Chemoradiation Vs Radical Cystectomy for Muscle-invasive Bladder Cancer: A Propensity Score-weighted Comparative Analysis Using the National Cancer Database

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OBJECTIVE To address the overarching question whether chemoradiation therapy (CMT) offers overall survival (OS) similar to that of radical cystectomy (RC) in muscle-invasive bladder cancer (MIBC), we performed analyses using the National Cancer Database.

MATERIALS AND METHODS Patients diagnosed with MIBC in 2004-2014 who underwent RC or received primary CMT were identified in the National Cancer Database. Survival was estimated using the weighted Kaplan-Meier method, and propensity score-weighted Cox proportional hazards model were used to evaluate association of clinicopathologic features with outcome.

RESULTS Of 484,367 patients with a diagnosis of bladder cancer, 35,856 underwent RC and 4050 received CMT. After applying the exclusion/inclusion criteria, data for 15,854 patients who underwent RC and 2083 who received CMT were available for analysis. Five-year OS was 40.4% in the RC group and 29.4% in the CMT group (P <.001). OS was significantly shorter in the CMT group than in the RC group in both multivariate analysis (hazards ratio [HR] 1.15, 95% CI 1.08-1.22; P <.001) and propensity score-weighted analysis (HR 1.18, 95% CI 1.07-1.30; P <.001). Interaction terms indicated better survival after RC in patients younger than 70 years (HR 1.61, 95% CI 1.34-1.93; P <.001); subgroup analyses identified a survival benefit in patients with N0/N1 disease who underwent RC (HR 1.21, 95% CI 1.09-1.33; P <.001).

CONCLUSION AND RELEVANCE OS after 1 year of treatment was increased in RC group compared to CMT group in patient with MIBC. Further studies are required to identify optimal treatment for specific patients. UROLOGY 133: 164–174, 2019. © 2019 Elsevier Inc.

There were approximately 79,030 new bladder cancer cases in the US in 2017 and 16,870 related deaths.[1] Radical cystectomy (RC) is the gold standard treatment for muscle-invasive bladder cancer (MIBC). Patients treated with surgery experience significant procedure-related morbidity and report poor overall satisfaction and health-related quality of life.[2] The current National Comprehensive Cancer Network Clinical Practice Guidelines indicate that bladder-preserving therapy, with cystectomy reserved for tumor recurrence, is a safe and effective alternative to RC for MIBC.[3]

According to the current National Comprehensive Cancer Network guidelines, chemoradiation therapy (CMT) is a curative treatment option in patients who are not surgical candidates, that is, those with extensive comorbidities and/or poor performance status. This combined modality approach consists of (1) maximal transurethral resection of bladder tumor, (2) induction external-beam radiation therapy with concurrent chemotherapy, (3) cystoscopic assessment of the response to treatment with prompt cystectomy for nonresponders, and (4) active cystoscopic surveillance with salvage cystectomy at the first sign of invasive recurrence. Retrospective studies have consistently shown that the majority of patients who undergo CMT achieve a clinical response, with preservation of the native bladder in more than 70% of cases and

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long-term survival rates comparable with those in the contemporary cystectomy series.[4-6]

CMT as an alternative to RC for muscle invasive bladder cancer is now endorsed by multiple international cancer organizations that have developed evidence-based consensus guidelines, including the American Urologic Association, American Society of Clinical Oncology, Society of Urologic Oncology, and European Association of Urology.

Our understanding of the role of CMT as an alternative to RC in the treatment of MIBC is evolving. Thus far, 4 studies have identified a reduction in the overall mortality risk after RC,[7-10] while 4 have found no difference in overall survival (OS) between patients who receive CMT and those who undergo RC.[11-13] However, most of the studies comparing RC with CMT have been systematic reviews and meta-analyses based on retrospective analyses of institutional cohorts and have discordant findings.[14-16] Given the paucity of data regarding the effects of these 2 treatment modalities and lack of randomized controlled trials, we performed this study to compare the OS rates between RC and CMT using the data in the National Cancer Database (NCDB).

MATERIALS AND METHODS

Data Source and Patient Selection

The NCDB is a joint project between the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The database is a hospital-based registry that includes data for 70% of all cancer cases in the US and draws data elements from more than 1500 Commission on Cancer-accredited programs. The data used in the study are derived from a deidentified NCDB file. The NCDB has established criteria to ensure the data submitted meet specific quality benchmarks. Our NCDB analysis was performed with the approval of the institutional review board (IRB# HSC20180347N). The need for informed consent was waived in view of the retrospective observational nature of the study and the anonymity of the data. We retrieved the records held in the NCDB for 484,367 patients diagnosed with bladder cancer (*International Classification of Diseases for Oncology, 3rd edition* topography codes C67.0-C67.9) from 2004 to 2014. Patients with localized MIBC clinically staged as cT2−T4M0 were identified according to the American Joint Committee on Cancer staging system. Patients with missing clinical or pathologic staging data were excluded. The patients were stratified according to the primary treatment received, which was either RC with or without perioperative chemotherapy or definitive CMT.

Receipt of RC was determined by surgery of the primary site code (excluding patients who underwent simple or partial cystectomy and those for whom there was no information on local treatment). CMT was defined as receipt of a regional dose of at least 50 Gy plus chemotherapy within 90 days of radiation (excluding patients who received less than 50 Gy and those who received either chemotherapy or radiation alone).

Covariates and Endpoints

The patient sociodemographic covariates included age, sex, race, Hispanic origin (yes or no), residence (urban metropolitan or rural), Charlson Comorbidity Index, insurance status, and income. Facility variables included facility type, which was calculated according to the number of patients diagnosed with bladder cancer annually and comprised community centers (100-500 cases), comprehensive community cancer centers (≥500 cases), and academic centers providing graduate medical training (≥500 cases). Tumor characteristics included histology, T stage, and N stage, with TNM staged according to the American Joint Committee on Cancer staging system. The primary outcome was OS from the initial diagnosis to the date of death or last follow-up.

Statistical Methods

Categorical outcomes were summarized as frequencies and percentages. Multiple imputation by chained equations was performed to produce imputed data sets that accounted for missing covariate values (year of diagnosis, age group, race, Hispanic origin, income, residence, Charlson Comorbidity Index, insurance status, education, type of facility, location of facility, histology, T stage, N stage, number of nodes examined, surgical margin, and nodal status) in the NCDB.[17,18] The significance of variation in survival time according to treatment was assessed using an unweighted and propensity score-weighted Cox proportional hazards model. Weighted Kaplan-Meier curves were computed from the average of the 5 propensity score weights. Median OS was determined from the Kaplan-Meier tabulation. The treatments (RC and CMT) were contrasted with regard to binary and categorical outcomes using weighted Pearson's chi-square statistics.

Propensity weights adjusted for the same covariates as those used in the imputation were computed using the covariate balancing propensity scores (CBPS) Package (R Foundation for Statistical Computing, Vienna, Austria).[19] All variables found significant (P <.05) on univariate analysis were included in the multivariate model. The treatments were compared for OS using a weighted multivariate proportional hazards model and described graphically using weighted Kaplan-Meier curves and the corresponding log-rank test. One thousand seven hundred and fifty-seven patients had missing survival time data so were excluded from the proportional hazards model analysis and Kaplan-Meier curve computations; the overall analysis sample size was 17,937 (RC, n = 15,854; CMT, n = 2083). We conducted exploratory analyses to determine the heterogeneity of the treatment effect by testing interaction terms within the adjusted Cox model. We identified variables that had a significant interaction with treatment effect and then performed separate stratified analyses dichotomized for the interacting variables. All statistical analyses were performed using R software (R Foundation for Statistical Computing) and SAS version 9.4 for Windows (SAS Institute Inc., Cary, NC). For imputational analyses, we used the Multivariate Imputation by Chained Equations package in R studio version1.1.453 and utilized 5 imputed data sets. All statistical testing was 2-sided with a significance level of 5%.

RESULTS

The search of the NCDB identified 484,367 patients who had been diagnosed with bladder cancer (including 67,242 with nonmetastatic MIBC) between 2004 and 2014. Of these patients, 35,856 had undergone RC and 4050 had received CMT. After application of the exclusion/inclusion criteria, data for 17,937

patients (RC, $n = 15,854$; CMT, $n = 2083$) were available for inclusion in the analysis (Fig. 1). Of 16,180 patients with survival information available, 932 (5.7%; RC, $n = 807$; CMT, $n = 125$) had at least 1 missing covariate value. All missing covariate values were imputed for the entire cohort. Unweighted and propensity score-weighted univariate comparisons of the sociodemographic, facility, and tumor characteristics in the 2 treatment groups are shown in Table 1. Treatment varied significantly with age; CMT was more common than RC in patients aged ≥80 years (32.6% vs 16.2%) whereas RC was more common than CMT in those aged 60-69 years (28.7% vs 21%). Treatment varied significantly with comorbidity ($P < .001$); comorbidity was more common in patients who underwent RC than in those who received CMT (31.3% vs 24.9%). Treatment varied significantly with facility ($P < .001$); more patients received RC than CMT at an academic/research facility (52.6% vs 32.2%) whereas more patients received CMT than RC in a Comprehensive Community Cancer Program (45.5% vs 32.1%). Treatment varied significantly with T stage ($P < .001$); RC was more common than CMT in patients with cT2 disease (78.6% vs 64.9%) whereas CMT was more common than RC in those with cT4 disease (21.2% vs 8.3%).

Overall Survival

The median OS for the entire cohort was 30.5 months and was longer in those who underwent RC than in those who received CMT (36.2 months vs 24.2 months). The 5-year OS was 35.3% for the entire cohort and was better in those who underwent RC than in those who received CMT (40.4% vs 29.4%; $P < .001$).

Based on the unweighted multivariate proportional hazards model (Table 2), OS was significantly decreased in patients after

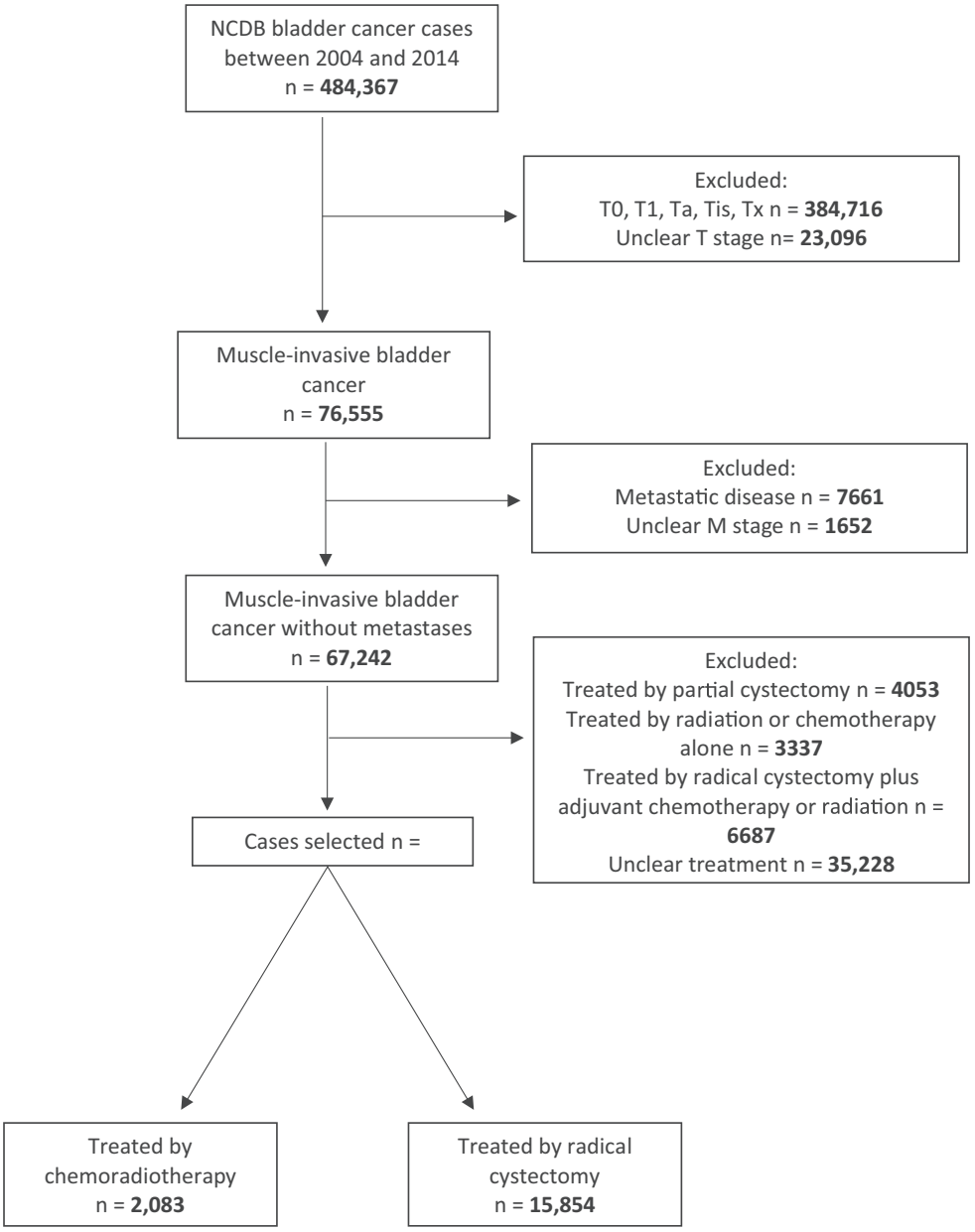

Figure 1. CONSORT flow diagram demonstrating the inclusion and exclusion criteria for the study cohort. CMT, chemoradiation therapy; NCDB, National Cancer Database; RC, radical cystectomy.

Table 1. Unweighted and weighted baseline characteristics

	Unweighted study Population				Weighted Study Population		
	Overall	Chemoradiation	Radical Cystectomy	*P* Value	Chemoradiation (%)	Radical Cystectomy (%)	*P* Value
n	17,937	2083	15,854				
Sex, *n* (%)				.294			.661
Male	13,455 (75.0)	1543 (74.1)	11,912 (75.1)		74.8	75.5	
Female	4482 (25.0)	540 (25.9)	3942 (24.9)		25.2	24.5	
Age, y *n* (%)[a]				<.001			.059
<60	3345 (18.6)	251 (12.0)	3094 (19.5)		16	18.9	
60-69	4993 (27.8)	438 (21.0)	4555 (28.7)		25.6	27.8	
70-79	6352 (35.4)	714 (34.3)	5638 (35.6)		38.6	35.3	
≥80	3247 (18.1)	680 (32.6)	2567 (16.2)		19.8	18	
Race, *n* (%)				.045			.536
White	16,401 (91.4)	1881 (90.3)	14,520 (91.6)		90.9	91.3	
Black	1013 (5.6)	145 (7.0)	868 (5.5)		6.5	5.8	
Asian	210 (1.2)	21 (1.0)	189 (1.2)		0.8	1.2	
Others	313 (1.7)	36 (1.7)	277 (1.7)		1.9	1.7	
Hispanic origin, *n* (%)	464 (2.7)	59 (3.0)	405 (2.7)	.411	2.1	2.8	.162
Income, *n* (%)				.001			.531
<$38,000	2903 (16.5)	371 (18.2)	2532 (16.3)		17.1	16.8	
$38,000-$47,999	4435 (25.2)	555 (27.3)	3880 (24.9)		25.5	25.3	
$48,000-$62,999	4908 (27.9)	551 (27.1)	4357 (28.0)		29.9	28	
$63,000+	5365 (30.5)	559 (27.5)	4806 (30.9)		27.5	29.8	
County type, *n* (%)				.504			.354
Metropolitan	13,841 (77.2)	1628 (78.2)	12,213 (77.0)		76.7	77.1	
Urban	2972 (16.6)	328 (15.7)	2644 (16.7)		15.4	16.5	
Rural	1124 (6.3)	127 (6.1)	997 (6.3)		7.8	6.4	
CCI, *n* (%)				<.001			.834
0	12,461 (69.5)	1565 (75.1)	10,896 (68.7)		68.9	69.3	
≥1	5476 (30.5))	518 (24.9)	4958 (31.3)		31.1	30.7	
Insurance status, *n* (%)				<.001			.267
Not insured	435 (2.4)	28 (1.3)	407 (2.6)		2.2	2.6	
Private insurance	5141 (28.7)	435 (20.9)	4706 (29.7)		25.5	28.8	
Medicaid	734 (4.1)	80 (3.8)	654 (4.1)		3.4	4	
Medicare	11,172 (62.3)	1436 (68.9)	9736 (61.4)		65.7	62	
Other government	206 (1.1)	69 (3.3)	137 (0.9)		1.4	1.3	
Insurance status unknown	249 (1.4)	35 (1.7)	214 (1.3)		1.8	1.4	
Facility type, *n* (%)				<.001			.284
Community Cancer Program	1244 (6.9)	264 (12.7)	980 (6.2)		8	7.3	
Comprehensive Community Cancer Program	6033 (33.6)	948 (45.5)	5085 (32.1)		35.9	33.7	
Academic/Research Program	9015 (50.3)	671 (32.2)	8344 (52.6)		47.1	50.4	
Integrated Network Cancer Program	1553 (8.7)	193 (9.3)	1360 (8.6)		9	8.7	

Continued

Table 1. Continued

	Unweighted study Population				Weighted Study Population		
	Overall	Chemoradiation	Radical Cystectomy	*P* Value	Chemoradiation (%)	Radical Cystectomy (%)	*P* Value
Histology, *n* (%)				<.001			.803
Pure urothelial	15,754 (87.8)	1800 (86.4)	13,954 (88.0)		87.2	88	
Squamous	807 (4.5)	87 (4.2)	720 (4.5)		5.5	4.5	
Neuroendocrine	253 (1.4)	66 (3.2)	187 (1.2)		1.5	1.3	
Adenocarcinoma	143 (0.8)	23 (1.1)	120 (0.8)		0.9	0.9	
Sarcomatoid	306 (1.7)	15 (0.7)	291 (1.8)		1.2	1.6	
Micropapillary component	164 (0.9)	14 (0.7)	150 (0.9)		1.1	0.9	
Other	510 (2.8)	78 (3.7)	432 (2.7)		2.6	2.8	
T stage, *n* (%)				<.001			.041
T2	13,818 (77.0)	1352 (64.9)	12,466 (78.6)		72.7	76.3	
T3	2355 (13.1)	290 (13.9)	2065 (13.0)		15.1	13.4	
T4	1764 (9.8)	441 (21.2)	1323 (8.3)		12.3	10.3	
N stage, *n* (%)				<.001			.604
N0	15,204 (84.8)	1667 (80.0)	13,537 (85.4)		82.6	84.1	
N1	585 (3.3)	109 (5.2)	476 (3.0)		3.8	3.3	
N2-N3	589 (3.3)	156 (7.5)	433 (2.7)		3.9	3.4	
Nx	1559 (8.7)	151 (7.2)	1408 (8.9)		9.7	9.2	

CCI, Charlson Comorbidity Index.

[a] Variables used for propensity score weighting are: age, race, ethnicity, income, county type, CCI, insurance status, facility type, histology type, T stage, and N stage.

Table 2. Unweighted and weighted multivariate analyses of predictors of overall survival for patients treated by RC and CMT

	Unweighted multivariate analysis		Weighted multivariate analysis	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Treatment				
RC	1 [Reference]		1 [Reference]	
CMT	1.15 (1.08-1.22)	<.001	1.18 (1.07-1.3)	<.001
Age, y				
<60	1 [Reference]		1 [Reference]	
60-69	1.17 (1.09-1.26)	<.001	1.07 (0.84-1.36)	.57
70-79	1.55 (1.44-1.67)	<.001	1.22 (0.94-1.57)	.11
≥80	2.22 (2.04-2.41)	<.001	1.71 (1.32-2.21)	<.001
Race				
White	1 [Reference]		1 [Reference]	
Black	1.15 (1.05-1.26)	.003	1.12 (0.9-1.39)	.3
Asian	0.84 (0.68-1.02)	.08	0.83 (0.47-1.47)	.51
Other	0.86 (0.72-1.02)	.08	0.91 (0.66-1.25)	.55
CCI				
0	1 [Reference]		1 [Reference]	
≥1	1.35 (1.3-1.41)	<.001	1.33 (1.2-1.47)	<.001
Insurance status				
Not insured	1 [Reference]		1 [Reference]	
Private insurance	0.94 (0.81-1.09)	.4	0.87 (0.63-1.2)	.39
Medicaid	1.13 (0.95-1.35)	.16	1.07 (0.71-1.62)	.74
Medicare	1.11 (0.96-1.29)	.17	1.11 (0.79-1.56)	.54
Other government	1.14 (0.9-1.44)	.29	1.18 (0.81-1.71)	.39
Insurance status unknown	0.92 (0.73-1.16)	.47	0.8 (0.43-1.5)	.47
Income				
<$38,000	1 [Reference]		1 [Reference]	
$38,000-$47,999	1.05 (0.98-1.13)	.13	0.93 (0.79-1.09)	.33
$48,000-$62,999	1.02 (0.95-1.09)	.63	0.9 (0.75-1.09)	.24
$63,000+	0.97 (0.89-1.05)	.43	0.82 (0.69-0.99)	.03
Facility type				
Community Cancer Program	1 [Reference]		1 [Reference]	
Comprehensive Community Cancer Program	1.02 (0.94-1.1)	.71	0.95 (0.83-1.09)	.48
Academic/Research Program	0.93 (0.85-1)	.06	0.88 (0.76-1.01)	.08
Integrated Network Cancer Program	1.07 (0.96-1.18)	.21	1.03 (0.85-1.24)	.75
Histology				
Pure urothelial	1 [Reference]		1 [Reference]	
Squamous	1.3 (1.18-1.44)	<.001	1.38 (1.08-1.77)	.008
Neuroendocrine	1.42 (1.21-1.68)	<.001	1.15 (0.87-1.52)	.31
Adenocarcinoma	1.26 (1.02-1.56)	.03	1.07 (0.78-1.48)	.66
Sarcomatoid	1.61 (1.38-1.88)	<.001	1.26 (0.8-2)	.31
Micropapillary component	1.35 (1.09-1.67)	.006	1.21 (0.72-2.03)	.46
Other	1.14 (1.01-1.28)	.03	1.21 (0.99-1.48)	.06
T stage				
T2	1 [Reference]		1 [Reference]	
T3	1.43 (1.35-1.51)	<.001	1.32 (1.11-1.56)	<.001
T4	1.79 (1.68-1.91)	<.001	1.84 (1.64-2.07)	<.001
N stage				
N0	1 [Reference]		1 [Reference]	
N1	1.47 (1.32-1.63)	<.001	1.38 (1.12-1.71)	.002
N2-N3	1.93 (1.74-2.13)	<.001	1.83 (1.51-2.23)	<.001
Nx	1.16 (1.08-1.24)	<.001	1.17 (1-1.37)	.05
Education[a]				
<7%	1 [Reference]		1 [Reference]	
≥21%	1.12 (1.03-1.22)	.007	1.03 (0.81-1.31)	.79
13%-20.9%	1.08 (1.01-1.16)	.02	0.99 (0.81-1.21)	.91
7%-12.9%	1.01 (0.95-1.07)	.73	0.99 (0.84-1.17)	.88

CI, confidence interval; CCI, Charlson Comorbidity Index; CMT, chemoradiation therapy; HR, hazards ratio; RC, radical cystectomy.
[a] This item provides a measure of the number of adults in the patient's zip code who did not graduate from high school.

1 year who received CMT than in those who underwent RC (hazards ratio [HR] 1.15; 95% CI 1.08-1.22; P <.001); covariates associated with decreased OS included advanced age, a higher comorbidity score, all histology types relative to pure urothelial carcinoma, T3 and T4 stages relative to T2, and all N stages relative to 0.

Propensity Score-weighted Analyses

Propensity score weighting was well matched between the 2 study groups (Table 1). Consistent with the multivariate analysis, patients who underwent RC had better OS than those who received CMT (HR 1.18; 95% CI 1.07-1.3; $P \leq .001$; Table 2). The weighted Kaplan-Meier survival curves and the corresponding log-rank test indicated that OS was shorter after CMT than after RC ($P < .001$; Fig. 2).

There was a significant interaction of treatment type with time. As shown in Fig. 2, the OS was shorter after RC than after CMT in the first year following treatment but improved thereafter such that OS was better after RC than after CMT and remained consistently so for the remainder of the study period.

We conducted further exploratory analyses to determine the heterogeneity of the treatment effect by testing interaction terms within the adjusted Cox model. We identified age, histology, and N stage as variables that had an interaction with treatment effect. We performed 3 separate stratified analyses for dichotomized age, histology, and N stage and constructed corresponding Kaplan-Meier survival curves (Supplementary Fig 1, 2, and 3) and a main effects Cox model (Supplementary Table 1). Interaction terms indicated that OS in patients aged younger than 70 years was better in those who underwent RC than in those who received CMT (HR 1.61, 95% CI 1.34-1.93; $P < .001$) but not in those aged 70 years or older (HR 1.04, 95% CI 0.92-1.17; $P = .52$). When patients were stratified by type of histology, there was an OS benefit of RC in patients with a non-neuroendocrine tumor (HR 1.19, 95% CI 1.08-1.31; $P < .001$); however, there was no significant difference in survival between RC and CMT in patients with neuroendocrine histology (HR 0.62, 95% CI 0.37-1.02; $P = .06$).

Subgroup analyses identified significantly better survival after RC than after CMT in patients with Nx/N0/N1 disease (HR 1.21, 95% CI 1.06-1.33; $P < .001$). There was no significant difference in survival between the 2 treatment modalities in patients with N2/N3 disease (HR 0.8, 95% CI 0.6-1.08; $P = .15$). Median lymph node yield in RC group was 11 (Interquartile range 5-19). Approximately 56.4% of all RC patients had ≥10 lymph node removed.

DISCUSSION

In this study, we compared the survival outcomes of RC and CMT in patients with T2-T4, M0 bladder cancer. After propensity score weighting and covariate adjustment, the results of our analysis suggest better survival after RC than after CMT. This finding is consistent with other reports of a survival advantage in patients with bladder cancer who receive RC.

Data regarding the comparative effectiveness of RC and CMT are limited. To date, 3 studies have used data from the NCDB to determine whether RC confers a survival benefit when compared with CMT. Ritch et al[7] performed propensity score matching in an RC group and a CMT group ($n = 1683$ in each); as in our study, they found that 5-year OS was significantly better after RC than after

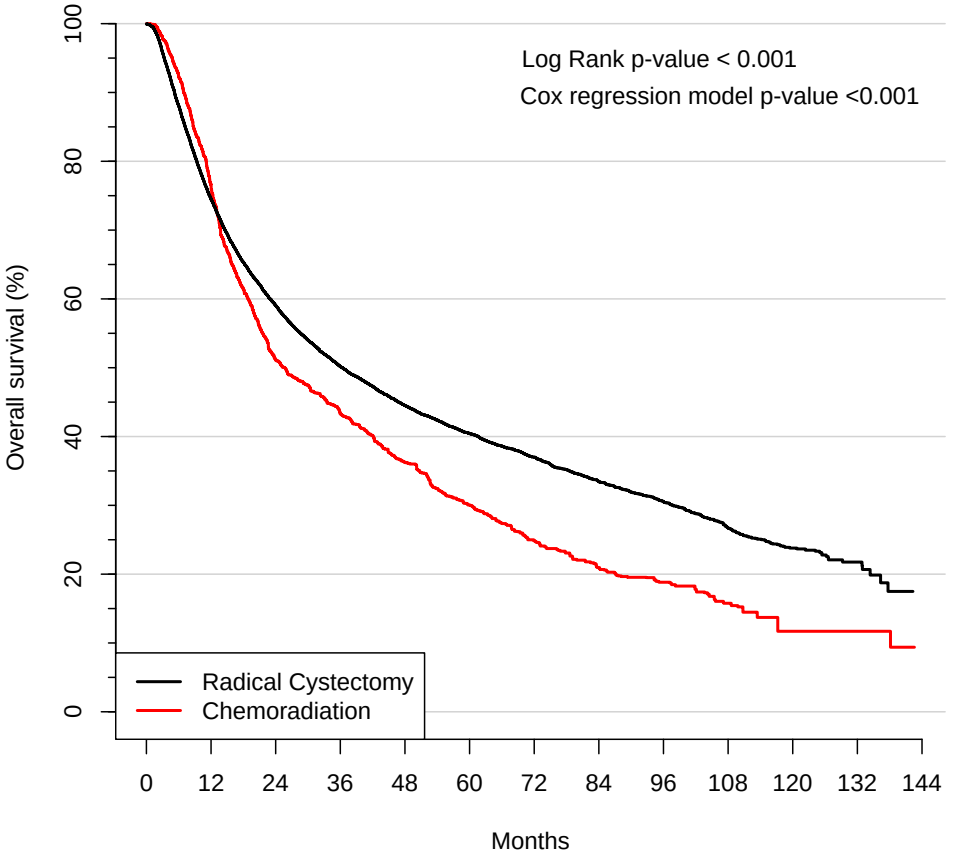

Figure 2. Weighted Kaplan-Meier curves comparing overall survival in patients with muscle-invasive bladder cancer treated by radical cystectomy vs chemoradiation therapy. (Color version available online.)

CMT (38% vs 30%, $P = .004$). Propensity score matching (used by Ritch et al) and propensity score weighting (used in the present study) are 2 popular methods of propensity score adjustment.[20] As intended, propensity score weighting using the CBPS algorithm provided a balance of covariates between the CMT and RC groups in our study. The relative performance of propensity score weighting vs propensity score matching is a topic of research interest.[20] We compared 4 propensity score methods using simulation technique: maximum likelihood, generalized boosting models, CBPS, and generalized additive models.[21] We considered 4 simulation scenarios differing by the complexity of a propensity score model and a range of exposure prevalence following the design of Setoguchi[22] et al. Propensity score weights were estimated using the maximum likelihood, generalized boosting models, CBPS, and generalized additive models using logistic regression and compared all 4 methods with each other. We used these propensity weights to estimate the average treatment effect among treated on a binary outcome. Simulations showed that the CBPS was generally superior across the 4 scenarios studied in terms of type I error, power, and mean squared error. As a result, we used the CBPS methodology in this comparison of RC and CMT with regard to patient survival.

Although our results favor RC, it is interesting that the mortality risk was higher after RC than after CMT during the first 12 months in our study. This increased risk may in part be related to the higher complication and mortality rates following RC. The 90-day adverse event rate after RC varies from 25% to 65%, with a resulting perioperative mortality of 5%-10%.[23-25]

Using the NCDB data for 2004-2011, Seisen et al[9] calculated the inverse probability of treatment by weighting-adjusted Cox regression analysis with a time-varying covariate and found that CMT was associated with a significantly decreased OS relative to RC (HR 1.37, 95% CI 1.16-1.59; $P < .001$). Our study included data for 3 additional years (2004-2014) and yielded similar results.

Bekelman et al[26] performed a similar retrospective, observational cohort study using registry and administrative claims data from the Surveillance, Epidemiology, and End Results-Medicare database in which they compared survival outcomes of RC relative to CMT and examined confounding factors and stage misclassification in their comparison using multivariable adjustment, propensity score-based adjustment as a continuously distributed covariate, instrumental variable analysis, and simulations. The study included 1843 patients, of whom 1426 underwent RC and 417 received CMT. Interestingly, the survival outcome differed according to the method used for the statistical analysis. Multivariable and propensity score covariate adjustment revealed greater mortality associated with CMT relative to RC (HR 1.31; 95% CI 0.97-1.77), as in our study. However, their instrumental variable analysis and simulation studies suggested that the 2 treatments had similar survival outcomes (HR 0.94; 95% CI 0.55-1.18). Gore et al[27] utilized similar Surveillance, Epidemiology, and End Results-linked databases and applied multivariate model and instrumental variable analyses to the data for approximately 3262 Medicare beneficiaries and found that OS was shorter after CMT than after RC (HR 1.5, 95% CI 1.3-1.8).

The findings of the present study are consistent with those of the recently published study by Cahn et al, who demonstrated significantly better OS after CMT than after RC in a pure cohort of patients with urothelial carcinoma identified in the NCDB.[10] However, the survival benefit was tempered when more stringent CMT criteria were applied and more rigorous statistical methods were used to control for confounding factors. Similarly, when we evaluated the heterogeneity of the treatment effect, we identified variables that had a significant interaction with treatment effect, that is, RC had a much stronger treatment effect in patients younger than 70 years, those with non-neuroendocrine histology, and those with N0/N1 stage disease. Interestingly, despite the challenges of using an administrative database such as the NCDB and the differences in statistical methodology and patient selection criteria between the 2 studies, our OS rates after RC and CMT (40.40% and 29.40%, respectively) are comparable with those reported by Cahn et al (48% and 30%).

In a single-institution series of 112 patients (RC, $n = 56$; CMT, $n = 56$), Kulkarni et al[13] observed no difference between RC and CMT in regard to OS (35.7% vs 39.3%; $P = .63$) or disease-specific survival (73.2% vs76.6%; $P = .49$). However, their study was limited by selection bias in that patients with multifocal disease, a large tumor (>5 cm), hydronephrosis, or carcinoma in situ were not candidates for CMT. This prescreening of patients in a retrospective study may have also introduced a degree of sampling bias that may have undermined the external validity of their results. Furthermore, advanced statistical techniques, such as instrumental variables, propensity score matching, and weighting and covariate adjustment, may not be able to overcome these sources of bias. We attempted to minimize exclusion of nonmetastatic MIBC by capturing a larger population (>16,000) of patients.

The NCDB has several advantages over other population databases, including a larger sample size, inclusion of a broader range of patient ages, and the availability of information on radiotherapy and chemotherapy. However, the NCDB is limited by its retrospective nature and the potential for miscoding. Inaccurate clinical staging is an inherent limitation of retrospective databases including the NCDB. Clinical nodal staging was utilized in both RC and CMT groups for the purpose of this analysis for bias reduction. Furthermore, the NCDB does not provide information on the quality of transurethral resection of bladder tumor performed prior to radiation therapy or on variation in concurrent use of chemotherapy. Our inability to control for these factors may have introduced a degree of selection bias in our CMT group. We were also unable to control for temporal variation in the radiation

therapy techniques used. Other limitations of this study include the lack of granular information on use of chemotherapy. Although the receipt and timing of chemotherapy were known, the specific chemotherapy agent, dose, and number of cycles administered were not. Finally, the NCDB does not report cancer-specific survival, disease-specific survival, or quality of life outcomes, so OS was the only outcome that could be included.

We acknowledge that the findings of this study can only be considered hypothesis-generating because information regarding toxic effects of CMT, the granular details of the various chemotherapeutic regimens used, and the quality of delivery of radiotherapy are not readily available in the NCDB.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2019.05.062.

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EDITORIAL COMMENT

The authors used the National Cancer Database (NCDB) to compare the survival of patients with muscle-invasive bladder cancer (MIBC) treated with either radical cystectomy (RC) or chemoradiotherapy (CRT).[1] The authors concluded that patients have better survival after RC than CRT. However, due to the innate limitations of registry-based observational studies, and potential bias in the patient selection, the validity and ability to apply this study's findings are limited.

Only randomization can truly control for known and unknown confounders when comparing treatment regimens. Although

investigators can use methods such as propensity-score weighting to attempt to account for some unknown confounding, the receipt of such drastically different treatment modalities is driven by multiple patient, clinician, and disease factors—all of which can create selection bias. In fact, a recent study compared the results of population-based observational studies with randomized trials in oncology comparing the same 2 treatment regimens and found no correlation between the observational studies and randomized trials beyond what would be expected with chance, regardless of the statistical methods used.[2] Therefore, it is not surprising, as the authors state, the results of other observational studies using population-based datasets are conflicting when it comes to comparing survival with RC and CRT. Interestingly, a recent publication comparing RC and CRT in an overlapping NCDB population found no difference in survival.[3] Frankly, studies using this design and data source seem no better than flipping a coin when comparing survival.

Moreover, the definition of the CRT group in this study was prone to selecting patients inherently at risk for worse survival. The authors selected patients who received as low as 50 Gy—well below the standard doses used for curative radiotherapy (~64 Gy using 1.8-2 Gy/fraction).[4] Although some hypofractionated regimens use 50 Gy, the use of these regimens is low in the NCDB.[5] Furthermore, patients were defined as having concurrent chemotherapy if they received chemotherapy within 90 days of radiation. To our knowledge, there are no radiosensitizing chemotherapy platforms that allow such a large time gap between concurrent chemotherapy and radiotherapy, thereby further questioning what proportion of patients received standard, curative, concurrent CRT.

Another source of bias in this study is that the CRT group included patients who were not candidates for surgery due to comorbidity. Although the authors controlled for comorbidity using the NCDB's Charlson/Deyo comorbidity score, the data in this variable are limited. It is coded as 0, 1, 2, or ≥3 based on patient comorbidities. In this study, it was dichotomized to 0 or ≥1—even further limiting the granularity. A patient with a score of ≥1 could be a patient with uncomplicated diabetes, or, could be a patient with hemiplegia, moderate to severe liver disease, dementia and a history of myocardial infarction. It's hard to believe this dichotomy can capture the impact of comorbidity on surgical candidacy or survival.

Ultimately, only a randomized trial can truly determine any differences in survival that exist between RC and CRT, but it's unlikely we will get an answer to this question anytime soon. Perhaps there are more practical avenues to pursue, such as optimizing the outcomes with each modality. For example, A031501 (NCT03244384) is determining the role of adjuvant immunotherapy after RC. In the setting of CRT, SWOG/NRG 1806 (NCT03775265) is studying the role of concurrent and adjuvant immunotherapy in node-negative MIBC, and ECOG/NRG 8185 is under development to study this approach in node-positive MIBC. These studies will hopefully improve the outcomes in patients undergoing either modality.

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Author Reply

"Striving to better, oft we mar what's well."

Williams Shakespeare

We agree with the authors URL-19-01203.[1] that well-designed adequately powered trials, evenly distributes the confounders among the control and intervention groups, thereby minimizing the potential for selection bias. Thus, randomized trials are widely encouraged as the ideal methodology for causal inference. However, some clinical scenarios have not, cannot, and will never be addressed in the context of a randomized trial.[2] The role of chemoradiotherapy (CRT) in muscle-invasive bladder cancer is a clear example.

We have recently reported screening logs from the recruitment phase of pilot feasibility trial (ClinicalTrials.gov Identifier-NCT02716896) to determine whether CRT offers overall survival similar to that of radical cystectomy (RC) in patients with muscle-invasive bladder cancer. Our results from this trial indicated that the number of patients eligible to receive chemotherapy and in whom cystectomy and radiation therapy were both valid options was not as high as previously reported in retrospective CRT series. Many patients were excluded after transurethral resection of bladder tumor. Our preliminary data indicate that only a very small subset of patients with muscle-invasive bladder cancer are ideal candidates for CRT.[3]

Thus, in the absence of randomized clinical trials, well-designed and analyzed observational studies are of utmost importance with benefits even surpassing randomized controlled trials.[2,4]

We acknowledged in our article the inherent limitations in retrospective observational studies including risks of selection bias. To address the editorial comments on dichotomization of Charlson/Deyo score, we would like to highlight that the NCDB reports a modified index in which the variables are truncated to 0, 1, and >1.[4] Even when reported in a continuous manner as suggested, a patient with controlled DM would have the same score as a patient with myocardial infarction or heart failure.[5] The editorial also questioned the selection criteria for patients with CRT. Interestingly, they mention in comment the reason

for choosing 50 Gy dose as a cutoff to include hypofractionation regimens.[6,7] The 90-day concurrent radiation/chemotherapy window has been also utilized in previous studies.[8]

Lastly, authors quote a recent report with overlapping NCDB population comparing the same treatment modalities. We find the results nonconflicting. Interestingly, in a more selective patient population, the study reported similar overall survival benefit associated with RC with median OS of 2.6 and 3.8 years for the CRT and surgery cohorts, respectively (P <.001). This overall survival benefit persisted but did not reach statistical significance after propensity score weighting in this highly selected group of patients.[9]

We agree that conducting observational registry-based studies can be fraught with challenges. In the absence of RCTs, the quality of such studies is crucial and is dependent on the stringency of their analysis and the intelligibility of their interpretation.

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