specialty training in oncology, and experience treating bladder cancer – did not explain the treatment variability. As Dr. Schroeck noted, other physician factors, such as the level of concern about side effects or awareness of and agreement with guidelines, may be important contributors to treatment variability.

We also agree that implementation science and mixed methods research may help identify ways to increase use of postoperative intravesical chemotherapy. However, studies of postoperative intravesical chemotherapy may need to go beyond the barriers typically focused on by implementation science studies, such as lack of guidelines or knowledge. This is because there is an unusually complicated set of inter-related factors that will need to be studied and addressed.

For example, it is possible that physicians may plan to use postoperative chemotherapy but then decide against it at the time of surgery for a variety of reasons (eg, tumor resection site was too extensive or too deep, in the physician's judgment, to use intravesical chemotherapy). Additionally, research on this topic may require more complex data collection because factors such as depth of tumor resection are difficult to capture and study; even identifying whether the physician thought the tumor resection was too deep to use postoperative chemotherapy may be challenging to capture. Similarly, for BCG immunotherapy, there have been medication shortages that may complicate or discourage treatment. Transdisciplinary research that focuses on these more subtle and complicated barriers to the use of postoperative intravesical chemotherapy (and BCG immunotherapy) could help advance research and clinical practice for bladder cancer, as well as make valuable contributions to implementation science.

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