Perioperative Intravesical Chemotherapy for Patients With Non–Muscle-invasive Bladder Cancer: Understanding the Extent of and Sources of Variation in Guideline-recommended Use

Devon K. Check, David S. Aaronson, Matthew E. Nielsen, Valerie S. Lee, Isaac J. Ergas, Janise M. Roh, Lawrence H. Kushi, Li Tang, and Marilyn L. Kwan

OBJECTIVE To examine intravesical chemotherapy (IVC) use according to non–muscle-invasive bladder cancer patient disease risk, and the contributions of multilevel factors to variation in proficient use among patients with low-intermediate disease.

METHODS This study included 988 patients diagnosed with non–muscle-invasive bladder cancer in an integrated health system in Northern California from 2015-2017. We calculated IVC receipt by disease risk, and among patients with low-intermediate risk disease, assessed the relationship between multilevel factors and IVC receipt using a logistic regression model with random intercepts for provider and service area, and patient-, provider-, and service area-level fixed effects. We further assessed the association of provider- and service area-level factors with IVC use by examining intraclass correlation coefficients.

RESULTS Similar proportions of low-intermediate (36%) and high-risk (34%) patients received IVC. In the multivariate analysis, including low-intermediate risk patients, service area volume was strongly and statistically significantly associated with IVC use (adjusted odds ratio, high- vs low-volume: 0.08, 95% Confidence Interval: 0.01-0.58). Provider- and service area-level intraclass correlation coefficients were large, (38%, $P = .0009$ and 39% $P = .03$, respectively) indicating that much of the variance in IVC use was explained by factors at these levels.

CONCLUSION Our findings highlight opportunities to improve proficient use of IVC. Future research should assess provider- and practice-level barriers to IVC use among low-intermediate risk patients. UROLOGY 124: 107–112, 2019. © 2018 Elsevier Inc.

In the United States, bladder cancer is the fifth most commonly diagnosed cancer, and the most expensive to treat on a per-patient basis.[1,2] Most patients (70%-80%) are diagnosed initially with non–muscle-invasive bladder cancer (NMIBC).[3] Patients with NMIBC have variable risk of disease recurrence (ranging from 50% to 80%) and progression to muscle-invasive disease (ranging from 1% to 30%), associated with factors such as stage and grade.[3-5] Clinical practice guidelines recommend risk-stratified approaches balancing heterogeneous risk and the morbidity associated with treatments. For example, guidelines recommend that patients who, at the time of initial transurethral resection of bladder tumors (TURBT) are suspected to have low or intermediate risk disease receive a single postoperative dose of intravesical chemotherapy (IVC).[6,7] For these patients, IVC results in an absolute reduction of recurrence risk by 10%-15%, compared to TURBT alone.[8-11] Recommendations for patients with high-risk features differ, and do not include perioperative IVC, given the less clear evidence supporting its benefit for those patients.[6,7]

Financial Disclosure: *All other authors declare that they have no relevant financial interests.*

Funding Support: *This study is supported by theNational Cancer Institute (NCI R01CA172855).Dr. Check's effort was supported by the Kaiser Permanente Northern California Delivery Science Fellowship.*

From the Kaiser Permanente Northern California Division of Research, Oakland, CA; the Department of Urology, Kaiser Permanente Northern California Oakland Medical Center, Oakland, CA; the Department of Urology, University of North Carolina at Chapel Hill, Chapel Hill, NC; and the Department of Cancer Prevention and Control, Roswell Park Comprehensive Cancer Institute, Buffalo, NY

Address correspondence to: Devon K. Check, Ph.D., Kaiser Permanente Northern California Division of Research, 2000 Broadway, 5th Floor, Oakland, CA 94612. E-mail: devon.k.check@kp.org

Submitted: June 2, 2018, accepted (with revisions): October 4, 2018

Despite level-one evidence supporting its use, adoption of perioperative IVC in practice appears to be suboptimal overall.[12-14] However, most prior studies on this topic have not measured proficiency of use in terms of patients' clinical risk for recurrence. In addition, limited data exist about the potential overuse of perioperative IVC among patients not recommended to receive it, despite the risk of function-limiting local side effects associated with receipt of mitomycin C,[15] the chemotherapeutic agent most commonly used for NMIBC.

Finally, the multilevel factors that help to explain variation in recommended use of perioperative IVC among low-intermediate patients are poorly understood. Knowledge of the potential contributions of patient-, clinician-, and practice-level factors to variation in use of perioperative IVC among patients recommended to receive it can inform the development of improvement strategies that target the relevant level(s) of care delivery.[16] Our study sought to address existing gaps in current knowledge about IVC use in practice, by (1) providing contemporary estimates of potential underuse of IVC among patients with low and intermediate risk disease, and potential overuse among patients with high-risk disease, and (2) investigating the contributions of multilevel factors to variation in use of IVC among low-intermediate risk patients (proficient use), with the goal of informing strategies to optimize IVC use in practice.

METHODS

Study Setting

Our study was conducted in an integrated delivery system that provides care to over 4 million members in Northern California. Members of this system are largely representative of the region's population but tend to be of higher socioeconomic status.[17] There are 126 urologists practicing in our system, organized into 15 service areas, each of which includes 1 or 2 out of 21 total medical centers.

Study Population

Our study included system members eligible for participation in an ongoing prospective cohort study of bladder cancer survivorship (the Be-Well study).[18] Patients eligible for Be-Well are those diagnosed with NMIBC (stage Ta, T1, or Tis), age 21 years or older, with no concurrent cancer or prior bladder cancer, and are able to speak English. Patients included in the present analysis were diagnosed between 1/1/2015 and 4/31/2017. They also had 1 year of continuous enrollment in the system (ie, no enrollment gap longer than 60 days) prior to NMIBC diagnosis, to calculate comorbidity burden, and 6 months of continuous enrollment after diagnosis, to examine initial treatment. Our system's Institutional Review Board approved this study.

Data Sources

The Be-Well study rapidly ascertained new cases of NMIBC using Systemized Nomenclature of Medicine clinical codes in electronic pathologic reports, and their eligibility for the study (as well as tumor grade) was confirmed using manual chart review. Patients' age at diagnosis, gender, race/ethnicity, diagnosing provider, and the medical center at which they were diagnosed were drawn from our system's Virtual Data Warehouse. Additional demographic characteristics (marital status, area-level measures of income and education), were also drawn from the Virtual Data Warehouse, along with Charlson comorbidity score,[19] treatment received, and provider characteristics. Bladder cancer stage (American Joint Commission on Cancer version 7) was obtained from our system's cancer registry.[20]

Variables

Our outcome was perioperative receipt of IVC. Patients were considered to have received perioperative IVC if they had an outpatient encounter record with a Healthcare Common Procedure Coding System, Current Procedural Terminology, International Classification of Diseases, 9th edition, Clinical Modification procedure, or system-specific code indicating receipt of any bladder instillation, any IVC, or use of 1 of 4 specific chemotherapeutic agents (mitomycin, doxorubicin, epirubicin, and gemcitabine) at the time of TURBT.

Patient disease risk (low-intermediate vs high) was defined based on the risk stratification system outlined in the 2016 update of the American Urological Association (AUA) guideline for NMIBC management.[6] Low-intermediate risk patients included those with low-grade Ta, low-grade T1 or high-grade (HG) Ta tumors. Patients with HG T1 tumors or any carcinoma in situ were considered high risk.

At the patient level, factors evaluated for their association with IVC use among low-intermediate risk patients included age at diagnosis, gender, race/ethnicity, Charlson comorbidity score, smoking status, marital status, and area-level measures of education and income. Provider-level covariates included number of years in practice and completion of a clinical fellowship (eg, urologic oncology, minimally invasive surgery). At the service area-level, we included the volume of NMIBC patients seen over the course of the study period (low: ≤47, medium: 48-69, high: ≥70) as a measure of practice size. Practice size cut-offs were established according to the distribution of our data.

Analytic Approach

We first described differences between recipients and nonrecipients of IVC — in terms of disease risk and other patient, provider, and service area-level characteristics — using chi-square tests. Then, in a multivariable model including low-intermediate risk patients ($N = 698$), we assessed the relationship between patient disease risk and IVC receipt, using multilevel modeling techniques to account for the hierarchical structure of the data (patients nested within providers nested within service areas). Specifically, we fit a generalized linear mixed model with a logit link and random intercepts for provider and service area. The statistical significance of the random effects was assessed using likelihood ratio tests. Patient-, provider-, and service area-level covariates were included in the model as fixed effects, and adjusted odds ratios and 95% CIs were calculated.

We further assessed the association of provider- and service area-level factors with IVC use by examining the estimates of the variance components and the intraclass correlation coefficients (ICCs). For a dichotomous outcome, the ICCs represent the percentage of variance in the outcome attributable to each random effect level (providers and service areas). ICCs were calculated first in a model adjusting only for patient-level covariates (ie, fixed effects) to

determine the proportion of variance not explained by patient fixed effects that is attributable to providers and service areas. We then calculated ICCs in the final model adjusting for provider and service area characteristics in addition to patient mix, to indicate the extent to which the provider and service area characteristics accounted for in our analysis explained between-provider and between-facility practice heterogeneity. All analyses were conducted using SAS 9.3 (Cary, NC).

Because risk-stratification was newly introduced in the 2016 AUA guideline, and our sample included patients diagnosed in 2015, we also calculated the proportions of low-intermediate and high-risk patients who received IVC among patients diagnosed after the release of the new guideline in April 2016 ($N = 422$). Because proportions were nearly equivalent to those calculated on our full sample, they are not reported here. Additionally, we conducted a secondary analysis with HG Ta patients ($N = 249$) classified as high (vs intermediate) risk. Depending on the size and number of bladder tumors, patients with HG Ta disease can fall into either disease risk category, according to the AUA guideline. We lacked data on size and number of tumors, but because large, multifocal (ie, high risk) HG Ta tumors are rare, our primary analysis classifies patients with HG Ta tumors as intermediate-risk. In our secondary analysis classifying HG Ta patients as high risk, our results were very similar to those observed in our primary analysis. Therefore, the results of that secondary analysis are not presented.

RESULTS

Characteristics of Recipients and Nonrecipients of IVC

Our analytic cohort included 988 patients with NMIBC (449 low risk, 249 intermediate risk, and 290 high risk). As shown in Table 1, nearly equivalent proportions of low-intermediate risk (36%) and high risk (34%) patients received IVC ($P = .46$). IVC recipients and nonrecipients were also similar with respect to demographic and other health-related characteristics, although recipients tended to be younger ($P = .02$). With respect to urologist and service area characteristics, IVC recipients were less likely to be treated by a urologist with 30 or more years in practice ($P = .004$), and more likely to be treated in a low-volume service area ($P < .0001$).

Adjusted Associations of Patient, Urologist, and Service Area Characteristics With IVC Receipt, Among Low-intermediate Risk Patients

Our multivariate model revealed no statistically significant associations between patient characteristics and IVC receipt (see Table 2). At the urologist level, the association of number of years in practice and IVC receipt was no longer statistically significant. At the service area-level, NMIBC patient volume remained statistically significantly associated with IVC receipt, with patients treated in high-volume service areas having 0.08 times the odds of receiving IVC relative to patients treated in low-volume service areas (adjusted odds ratio: 0.08, 95% CI: 0.01-0.58).

Urologist and Facility-attributable Variation in Patient IVC Receipt

Before adding urologist and service area characteristics to the model, the urologist- and service area-level ICCs were statistically significant at 39% ($P = .0008$) and 38% ($P = .02$), respectively, indicating that 39% of the heterogeneity in patients' IVC receipt is explained by urologist characteristics and 38% is explained by service area characteristics. In the final model including urologist and service area characteristics, the service area-level ICC became smaller (29%, $P = .03$), and the urologist-level ICC was unchanged (39%, $P = .0009$). The change in service area-level ICC indicates that patient volume explained 10% of the heterogeneity in IVC use observed at the service area level. The urologist-level characteristics included in our model (years in practiced and fellowship training) explained none of the urologist-level heterogeneity in patients' IVC receipt.

COMMENT

In our sample of patients diagnosed with NMIBC, only 36% of patients with low-intermediate risk disease received IVC. A very similar proportion of patients with high-risk disease (34%) received IVC, despite guideline recommendations discouraging use among patient with high-risk features. In a multivariate analysis intended to identify potential predictors of proficient IVC use among low-intermediate risk patients, no patient or urologist characteristics were statistically significantly associated with IVC use. Rather, we found that service area volume was strongly and negatively associated with IVC receipt. Our results also indicate that large and statistically significant proportions of the total variation in patients' IVC receipt can be attributed to service area and urologist characteristics. Patient volume explained some but not all of the variation at the service area level.

Prior studies of IVC use among patients with NMIBC are few. Most have been based on data from patients diagnosed between 1992 and 2002,[12-14] well before recommendations for perioperative IVC appeared in AUA guidelines in 2007.[21] Not unexpectedly, these prior studies concluded that IVC is vastly underused, with less than 6% of all patients receiving IVC. Our estimate of IVC receipt is more consistent with that from a quality improvement study of nearly 2800 patients from 5 U.S. urology practices published in 2013 by Barocas and colleagues.[22] Taken together, ours and the Barocas study — which used data from 2010 to 2012 — suggest that the proportion of NMIBC patients receiving IVC has increased over time.

Despite this apparent increase, our results, as well as those from the Barocas study, suggest that, among low-intermediate risk patients, use of the therapy remains suboptimal. Low IVC uptake is often attributed to barriers associated with what is, to date, the chemotherapeutic agent most widely recommended and used for this indication in the U.S. — mitomycin C. Namely, the cost of mitomycin C[23] and its potential for serious albeit rare complications[15] are thought to limit its use in practice.[22] However, to our knowledge, empirical evaluations of the barriers to and facilitators of proficient IVC use are lacking. This is an important gap in understanding, particularly in the context of a recently published randomized

Table 1. Distribution of NMIBC cohort characteristics by receipt of perioperative intravesical chemotherapy

	Total Patients ($N = 988$) *N* (%)	IVC Recipients ($N = 351$) *N* (%)	IVC Nonrecipients ($N = 637$) *N* (%)	*P* Value
Patient characteristics				
Age at diagnosis (y)				
≤65	308 (31.2)	124 (40.3)	184 (59.7)	.02
66-79	436 (44.1)	156 (35.8)	280 (64.2)	
≥80	244 (24.7)	71 (29.1)	173 (70.9)	
Gender				
Male	781 (79.1)	273 (35.0)	508 (65.0)	.47
Female	207 (20.9)	78 (37.7))	129 (62.3)	
Charlson comorbidity score				
0	159 (16.1)	66 (41.5)	93 (58.5))	.27
1-2	287 (29.1)	101 (35.2)	186 (64.8)	
3-4	169 (17.1)	62 (36.7)	107 (63.3)	
≥5	373 (37.8)	122 (32.7)	251 (67.3)	
Smoking status				
Never	317 (32.1)	108 (34.1)	209 (65.9)	.09
Former	537 (54.4)	184 (34.3)	353 (65.7)	
Current	134 (13.6)	59 (44.0)	75 (56.0)	
Race/ethnicity				
Non-Hispanic white	759 (76.8)	263 (34.7)	496 (65.4)	.48
Black	49 (5.0)	16 (32.7)	33 (67.4)	
Hispanic/Latino	79 (8.0)	28 (35.4)	51 (64.6)	
Asian/Pacific Islander	78 (7.9)	33 (42.3)	45 (57.7)	
Other	23 (2.3)	11 (47.8)	12 (52.2)	
Marital status				
Single	276 (27.9)	90 (32.6)	186 (67.4)	.41
Married/partnered	570 (57.7)	212 (37.2)	358 (62.8)	
Unknown	142 (14.4)	49 (34.5)	93 (65.5)	
Median household income in census track				
$15,521-56,562	236 (23.9)	84 (35.6)	152 (64.4)	.45
$56,563-77,056	239 (24.2)	84 (35.2)	155 (64.9)	
$77,057-102,893	264 (26.7)	94 (35.6)	170 (64.4)	
≥$102,894	247 (25.0)	87 (35.2)	160 (64.8)	
Unknown	2 (0.2)	2 (0.6)	0 (0.0)	
Proportion of adult population with < high school education in census track				
0%-11%	239 (24.2)	74 (31.0)	165 (69.0)	0.20
12%-18%	249 (25.2)	92 (37.0)	157 (63.0)	
19%-26%	265 (26.8)	91 (34.3)	174 (65.7)	
≥27%	235 (23.8)	94 (40.0)	141 (60.0)	
Patient characteristics				
Disease risk group				
Low-intermediate	698 (70.7)	253 (36.3)	445 (63.8)	.46
High	290 (29.3)	98 (33.8)	192 (66.2)	
Urologist characteristics				
Urologist gender				
Male	745 (75.4)	242 (32.5)	503 (67.5)	.0005
Female	243 (24.6)	109 (44.8)	134 (55.1)	
Number of years in practice				
≤12	319 (32.3)	124 (38.9)	195 (61.1)	.004
13-30	546 (55.3)	201 (36.8)	345 (63.2)	
≥30	117 (11.8)	24 (20.5)	93 (36.8)	
Unknown	6 (0.6)	2 (0.6)	4 (0.6)	
Fellowship training				
Yes	298 (30.2)	105 (35.2)	193 (64.8)	.35
No	650 (65.8)	236 (36.3)	414 (63.7)	
Unknown	40 (40.0)	10 (25.0)	30 (75.0)	
Service area characteristics				
Service area volume				
Low (≤47 patients)	157 (15.9)	88 (56.1)	69 (44.0)	<.0001
Medium (48-69 patients)	418 (42.3)	148 (35.4)	270 (64.6)	
High (70+ patients)	413 (41.8)	115 (27.9)	298 (72.2)	

IVC, intravesical chemotherapy; NMIBC, non—muscle-invasive bladder cancer.

Table 2. Adjusted odds of perioperative IVC receipt among NMIBC patients

Predictor	Odds Ratio (95% Confidence Interval)
Patient characteristics	
Age at diagnosis (y)	
<50	1.00 (REF)
50-65	1.14 (0.60-2.14)
66-79	1.03 (0.53-1.99)
≥80	0.68 (0.34-1.32)
Charlson comorbidity score	
0	1.00 (REF)
1-2	0.96 (0.50-1.86)
3-4	0.96 (0.48-1.92)
≥5	1.38 (0.63-2.97)
Gender	
Male	1.00 (REF)
Female	0.93 (0.55-1.57)
Race/ethnicity	
Non-Hispanic white	1.00 (REF)
Black	0.95 (0.31-2.94)
Hispanic/Latino	0.90 (0.40-2.03)
Asian/Pacific Islander	1.35 (0.58-3.16)
Other	2.36 (1.92-10.70)
Marital status	
Single	1.00 (REF)
Married/partnered	1.45 (0.85-2.46)
Median household income in census track	
$15,521-56,562	1.00 (REF)
$56,563-77,056	0.96 (0.50-1.86)
$77,057-102,893	1.04 (0.48-1.92)
≥$102,894	1.27 (0.60-2.69)
Proportion of adult population with < high school education in census track	
0%-11%	1.00 (REF)
12%-18%	1.14 (0.67-1.96)
19%-26%	1.09 (0.61-1.92)
≥27%	1.38 (0.63-2.97)
Urologist characteristics	
Number of years in practice	
≤12	1.00 (REF)
13-30	1.35 (0.55-3.29)
≥30	1.99 (0.45-8.67)
Fellowship training	
No	REF
Yes	1.23 (0.51-2.97)
Service area characteristics	
Service area volume	
Low	1.00 (REF)
Medium	0.12 (0.02-0.73)
High	0.08 (0.01-0.58)
Percent of variance unexplained by patient-level fixed effects that is explained by this other level effect	
Urologist-level	25%
Service area-level	31%

controlled trial demonstrating, among patients with low-grade NMIBC, an absolute reduction in recurrence of 12% with IVC using gemcitabine vs placebo.[24] Because gemcitabine is generally less expensive than mitomycin C, and has an adverse event profile similar to placebo, it may help to overcome perceived barriers to IVC with mitomycin C. However, to the extent that IVC uptake has been limited by factors other than concerns about cost and toxicity, the potential of the gemcitabine findings to improve patient outcomes may be limited.[25] The persistent underuse of IVC highlighted by our study indicates a clear need for the empirical study of barriers to IVC use as currently recommended, and whether they may also apply to gemcitabine.

As the first study, to our knowledge, to examine the contributions of practice- and provider- level factors in explaining variation in proficient IVC use, our results also offer insight into potential next steps for investigating barriers to proficient IVC use in practice. First, we observed that a large and statistically significant amount of variation in IVC use was explained by factors at the provider and practice levels, indicating substantial opportunities for quality improvement at both levels.[16] Second, we observed a strong and statistically significant relationship between service area volume and IVC use. Specifically, patients seen in high-volume service areas had much lower odds of receiving IVC than patients seen in lower-volume service areas. The specific factors underlying this relationship are unclear and require further investigation as part of efforts to understand barriers to proficient IVC use. One possible explanation is that providers practicing in high-volume practices may have had more exposure to the rare but severe toxicities associated with mitomycin. Prior experience caring for patients experiencing these toxicities could discourage providers from administering IVC to future patients. Another explanation is that practices seeing large volumes of patients with NMIBC may have established pathways for surveillance following initial resection of bladder tumors. If providers in these practices are confident that their patients will be closely monitored for recurrence, they may be less inclined to administer IVC at the time of resection.

Another unique contribution of our study is its estimated overuse of perioperative IVC among high-risk patients, given that high-risk patients in our sample were nearly as likely (34%) as low-to-intermediate risk patients to receive perioperative IVC prior to adjustment. Our sample of high-risk patients was too small to examine the independent predictors of IVC use within this population, but this is an important area for future research, to guide deimplementation of low-value use of therapy.[26]

Our study has some limitations. First, we lacked data on the number and size of patients' bladder tumors, and therefore our definitions of disease risk group differed slightly from those set forth by clinical practice guidelines, and we may have misclassified some patients with HG Ta disease. We attempted to address this limitation through our secondary analysis classifying HG Ta patients as high vs intermediate risk. Second, our limited sample size may have resulted in an inability to detect some associations. Third, we were unable to systematically analyze data from provider notes, meaning we could not identify potential reasons underlying apparent under- or overuse of IVC. Finally, we focused on a single healthcare system, which could limit the generalizability of our findings. However, the similarity of our estimates of IVC use to those reported

in the Barocas study — which included several diverse urology practices from across the country — suggest that the patterns we observed are not unique to our system.

CONCLUSION

Altogether, our results suggest that IVC use in practice is much higher than reported in most previous studies of NMIBC care. Even so, our findings point to substantial room for improvement in proficient use of IVC. Our findings suggest that strategies targeting urology providers and/or practices are appropriate and will inform further mixed methods work to understand barriers to and facilitators of guideline-concordant IVC use at both levels, with the goal of intervention development to improve proficient use.

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin*. 2014;64:9–29.
2. Botteman MF, Pashos CL, Redaelli A, Laskin B, Hauser R. The health economics of bladder cancer: a comprehensive review of the published literature. *Pharmacoeconomics*. 2003;21:1315–1330.
3. Avritscher EB, Cooksley CD, Grossman HB, et al. Clinical model of lifetime cost of treating bladder cancer and associated complications. *Urology*. 2006;68:549–553.
4. Holmang S, Hedelin H, Anderstrom C, Johansson SL. The relationship among multiple recurrences, progression and prognosis of patients with stages Ta and T1 transitional cell cancer of the bladder followed for at least 20 years. *J Urol*. 1995;153:1823–1826. discussion 6-7.
5. Pow-Sang JM, Seigne JD. Contemporary management of superficial bladder cancer. *Cancer Control*. 2000;7:335–339.
6. Chang SS, Boorjian SA, Chou R, et al. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO guideline. *J Urol*. 2016;196:1021–1029.
7. Babjuk M, Bohle A, Burger M, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2016. *Eur Urol*. 2017;71:447–461.
8. Tolley DA, Parmar MK, Grigor KM, et al. The effect of intravesical mitomycin C on recurrence of newly diagnosed superficial bladder cancer: a further report with 7 years of follow up. *J Urol*. 1996;155:1233–1238.
9. Solsona E, Iborra I, Ricos JV, Monros JL, Casanova J, Dumont R. Effectiveness of a single immediate mitomycin C instillation in patients with low risk superficial bladder cancer: short and long-term followup. *J Urol*. 1999;161:1120–1123.
10. Sylvester RJ, Oosterlinck W, Holmang S, et al. Systematic review and individual patient data meta-analysis of randomized trials comparing a single immediate instillation of chemotherapy after transurethral resection with transurethral resection alone in patients with stage pTa-pT1 urothelial carcinoma of the bladder: which patients benefit from the instillation? *Eur Urol*. 2016;69:231–244.
11. Bosschieter J, Nieuwenhuijzen JA, van Ginkel T, et al. Value of an immediate intravesical instillation of mitomycin C in patients with non-muscle-invasive bladder cancer: a prospective multicentre randomised study in 2243 patients. *Eur Urol*. 2018;73:226–232.
12. Chamie K, Saigal CS, Lai J, et al. Compliance with guidelines for patients with bladder cancer: variation in the delivery of care. *Cancer*. 2011;117:5392–5401.
13. Chamie K, Saigal CS, Lai J, et al. Quality of care in patients with bladder cancer: a case report? *Cancer*. 2012;118:1412–1421.
14. Madeb R, Golijanin D, Noyes K, et al. Treatment of nonmuscle invading bladder cancer: do physicians in the United States practice evidence based medicine? The use and economic implications of intravesical chemotherapy after transurethral resection of bladder tumors. *Cancer*. 2009;115:2660–2670.
15. Filson CP, Montgomery JS, Dailey SM, et al. Complications associated with single-dose, perioperative mitomycin-C for patients undergoing bladder tumor resection. *Urol Oncol*. 2014;32:40. e1—40.e8.
16. Selby JV, Schmittdiel JA, Lee J, et al. Meaningful variation in performance: what does variation in quality tell us about improving quality? *Med Care*. 2010;48:133–139.
17. Gordon N. *How Does the Adult Kaiser Permanente Membership in Northern California Compare With the Larger Community?* Kaiser Permanente Northern California Division of Research; 2016.
18. Kwan ML KL, Quinn VP, Ghai NR, et al. Identifying lifestyle and genetic factors to prevent recurrence of non-muscle invasive bladder cancer in a prospective cohort study at Kaiser Permanente (The Be-Well Study). *American Association for Cancer Research (AACR) Annual Meeting*. New Orleans, LA; 2016.
19. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45:613–619.
20. Oehrli MDQC. *Northern California Cancer Registry: 2016 Annual Report on Trends, Incidence, and Outcomes*. Kaiser Permanente, Northern California Cancer Registry; 2017.
21. Hall MC, Chang SS, Dalbagni G, et al. Guideline for the management of nonmuscle invasive bladder cancer (stages Ta, T1, and Tis): 2007 update. *J Urol*. 2007;178:2314–2330.
22. Barocas DA, Liu A, Burks FN, et al. Practice based collaboration to improve the use of immediate intravesical therapy after resection of nonmuscle invasive bladder cancer. *J Urol*. 2013;190:2011–2016.
23. Davies BJ, Hwang TJ, Kesselheim AS. Ensuring access to injectable generic drugs - the case of intravesical BCG for bladder cancer. *N Engl J Med*. 2017;376:1401–1403.
24. Messing EM, Tangen CM, Lerner SP, et al. Effect of intravesical instillation of gemcitabine vs saline immediately following resection of suspected low-grade non-muscle-invasive bladder cancer on tumor recurrence: SWOG S0337 randomized clinical trial. *JAMA*. 2018;319:1880–1888.
25. Kaffenberger SD, Miller DC, Nielsen ME. Simplifying treatment and reducing recurrence for patients with early-stage bladder cancer. *JAMA*. 2018;319:1864–1865.
26. Nielsen ME, Birken SA. Implementation science theories to inform efforts for de-implementation of urologic oncology care practices resulting in overuse and misuse. *Urol Oncol*. 2018;36:252–256.