Factors predicting early mortality after radical cystectomy for urothelial carcinoma in a contemporary cohort of patients

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Abstract

Introduction: We aimed to identify preoperatively available patient variables associated with increased mortality within 30 and 90 days of radical cystectomy (RC) for localized urothelial carcinoma (UC), and to evaluate temporal trends in early mortality rates.

Methods: We reviewed the National Cancer Database to identify patients who underwent RC for UC between 2006 and 2013. Preoperatively available patient-specific demographics and mortality rates at 30 and 90 days postoperatively were analyzed. Univariable and multivariable logistic regression analyses were performed to examine factors associated with 30- and 90-day mortality.

Results: We identified 37 366 patients who underwent RC between 2006 and 2013. Overall mortality rates remained stable over time. From 2006–2013, 936 patients (2.5%) and 2554 patients (6.8%) died of any cause within 30 and 90 days post-RC, respectively. On multivariable analysis, increased age, higher clinical T and N stage, increased Charlson-Deyo comorbidity classification, African-American race, lower hospital volume, non-academic centers, lower patient income, and absence of insurance were each significantly associated with increased early mortality after RC ($p<0.05$). The protective effect of higher hospital volume was similar regardless of patient's age, clinical stage, or comorbidity status.

Conclusions: Our study identified patient-specific variables that are significantly associated with increased early mortality after RC. These findings can be used in counselling to identify ideal candidates for RC to decrease patient harm. Furthermore, early mortality rates after RC have remained stable over time, indicating that ongoing quality improvement is essential to improve outcomes.

Introduction

Bladder cancer is one of the most common malignancies in North America. In the U.S. alone in 2018, there were approximately 81 190 new diagnoses of bladder cancer with 17 240 deaths attributed to the disease.[1] Radical cystectomy (RC) is the gold standard treatment for patients with muscle-invasive bladder cancer (MIBC) and for those with non-MIBC who are unresponsive to intravesical therapy.[2] There is a known high risk of perioperative morbidity and mortality given the complexity of RC and urinary diversion, especially in the elderly or frail populations. Variations exist in published early mortality rates, which have been estimated to be up to 20% in early studies, down to 1.1–2.7% in more recent literature, with an overall complication rate of approximately 34%.[3-6] As life expectancy increases, the number of RCs offered is predicted to increase, particularly in elderly patients.[7] Given the high risk of morbidity and mortality associated with RC, it is important to gain a more granular understanding of postoperative mortality to inform patients. Counselling and discussing the predicted risks and benefits of this treatment with patients in order to select appropriate candidates for this procedure will help reduce patient harm.

Although several previous studies have investigated postoperative mortality after RC and nomograms have been developed, many of these studies have focused on postoperative variables in their models.[8-13] This limits their applicability to preoperative clinical decision-making and patient counselling. In addition, rates of change in early mortality over time have not been thoroughly investigated. Herein, we examine temporal trends in early mortality rates after RC and investigate preoperatively available patient variables associated with early mortality.

Methods

Data source

The National Cancer Database (NCDB), a joint effort between the American Cancer Society and the American College of Surgeons Commission on Cancer, includes information from patients who received an initial diagnosis or first course of treatment for cancer at one of the nearly 1500

Commission on Cancer-accredited cancer centers.[14] The Commission on Cancer-accredited centers are expected to maintain high-quality cancer registries, using trained personnel and standardized methodology to abstract clinical, pathological, treatment, and demographic data. The dataset includes information from more than 70% of incident malignancies within the U.S.[14] All patient information has been de-identified and thus, the study's international review board approval for ethics was exempted.

Study population

We identified all patients in the NCDB who were diagnosed with urothelial carcinoma (UC) of the bladder (all variants) between 2006 and 2013. Patients diagnosed with non-urothelial histology were excluded.

Outcomes of interest

The primary aim was to report on the 30- and 90- day mortality rates after RC for UC. The secondary aims were to examine clinical, demographic, and socioeconomic factors associated with 30- and 90-day mortality after RC.

Statistical analysis

Baseline clinical and demographic characteristics between patients who died or did not die within 30 and 90 days of RC were compared using the t-test for independent means for continuous variables and Chi-squared test for categorical variables. The proportion of patients who died each year within 30 and 90 days of RC were calculated, and trends were plotted by year. Multivariable logistic regression analyses were used to examine factors associated with 30- and 90-day mortality. Variables for inclusion into the multivariable model were chosen clinically. Additionally, due to the well-described association between hospital volume and mortality after RC, we performed interaction analyses to determine whether this association was present across patients of different ages, comorbidity status, and cT stage. We hypothesized that the impact of hospital volume would be greater among older, more comorbid patients with higher stage of disease.

Statistical analyses were performed using R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria). All tests were two-sided, with $p<0.05$ considered statistically significant.

Results

Baseline characteristics

We identified 37 366 patients who underwent RC for UC from 2006–2013. The mean age was 67.85 (±10.39) years; 75.8% were male and 38.0% had cT2 disease. Most patients were Caucasian (91.1%) and a Charlson-Deyo comorbidity index of 0 was noted in 79.6% of patients. Table 1 provides the baseline characteristics of all included patients.

Temporal trends in mortality

From 2006–2013, 936 patients (2.5%) and 2554 patients (6.8%) died of any cause at 30 and 90 days post-RC, respectively. Over the study period, the 30- and 90-day mortality rates remained stable within the patient population captured in the NCDB (Fig. 1).

Factors associated with mortality

Baseline differences between those who died and those who did not die are summarized in Table 2, and multivariable analysis of factors associated with increased mortality at 30 and 90 days post-RC is demonstrated in Table 3. Increased age, higher clinical T stage, African-American race, and increased Charlson-Deyo comorbidity index were associated with increased mortality on multivariable analysis at both 30 and 90 days. Within the NCDB database dictionary, the Charlson-Deyo score was calculated excluding the patient's primary cancer, and the score is truncated so that a score of 2 is the maximum reported value. Receipt of neoadjuvant chemotherapy was associated with decreased mortality at

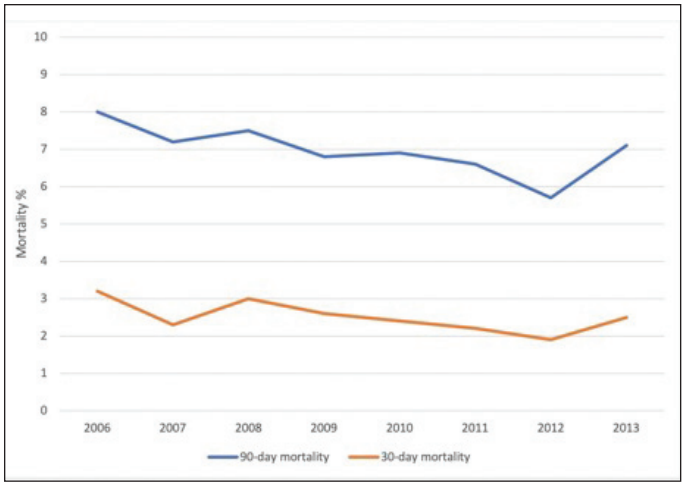

Fig. 1. Temporal trends in mortality post-radical cystectomy (RC) between 2006 and 2013 at 30 and 90 days after RC, as captured in the National Cancer Database.

Table 1. Baseline characteristics of the study population (n=37 366)

Number of patients	37 366
Mean age (SD)	67.85 (10.39)
Female sex (%)	9056 (24.2)
Clinical stage (%)	
cT1	4890 (13.1)
cT2	14187 (38.0)
cT3	2596 (6.9)
cT4	1931 (5.2)
cTa	838 (2.2)
cTis	479 (1.3)
cT N/A	12 445 (33.3)
Clinical N stage (%)	
cN0	25 915 (69.4)
cN1	2148 (5.7)
cNX	9303 (24.9)
Clinical M stage (%)	
cM0	35 227 (94.3)
cM1	579 (1.5)
cM N/A	1560 (4.2)
Patients with neoadjuvant chemotherapy (%)	6352 (17)
Race (%)	
Caucasian	34 031 (91.1)
African-American	2133 (5.7)
Other	818 (2.2)
N/A	384 (1.0)
Charlson-Deyo comorbidity index (%)	
0	26 381 (70.6)
1	8423 (22.5)
2	2562 (6.9)
Insurance (%)	
No insurance	1092 (2.9)
Private	11 859 (31.7)
Medicaid	1614 (4.3)
Medicare	21 587 (57.8)
Other government	361 (1.0)
N/A	853 (2.3)
Patient income (%)	
Low (<$46 000)	21 480 (57.5)
High (≥$46 000)	14 478 (38.7)
N/A	1408 (3.8)
Community (%)	
Metro	28 405 (76.0)
Urban	5440 (14.6)
Rural	2153 (5.8)
N/A	1368 (3.7)
Hospital facility (%)	
Non-academic	17 911 (47.9)
Academic	19 213 (51.4)
N/A	242 (0.6)
Hospital volume per year (%)	
<10	20 148 (53.9)
10–20	6925 (18.5)
>20	10 293 (27.5)
Education (%)*	
>20% (lower education)	5439 (14.6)
<20% (higher education)	31 401 (84.0)
N/A	526 (1.4)

*Education: Patient's measure of education was estimated by their area of residence by zip code and the proportion of adults in that zip code that did not graduate from high school from 2008–2012. N/A: not available; SD: standard deviation.

both 30 and 90 days. Females were less likely to die at 30 days but not at 90 days. Lymph node metastases was associated with increased risk of death at 90 days but not at 30 days. Higher income status, hospital volume, and use of private insurance were associated with decreased mortality at 90 days post-RC.

No interaction was identified in 90-day mortality between hospital volume and age, comorbidity status, or cT stage, suggesting that the association between hospital volume and mortality is similar regardless of patient characteristics (all $p>0.05$).

Discussion

Herein, we examined trends in early mortality rates after RC for UC and explored factors associated with such. We identified that mortality rates remained similar at 30 and 90 days post-RC from 2006–2013. In addition, several preoperative factors were identified as being associated with early mortality.

Given that our study population from the NCDB draws records from Commission on Cancer-accredited cancer centers only, our study population may underestimate the total mortality rates if all centers, including non-accredited cancer centers performing RCs, were taken into account. When comparing the mortality rates among institutions by hospital volume of RC, there was a clear difference in terms of hospital volume, with some centers performing less than 10 RCs per year and others performing close to 1000 RCs per year. Our study demonstrates that mortality post-RC is decreased at 90 days at high-volume centers. Previous studies have also demonstrated significant association between hospital and surgeon-specific volume with morbidity and mortality post-RC.[15,16] Thus, the average mortality per year may be quite different depending on the type of institution and hospital volume. Our study additionally found that the

Table 2. Characteristics of patients stratified by mortality status at 30 and 90 days post-RC as captured in the NCDB from 2006–2013 (n=36 738)

	30 days			90 days		
	Alive	Dead	p	Alive	Dead	p
Number of patients	36 089	936		34 184	2554	
Age (SD)	67.69 (10.37)	73.69 (9.36)	<0.001	67.50 (10.34)	72.48 (9.86)	<0.001
Female sex (%)	8754 (24.3)	222 (23.7)	0.733	8249 (24.1)	662 (25.9)	0.044
Clinical T stage (%)			0.001			<0.001
cT1	4736 (13.1)	94 (10.0)		4566 (13.4)	224 (8.8)	
cT2	13 728 (38.0)	343 (36.6)		13 109 (38.3)	851 (33.3)	
cT3	2505 (6.9)	69 (7.4)		2334 (6.8)	227 (8.9)	
cT4	1848 (5.1)	68 (7.3)		1651 (4.8)	252 (9.9)	
cTa	809 (2.2)	16 (1.7)		780 (2.3)	34 (1.3)	
cTis	468 (1.3)	6 (0.6)		451 (1.3)	17 (0.7)	
cT N/A	11 995 (33.2)	340 (36.3)		11 293 (33.0)	949 (37.2)	
Clinical N stage (%)			<0.001			<0.001
cN0	25 096 (69.5)	585 (62.5)		23 915 (70.0)	1538 (60.2)	
cN1	2073 (5.7)	58 (6.2)		1877 (5.5)	242 (9.5)	
cNX	8920 (24.7)	293 (31.3)		8392 (24.5)	774 (30.3)	
Clinical M stage (%)			0.001			<0.001
cM0	34 054 (94.4)	866 (92.5)		32 369 (94.7)	2286 (89.5)	
cM1	548 (1.5)	28 (3.0)		420 (1.2)	153 (6.0)	
cM N/A	1487 (4.1)	42 (4.5)		1395 (4.1)	115 (4.5)	
Neoadjuvant chemotherapy (%)	6198 (17.2)	85 (9.1)	<0.001	5910 (17.3)	312 (12.2)	<0.001
Race (%)			0.166			0.007
Caucasian	32 895 (91.1)	836 (89.3)		31 179 (91.2)	2310 (90.4)	
African-American	2042 (5.7)	68 (7.3)		1907 (5.6)	179 (7.0)	
Other	784 (2.2)	20 (2.1)		747 (2.2)	44 (1.7)	
N/A	368 (1.0)	12 (1.3)		351 (1.0)	21 (0.8)	
Charlson-Deyo comorbidity index (%)			<0.001			<0.001
0	25 564 (70.8)	556 (59.4)		24 370 (71.3)	1547 (60.6)	
1	8091 (22.4)	267 (28.5)		7572 (22.2)	719 (28.2)	
2	2434 (6.7)	113 (12.1)		2242 (6.6)	288 (11.3)	
Insurance (%)			<0.001			<0.001
No insurance	1068 (3.0)	11 (1.2)		1008 (2.9)	53 (2.1)	
Private	11 600 (32.1)	153 (16.3)		11 182 (32.7)	477 (18.7)	
Medicaid	1565 (4.3)	29 (3.1)		1462 (4.3)	115 (4.5)	
Medicare	20 678 (57.3)	720 (76.9)		19 400 (56.8)	1848 (72.4)	
Other government	353 (1.0)	4 (0.4)		337 (1.0)	18 (0.7)	
N/A	825 (2.3)	19 (2.0)		795 (2.3)	43 (1.7)	
Patient income (%)			0.043			<0.001
Low (<$46 000)	20 733 (57.4)	562 (60.0)		19 571 (57.3)	1560 (61.1)	
High (≥$46 000)	14 007 (38.8)	330 (35.3)		13 353 (39.1)	877 (34.3)	
N/A	1349 (3.7)	44 (4.7)		1260 (3.7)	117 (4.6)	
Community (%)			0.298			0.004
Metro	27 423 (76.0)	713 (76.2)		26 006 (76.1)	1919 (75.1)	
Urban	5269 (14.6)	131 (14.0)		4985 (14.6)	377 (14.8)	
Rural	2083 (5.8)	48 (5.1)		1977 (5.8)	133 (5.2)	
N/A	1314 (3.6)	44 (4.7)		1216 (3.6)	125 (4.9)	

*Education: Patient's measure of education was estimated by their area of residence by zip code and the proportion of adults in that zip code that did not graduate from high school from 2008–2012. N/A: not available; NCDD: National Cancer Database; RC: radical cystectomy; SD: standard deviation.

Table 2 (cont'd). Characteristics of patients stratified by mortality status at 30 and 90 days post-RC as captured in the NCDB from 2006–2013 (n=36 738)

	30 days			90 days		
	Alive	Dead	p	Alive	Dead	p
Hospital facility (%)			0.001			<0.001
Non-academic	17 253 (47.8)	505 (54.0)		16 325 (47.8)	1323 (51.8)	
Academic	18 599 (51.5)	428 (45.7)		17 632 (51.6)	1222 (47.8)	
N/A	237 (0.7)	3 (0.3)		227 (0.7)	9 (0.4)	
Hospital volume per year (%)			<0.001			
<10	19 384 (53.7)	564 (60.3)		18 305 (53.5)	1502 (58.8)	
10–20	6707 (18.6)	164 (17.5)		6373 (18.6)	452 (17.7)	
>20	9998 (27.7)	208 (22.2)		9506 (27.8)	600 (23.5)	
Education (%)*			0.002			<0.001
>20 (lower education)	30 363 (84.1)	759 (81.1)		4904 (14.3)	432 (16.9)	
<20 (higher education)	5228 (14.5)	153 (16.3)		28 829 (84.3)	2059 (80.6)	
N/A	498 (1.4)	24 (2.6)		451 (1.3)	63 (2.5)	

*Education: Patient's measure of education was estimated by their area of residence by zip code and the proportion of adults in that zip code that did not graduate from high school from 2008–2012. N/A: not available; SD: standard deviation.

protective effect of increasing hospital volume was present regardless of patient characteristics. These data argue for the centralization of RC to higher-volume centers.

Our study has identified several socioeconomic variables associated with increased mortality following RC. First, African-American race was associated with significant increase in risk of death at both 30 and 90 days postoperatively. This is in keeping with previously published literature, which suggested that black race is associated with increased length of hospital stay and inferior overall survival in a cohort of patients undergoing RC for MIBC.[17] Previous work has shown that African-Americans are less likely to receive care at high-volume centers, thereby placing them at higher risk for postoperative complications and mortality.[18] Second, we identified that higher income level and availability of private insurance were associated with decreased mortality following RC, which is also in keeping with previously published literature.[19] The results of our study highlight an ongoing and unmet need to decrease current gaps in racial and socioeconomic disparities observed in patients with bladder cancer.

The baseline characteristics of our study population who underwent RC were consistent with current literature, which demonstrates that patients who are younger, have fewer comorbidities, and localized disease are more likely to undergo RC for management of their bladder cancer.[5,8-13,20-24] Our study also found that increased age, advanced clinical stage, increased comorbidity, and decreased hospital volume were significantly associated with increased mortality. Interestingly, we identified a significantly decreased mortality among patients receiving neoadjuvant chemotherapy (NAC) prior to RC at both 30 and 90 days after RC. As it is unlikely that advantages in early mortality from NAC would be seen this soon after RC, this may simply reflect a selection bias, with healthier patients receiving NAC.[25,26] Recent studies have demonstrated that use of NAC does not increase early postoperative complications or mortality rates and, therefore, our mortality data also supports routine use of NAC in patients undergoing RC for MIBC.[27]

Our study demonstrates relatively stable temporal trends in post-cystectomy mortality rates from 2006–2013. This suggests that there remain significant gains to be made with respect to quality improvement and patient survival. Recently, there has been increased awareness and implementation of RC-specific enhanced recovery after surgery (ERAS) protocols with promising outcomes. Recent systemic review and meta-analyses of patient outcomes post-RC who underwent ERAS protocols demonstrated a shorter time for bowel recovery and decreased hospital stay, as well as lower rates of postoperative complications, such as ileus and cardiovascular complications.[28,29] Based on the data published herein, it will be interesting and imperative to investigate whether such protocols lead to improved early mortality as well. Other variables to consider in the future will include novel and emerging drug agents, specifically immunotherapy in the neoadjuvant setting, and their effects on postoperative morbidity and mortality.

One of the biggest benefits of using a national database such as the NCDB is the number of patients we were able to incorporate into our analysis. To date, our study is the largest published analysis looking into mortality associated with RC, with over 30 000 patients included. However, we acknowledge several limitations to this study associated with using such a large database. First, as with all retrospective studies, the present analysis is limited by potential unmeasured effect modifiers and, thus, we can only identify associations and not causality. Second, the NCDB draws its data from a non-population-based database, and presumably our study population could underestimate the actual observed

Table 3. Multivariable analysis of factors associated with mortality at 30 and 90 days post-RC for localized urothelial carcinoma

	30-day mortality		90-day mortality	
	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
Age (per 10-year increase)	1.05 (1.04–1.06)	<0.001	1.05 (1.04–1.05)	<0.001
Sex (ref=male)	0.78 (0.63–0.96)	0.02	0.96 (0.84–1.08)	0.47
cT stage (ref=pT≤1)				
cT2	1.23 (0.99–1.54)	0.064	1.30 (1.13–1.51)	0.001
cT3	1.34 (0.97–1.86)	0.075	1.74 (1.43–2.12)	<0.001
cT4	1.72 (1.22–2.40)	0.002	2.72 (2.23–3.32)	<0.001
cN stage (ref=cN0)				
cN1	1.13 (0.80–1.60)	0.493	1.87 (1.56–2.24)	<0.001
cNx	1.12 (0.84–1.50)	0.434	1.37 (1.15–1.64)	<0.001
Neoadjuvant chemotherapy (ref=no NAC)	0.53 (0.39–0.72)	<0.001	0.75 (0.64–0.88)	<0.001
Race (ref=Caucasian)				
African-American	1.44 (1.01–2.04)	0.043	1.34 (1.08–1.68)	0.008
Other	1.05 (0.59–1.88)	0.870	0.86 (0.58–1.28)	0.459
Charlson-Deyo comorbidity index (ref=0)				
1	1.32 (1.08–1.60)	0.006	1.40 (1.24–1.58)	<0.001
≥2	1.88 (1.44–2.45)	<0.001	1.86 (1.56–2.21)	<0.001
Income level (ref=low)				
High	0.93 (0.78–1.10)	0.391	0.87 (0.78–0.98)	0.012
Hospital volume per year (ref ≤10)				
10–20	0.85 (0.67–1.07)	0.165	0.94 (0.81–1.08)	0.319
>20	0.82 (0.66–1.00)	0.056	0.90 (0.79–1.02)	0.038
Insurance (ref=no insurance)				
Medicare	0.94 (0.48–1.83)	0.865	0.71 (0.49–1.02)	0.055
Medicaid	0.71 (0.30–1.66)	0.428	0.94 (0.61–1.45)	0.751
Private	0.69 (0.36–1.35)	0.281	0.58 (0.40–0.84)	0.003
Other government	0.57 (0.15–2.12)	0.404	0.71 (0.37–1.38)	0.284

CI: confidence interval; ref: reference value used for multivariable analysis

mortality rates after RC in non-accredited cancer centers, or overestimate the mortality in accredited cancer centers of excellence with a high volume of RC. The wide variances in the hospital volume of RC introduces the element of surgeon volume-specific bias and differences in mortality, and this was not able to be accounted for in our study. Furthermore, high volume in this study was measured as >20 cases per year, which does not reflect true high-volume centers, where RC numbers may approach the hundreds. Third, the population in this study was overwhelmingly Caucasian, and the effect sizes demonstrated in our study might not be applicable to other races that were not significantly represented in our population.

In addition, although the NCDB performs validation and data quality studies, there is nonetheless the possibility of errors within the database. Calculation of temporal trends rely on study populations remaining stable over time and this is another known limitation of using the NCDB for trend analysis. In our study, the number of hospital centers and cystectomies increased over time in the NCDB, with no significant variation in early mortality after RC. Lastly, the use of a retrospective database for our study limits our ability to analyze the specific cause of death. We hypothesize that deaths in the early postoperative period at 30 and 90 days post-RC were related to the surgery itself.

The mortality rates from our study demonstrates important data for preoperative patient counselling. These variables can be used to identify at-risk patients who are female, older, have higher Charlson-Deyo comorbidity indexes, or higher clinical T stage to facilitate candid discussions with patients. These discussions might help prevent inappropriate patient selection for this high-risk surgery, thus reducing mortality in significantly comorbid patients who might be considering RC as a therapy.

Conclusions

Early mortality after RC has remained relatively stable and significant over time. Our study demonstrates the importance of careful discussion and selection of patients for management of MIBC with RC by taking into account pre-existing patient variables. In addition, the stable mortality rate also highlights the need for ongoing quality improvement and national databases to monitor improvements in patient care

and trends over time. High-quality databases and ongoing research will help identify the best candidates or help optimize patients preoperatively prior to their RC, reducing patient morbidity and mortality.

Competing interests: Dr. Rendon has been an advisory board and speakers' bureau member for, and has received honoraria from AbbVie, Amgen, Astellas, AstraZeneca, Bayer, Ferring, Jansen, and Sanofi. The remaining authors report no competing personal or financial interests related to this work.

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