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Radical Cystectomy *Versus* Chemoradiation for Muscle-invasive Bladder Cancer: Impact of Treatment Facility and Sociodemographics

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Abstract. *Background: The present study sought to compare the differences in practice patterns, as well as clinical outcomes for patients with muscle-invasive bladder cancer undergoing treatment with either radical cystectomy (RC) or concurrent chemoradiaiton (CRT). Patients and Methods: The National Cancer Data Base (NCDB) was queried for patients diagnosed with T2/T3/T4aN0M0 bladder cancer, between 2004-2013, that received definitive treatment with either RC or CRT. Results: 16,960 patients met the inclusion criteria; 1,450 (8.5%) underwent CRT, while 15,510 (91.5%) were treated with RC. Patients undergoing CRT were older, more likely to be female, African American, received treatment at an academic facility, and lived <20 miles of the treatment facility. CRT was associated with worse median OS (32.8 months vs. 36.1 months; p=0.0004). Conclusion: Older patients are more likely to undergo bladder preservation therapy, while those living farther away from treatment facilities are less likely to under CRT.*

Although the historical treatment for muscle-invasive bladder cancer (MIBC, cT2-T4a N0 M0) has involved radical cystectomy (RC)-based approaches, attempts to preserve the bladder in efforts to maintain organ function and quality of life have been studied prospectively for over three decades (1-3). The encouraging results of these trials in well-selected patients resulted in subsequent studies evaluating novel chemoradiotherapeutic approaches to preserve the bladder (4-6). As experiences of bladder conservation therapy, most commonly chemoradiation (CRT), have accumulated over time, data have indeed demonstrated appropriate clinical outcomes as well as quality of life endpoints. Though to date there have not been randomized trials comparing the outcomes between RC and CRT for the management of muscle-invasive bladder cancer (7, 8).

As such, the National Comprehensive Cancer Network (NCCN) currently recommends two major approaches for MIBC: RC-based therapy (with neoadjuvant or adjuvant chemotherapy) or concurrent CRT (with preceding transurethral resection of bladder tumor (TURBT)) (9).

Due to the multiple-recommended regimens to treat this relatively common neoplasm, this study was conducted using the large, contemporary dataset of the National Cancer Data Base (NCDB) to assess practice patterns regarding the utilization of RC *versus* bladder-preserving CRT with respect to treatment facility and sociodemographics. Outcomes of both paradigms were then evaluated.

Patients and Methods

This study analyzed the NCDB, which is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society, which consists of de-identified information regarding tumor characteristics, patient demographics, and patient survival for approximately 70% of the US population (10). The NCDB contains information not included in the Surveillance, Epidemiology, and End Results database, including details regarding use of systemic therapy and radiation dose. The data used in the study were derived from a de-identified NCDB file. The American College of Surgeons and the CoC have not verified and are neither responsible for the analytic or statistical methodology employed nor the conclusions drawn from these data by the investigators. As all patient information in the NCDB database is de-identified, this study was exempt from institutional review board evaluation.

The most recently released NCDB dataset corresponded to the years 2004-2013. Inclusion criteria for this study involved patients

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age ≥18 with cT2-T4a N0 M0 bladder cancer comprising histologic codes of urothelial cancer, squamous cell carcinoma, or adenocarcinoma. For inclusion, patients required histological diagnostic confirmation, and receipt of one of two major treatment paradigms. These included either RC with or without chemotherapy, or definitive CRT [defined as external beam radiation to a dose of ≥55 Gray and receipt of chemotherapy within 15 days of radiation, based on national recommendations (9)] with previous TURBT.

Information collected on each patient broadly included demographic data, comorbidity information, clinicopathologic tumor parameters, and treatment facility characteristics. For the purposes of this study, the facility status was based on the cancer program category as designated by the American College of Surgery. All statistical tests were two-sided, with a threshold of $p<0.05$ for statistical significance, and were performed using STATA (version 14, College Station, TX). Fisher's exact or χ^2 test analyzed categorical proportions between groups in the non-parametric and parametric settings, respectively. Multivariable logistic regression modeling was utilized to determine characteristics that were predictive for receipt of CRT. The Kaplan-Meier method was used for survival analysis, and comparisons between groups receiving CRT *versus* RC were performed with the log-rank test. OS was defined as the interval between the date of diagnosis and the date of death or last contact. Lastly, stratified multivariate analyses as part of Cox proportional hazards modeling were additionally used to identify variables associated with OS in the entire cohort. Log-log survival plots were used to graphically check the proportional hazards assumption.

Results

Patients that met study analysis criteria were 16,960 [n=15,510 (91.5%) RC, n=1,450 (8.5%) CRT]. Temporal trends were first analyzed, showing that the high rate of RC-based therapy has stayed relatively constant over time (Figure 1A).

Table I displays clinical characteristics of the analyzed patients. Of note, there were salient differences in demographic characteristics between groups; there were no statistical differences in terms of histology, stage, or comorbidity indices. Additionally, the patients in the RC group were younger; Figure 1B illustrates that CRT was more likely to be utilized with increasing age.

Multivariable logistic regression analysis ascertained factors independently associated with receipt of CRT by adjusting for potential confounders (Table II). This corroborated that advancing age was independently associated with receipt of CRT. Other noteworthy sociodemographic disparities were also observed. Females and African-Americans were more likely to receive CRT, whereas Hispanics and males were more likely to receive RC. Patients receiving Medicare or other governmental insurance were also more likely to undergo CRT. Facility characteristics were also important, as patients receiving CRT were more often treated at academic centers and lived closer to the treating facility.

Median follow-up was 25.8 months (inter-quartile range, 11.5-54.1 months). Kaplan-Meier estimates comparing RC *versus* CRT are illustrated in Figure 2, demonstrating that

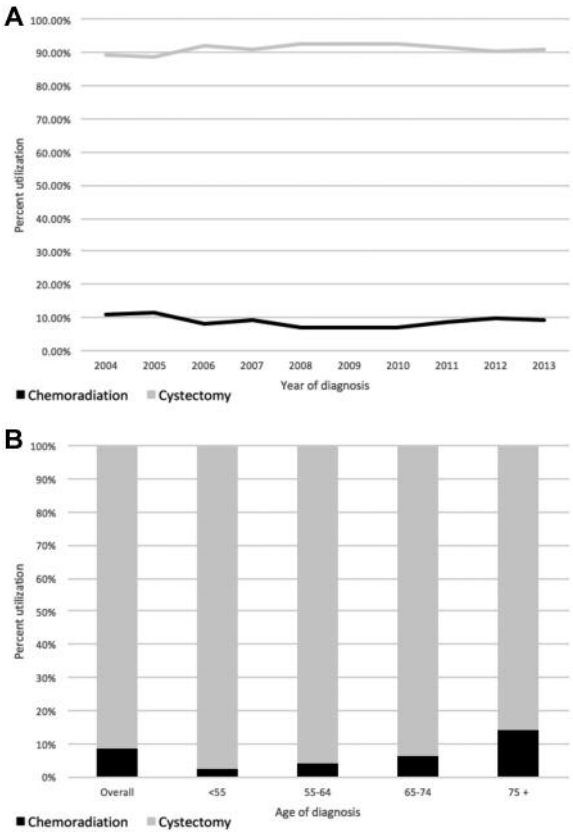

Figure 1. *(A) Line graph illustrating the proportion of patients receiving each type of treatment by year of diagnosis. (B) Bar graph illustrating the proportion of patients receiving each type of treatment by age of diagnosis.*

RC was associated with improved OS (median 36.1 *vs*. 32.8 months; $p=0.0004$).

Multivariate Cox proportional hazards modeling when stratifying patients based on the treatment type examining independent predictors of OS is displayed in Table III. There were several factors associated with improved OS in both treatment groups: age ≤65, lower T stage (extent of the primary tumor), and fewer comorbidities ($p<0.05$ for all). Of note, certain factors, including male gender, Hispanic/Asian/Native American race, private income, the highest socioeconomic status, and receipt of treatment at an academic institution predicted for superior OS for patients undergoing RC, but not for patients receiving treatment with CRT.

Discussion and Conclusion

This study of a large, contemporary database offers several salient observations when evaluating definitive therapy for MIBC. First, among the two major recommended treatment

Table I. *Baseline characteristics of patients with bladder cancer receiving either radical cystectomy or chemoradiation.*

Characteristic	Cystectomy; n=15510 (%)	Chemoradiation; n=1450 (%)	*p*-Value
Age			
<65	4938 (31.8%)	189 (13%)	**<0.001**
65+	10572 (68.2%)	1261 (87%)	
Gender			
Male	12980 (83.7%)	1099 (75.8%)	**<0.001**
Female	2530 (16.3%)	351 (24.2%)	
Race			
White	13844 (89.3%)	1289 (88.9%)	**0.004**
African American	787 (5.1%)	101 (7%)	
Hispanic	424 (2.7%)	26 (1.8%)	
Asian/Native American/ Pacific Islander	223 (1.4%)	18 (1.2%)	
Not recorded	232 (1.5%)	16 (1.1%)	
Histology			
Urothelial carcinoma	14871 (95.9%)	1409 (97.2%)	0.054
Squamous cell	466 (3%)	29 (2%)	
Adenocarcinoma	173 (1.1%)	12 (0.8%)	
T Stage			
2a/2b	13142 (84.7%)	1248 (86.1%)	0.391
3a/3b	1519 (9.8%)	131 (9%)	
4a	849 (5.5%)	1 (4.9%)	
Charlson Deyo Score			
0	10798 (69.6%)	979 (67.5%)	0.232
1	3510 (22.6%)	347 (23.9%)	
2	1202 (7.8%)	124 (8.6%)	
Facility Type			
Non academic	6620 (42.7%)	361 (24.9%)	**<0.001**
Academic	8890 (57.3%)	1089 (75.1%)	
Insurance			
Private	4584 (29.6%)	238 (16.4%)	**<0.001**
Medicare	9555 (61.6%)	1119 (77.2%)	
Medicaid	588 (3.8%)	31 (2.1%)	
Not insured	427 (2.7%)	21(1.5%)	
Other	356 (2.3%)	41 (2.8%)	
Income			
<$38000	2401 (15.5%)	220 (15.2%)	0.974
$38000-$47999	3854 (24.8%)	358 (24.7%)	
$48000-$62999	4242 (27.4%)	398 (27.4%)	
$63000 +	727 (30.5%)	450 (31%)	
Not recorded	286 (1.8%)	21 (1.7%)	
Distance from treating facility			
≤20 miles	9493 (61.2%)	1137 (78.4%)	**<0.001**
>20 miles	5745 (37%)	291 (20.1%)	
Not recorded	272 (1.8%)	22 (1.5%)	
Year of diagnosis			
2004-2008	6408 (41.3%)	638 (44%)	**0.047**
2009-2013	9102 (58.7%)	812 (56%)	
Chemotherapy use			
Yes	6993 (45.1%)	1450 (100%)	**<0.001**
No	7832 (50.5%)	0 (0%)	
Not recorded	685 (4.4%)	0 (0%)	

Statistically significant *p*-values are shown in bold.

Table II. *Characteristics predictive for chemoradiaiton on multivariable logistic regression analysis.*

Characteristic	OR	95% CI	*p*-Value
Age			
<65	1 (reference)		
65+	2.492	2.046-3.036	**<0.001**
Gender			
Male	1 (reference)		
Female	1.401	1.229-1.597	**<0.001**
Race			
White	1 (reference)		
African American	1.355	1.077-1.703	**0.009**
Hispanic	0.663	0.441-0.996	**0.048**
Asian/Native American/ Pacific Islander	0.95	0.581-1.554	0.837
Not recorded	0.904	0.538-1.517	0.701
Histology			
Urothelial carcinoma	1 (reference)		
Squamous cell	0.612	0.416-0.899	**0.012**
Adenocarcinoma	0.802	0.441-1.458	0.469
T Stage			
2a/2b	1 (reference)		
3a/3b	0.965	0.797-1.169	0.718
4a	0.930	0.722-1.198	0.574
Charlson Deyo Score			
0	1 (reference)		
1	0.984	0.863-1.121	0.806
2	0.993	0.814-1.213	0.949
Facility Type			
Non academic	1 (reference)		
Academic	1.763	1.548-2.008	**<0.001**
Insurance			
Private	1 (reference)		
Medicare	1.289	1.084-1.533	**0.004**
Medicaid	1.100	0.743-1.629	0.633
Not insured	1.199	0.752-1.912	0.446
Other	1.909	1.334-2.731	**<0.001**
Income			
<$38000	1 (reference)		
$38000-$47999	0.985	0.821-1.182	0.873
$48000-$62999	0.935	0.781-1.120	0.468
$63000 +	0.937	0.783-1.123	0.482
Not recorded	1.466	0.408-5.265	0.557
Distance from treating facility			
≤20 miles	1 (reference)		
>20 miles	0.515	0.446-0.593	**<0.001**
Not recorded	0.466	0.124-1.756	0.259

Statistically significant *p*-values are shown in bold. OR, Odds ratio; CI, confidence interval

options by the NCCN, the vast majority of patients received RC. Next, several health differences were associated with the receipt of both RC and CRT, including factors related to treatment facility and sociodemographics. Lastly, a novel observation herein was the independent correlation between higher survival and treatment at an academic facility for

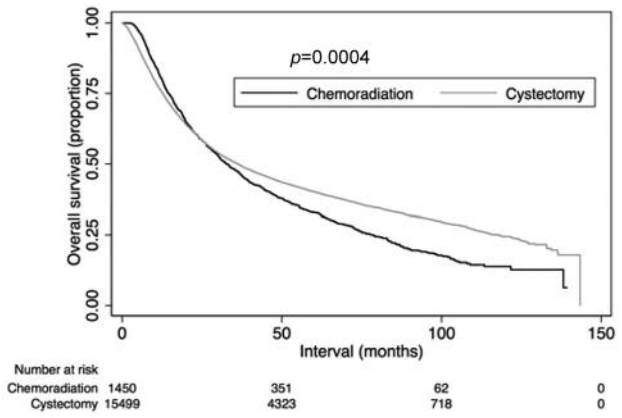

Figure 2. *Kaplan–Meier overall survival curves comparing those receiving chemoradiation versus radical cystectomy.*

patients undergoing RC, but not for patients receiving treatment with CRT.

In patients receiving NCCN-recommended treatment for MIBC, RC remains the dominant form of therapy. This is consistent with data from the Retrospective International Study of Cancers of the Urothelial Tract and could relate to the vastly greater experience with RC over bladder preservation, patient selection and eligibility for bladder preservation, referral patterns, and/or the lack of phase III evidence demonstrating equivalence between RC and CRT-based approaches (11). These could also explain the temporal trends observed herein; the finding of increase in CRT-based therapy with increasing age is likely a function of surgical candidacy and/or willingness to operate. Although this latter statement seemingly conflicts with other data displaying an increase in cystectomy in the elderly (12), that study took nonstandard (non-recommended) treatments into account, which could account for the observed difference.

The major finding herein is related to differences in patient characteristics in receipt of a particular form of treatment. Receipt of RC *versus* CRT was related to a multitude of sociodemographic factors (including age, gender, race, insurance status); patients who were treated with CRT tended to live close to the treating facility (which was more often an academic institution), whereas those receiving RC lived farther and were more commonly treated at community centers. Access to high quality of care in MIBC has been extensively addressed elsewhere and is further exemplified in our dataset (13). Factors that can impact the management of MIBC include patient education, referral patterns to community *versus* academic centers, as well as monetary aspects of treatment. Moreover, the finding of subpopulations, such as the elderly, women, and African-Americans, being associated with less likelihood of receiving RC in this study may be juxtaposed with decade-old data demonstrating similar findings and lower survival in each of these subpopulations (14, 15). It is remarkable that, in our study, such sociodemographic differences in the receipt of a particular paradigm were observed, while there were no differences between cohorts in terms of T stage or comorbidity index. This indicates that perhaps clinical decision-making in MIBC is to a greater degree influenced by sociodemographic factors than clinical factors, which must be further addressed going forward in order to allow equal opportunities for all patients to receive particular forms of therapy, as elaborated elsewhere (16).

Another novel finding from this investigation is critical to patient counseling and management by both oncologists and referring providers. Treatment at academic facilities was independently correlated with survival for patients undergoing RC but not CRT, which is in concordance with data from multiple other neoplastic diseases demonstrating improved surgical outcomes at academic and/or high-volume facilities (17, 18). There are several potential reasons for this, not limited to greater multimodality coordination, streamlined diagnostic processes, and perhaps most importantly, the technical expertise of a major surgical procedure. Nevertheless, this finding may impact any case of newly-diagnosed MIBC and could warrant revisions in patterns of patient education.

Limitations of this investigation are readily acknowledged. The evaluation of optimal bladder preservation candidacy based on tumor size, location, bladder function, and other variables is not provided by the NCDB, and hence it is unknown how many candidates for bladder preservation actually received this therapy. The NCDB also does not keep track of several noteworthy variables, such as specific chemotherapeutic agents, degree of TURBT, radiotherapy fields (including nodal coverage) reasons for a particular treatment, and salvage therapies, which could all confound conclusions presented herein. It also does not record other end-points such as tolerance of therapy (including premature cessation of chemotherapy and/or radiation), cancer-specific survival, and local/regional control. Importantly, while the NCDB does record the Charlson Deyo Comorbidity Index (CCCI), this may not necessarily be an accurate representation of performance status, as the NCDB reports CCCI values of either 0 for 0 comorbidities, 1 for 1 comorbid conditions, or 2 for the presence of ≥2 comorbidities. In order to truly compare the outcomes of each type of treatment, an accurate record of performance status is required. Nevertheless, the patterns of care findings described herein are novel and likely valid, given the volume of patients studies, though further investigation is warranted corroborate these conclusions.

This study demonstrates that the vast majority of patients with MIBC receiving NCCN-recommended therapy are not treated with bladder-preserving approaches. Health disparities in treatment of MIBC exist, as there are several sociodemographic and facility-related factors associated with the choice of treatment.

Table III. *Stratified cox multivariate analysis of factors predictive of overall survival for patients with bladder cancer.*

	Multivariate analysis cystectomy			Multivariate analysis chemoradiation		
Characteristic	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age						
<65	1 (reference)			1 (reference)		
65+	1.432	1.341-1.529	**<0.001**	1.571	1.216-2.028	**0.001**
Gender						
Male	1 (reference)			1 (reference)		
Female	1.226	1.160-1.295	**<0.001**	1.091	0.938-1.269	0.259
Race						
White	1 (reference)			1 (reference)		
African American	1.098	0.997-1.209	0.057	1.067	0.822-1.384	0.626
Hispanic	0.869	0.758-0.995	**0.042**	0.665	0.391-1.133	0.133
Asian/Native American/Pacific Islander	0.766	0.632-0.929	**0.007**	0.627	0.310-1.265	0.192
Not recorded	0.874	0.728-1.049	0.148	1.580	0.888-2.811	0.120
Histology						
Urothelial carcinoma	1 (reference)			1 (reference)		
Squamous cell	1.389	1.240-1.556	**<0.001**	0.816	0.494-1.346	0.425
Adenocarcinoma	1.033	0.848-1.259	0.749	1.054	0.542-2.049	0.876
T Stage						
2a/2b	1 (reference)			1 (reference)		
3a/3b	1.261	1.179-1.348	**<0.001**	1.445	1.176-1.777	**<0.001**
4a	1.388	1.27-1.514	**<0.001**	1.796	1.366-2.362	**<0.001**
Charlson Deyo Score						
0	1 (reference)			1 (reference)		
1	1.230	1.171-1.293	**<0.001**	1.333	1.145-1.551	**<0.001**
2	1.593	1.483-1.713	**<0.001**	1.886	1.518-2.343	**<0.001**
Facility Type						
Academic	1 (reference)			1 (reference)		
Non academic	1.121	1.071-1.172	**<0.001**	1.047	0.896-1.225	0.562
Insurance						
Medicare	1 (reference)			1 (reference)		
Private	0.802	0.752-0.855	**<0.001**	0.985	0.802-1.210	0.888
Medicaid	0.956	0.844-1.083	0.483	1.243	0.772-1.003	0.371
Not insured	0.958	.825-1.113	0.574	0.582	0.265-1.281	0.179
Other	0.923	0.797-1.071	0.291	1.503	1.048-2.154	**0.027**
Income						
<$38000	1 (reference)			1 (reference)		
$38000-$47999	0.992	0.928-1.061	0.823	0.970	0.783-1.202	0.781
$48000-$62999	0.952	0.890-1.018	0.149	0.945	0.767-1.165	0.596
$63000 +	0.915	0.855-0.979	**0.010**	0.901	0.729-1.112	0.331
Not recorded	1.403	0.925-2.129	0.111	0.431	0.060-3.100	0.403
Distance from treating facility						
≤20 miles	1 (reference)			1 (reference)		
>20 miles	0.909	0.867-0.953	**<0.001**	0.935	0.790-1.107	0.434
Not recorded	1.416	0.928-2.162	0.107	3.314	0.440-24.970	0.245
Year of diagnosis						
2004-2008	1 (reference)			1 (reference)		
2009-2013	1.004	0.961-1.049	0.854	1.048	0.916-1.200	0.496

Statistically significant *p*-values are shown in bold. HR, Hazard ratio; CI, confidence interval.

Conflicts of Interest

None.

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