Survival Benefit Persists With Delayed Initiation of Adjuvant Chemotherapy Following Radical Cystectomy for Locally Advanced Bladder Cancer

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OBJECTIVE To determine if delaying the initiation of adjuvant chemotherapy following radical cystectomy for locally advanced bladder cancer worsens overall survival.

METHODS This is a retrospective cohort study utilizing the National Cancer Database from 2006 to 2013. We included treatment-naïve patients who underwent radical cystectomy for muscle-invasive bladder cancer found to have locally advanced disease (pT3-T4 and/or pN+). Patients received no chemotherapy or multiagent adjuvant chemotherapy between 30 and 180 days following surgery. We used a multivariable Cox Regression to assess for differences in overall survival according to when patients initiated adjuvant chemotherapy.

RESULTS We identified 3590 patients: 2581 received no chemotherapy and 1009 received multiagent adjuvant chemotherapy. Adjuvant chemotherapy began 31-60 days postsurgery in 538 patients, 61-90 days in 321 patients, and 91-180 days in 150 patients. Relative to patients who did not receive chemotherapy, adjuvant chemotherapy decreased mortality when started 31-60 days (hazard ratio [HR], 0.60; 95% confidence interval [CI], 0.52-0.69; P <.001), 61-90 days (HR, 0.62; 95% CI, 0.53-0.74; P <.001), and 91-180 days following radical cystectomy (HR, 0.69; 95% CI, 0.55-0.87; P = .002).

CONCLUSION Adjuvant chemotherapy offers a survival benefit when started up to 6 months after radical cystectomy in patients with high-risk disease who did not receive neoadjuvant chemotherapy. Patients who require delayed initiation of adjuvant chemotherapy can still benefit from treatment. UROLOGY 132: 143–149, 2019. © 2019 Elsevier Inc.

Muscle invasive bladder cancer (MIBC) makes up approximately 25% of all bladder cancer diagnoses.[1] Despite level one evidence supporting the use of neoadjuvant chemotherapy (NAC) there remains a significant proportion of patients who do not receive upfront chemotherapy and have a pathologic indication for adjuvant chemotherapy (AC) following cystectomy.[2-4] Reasons for these practice patterns are likely multifactorial, including patient and provider factors. For example, a recent study by Chu et al addressing the timing of radical cystectomy (RC) found worse survival in a subset of patients who did not receive NAC and had a delay in definitive surgical management, as well as in patients who did receive NAC and had delayed time to surgery.[5] Providers may choose to forego NAC to ensure a more timely initiation of RC. In prior studies, up to one third of patients with organ-confined disease on preoperative imaging were found to have non-organ confined disease at the time of RC.[6] Importantly, RC carries significant postoperative morbidity that may prevent the initiation of AC in a timely fashion.[7,8] Furthermore, the timing, use, and benefit of NAC and AC are important questions to address in providing patient-centered care, and these questions should be prioritized in studies for the benefit of patients.[9]

While AC has a demonstrated survival benefit compared to observation following RC, especially in patients

Disclaimer: *The data contained within the NCDB and used in this study are deidentified. The methodology and conclusions drawn from these data belong to those of the investigators and are not the responsibility of or have been verified by the American College of Surgeons and the Commission on Cancer.*

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with locally advanced disease, few studies adequately address the optimal timing of AC.[10-13] Studies for some, but not all malignancies have found that delaying initiation of AC affects survival.[14-19] Given the morbidity associated with RC, it is important to understand whether the timing of AC affects its efficacy. Therefore, we conducted an observational study to assess whether delaying AC affects survival in those with locally advanced bladder cancer using the National Cancer Database (NCDB). We hypothesized that a delay in initiation of AC following RC would result in worse overall survival. To that end, our secondary objective was to determine if there were any factors that could accurately predict which patients were more likely to have a delay in their initiation of AC.

MATERIALS AND METHODS

Study Population

The NCDB is jointly managed by the American College of Surgeons and the American Cancer Society and is increasingly used to study the management of cancer patients in the United States.[20] It captures data from over 1500 facilities and over 70% of newly diagnosed malignancies. To remain consistent with the AUA recommendations for AC for locally advanced bladder cancer, we identified all patients within the NCDB who underwent RC that revealed pathologic locally advanced bladder cancer ([p]T3-T4 and/or nodal involvement [pN+]) between 2006 and 2013.

Patients received either no chemotherapy or multiagent AC between 30 and 180 days following surgery. We included patients only with urothelial carcinoma histology. We excluded patients who received NAC, as well as those who received radiation therapy or additional systemic treatments. Patients who had delayed definitive surgical management greater than 120 days, and those who died within 30 days of RC were also excluded. We determined time to initiation of AC by comparing the start dates for RC and AC. We defined AC as occurring between 30 and 180 days following RC to avoid outliers and those treated with salvage chemotherapy at the time of disease recurrence, respectively. Patients receiving AC were categorized, based on time from RC to AC, into early (31-60 days), middle (61-90 days), and late (91-180 days) groups. These intervals were based on those used in previous studies in breast, colon, lung, and bladder cancer.[11,14-16,21,22] We used these same criteria to determine patients who underwent RC alone for comparison. Patient selection is summarized in Supplementary Figure 1.

Analysis

AC groups were compared with respect to patient-, tumor-, and facility-level characteristics including age, sex, race, Charlson-Deyo Comorbidity score, insurance, median household income, education level, home location, facility location (data not shown), facility type, pathologic tumor and nodal staging, and surgical margin assessment. After comparing the 3 AC-treated groups, comparisons were repeated including patients treated with surgery alone.

Statistical analysis was performed using Stata (version 15.1; StataCorp. 2017. College Station, TX). Treatment group characteristics were compared using ANOVA or Pearson's χ^2 test to assess for differences between the cohorts. Overall survival was measured from the date of RC to the date of death from any cause as bladder cancer-specific mortality and recurrence free survival are not available in the NCDB. To assess the primary objective, overall survival, a multivariable Cox model was built using those who did not receive chemotherapy following RC as the reference group to determine hazard ratios (HRs), adjusting for the previously listed treatment group variables. For our secondary objective, to assess for factors associated with delayed AC initiation, we performed a logistic regression, separating treatment groups into 31-60 days as early AC initiation and 61-180 days as late initiation. All testing was conducted at the 5% level of significance.

RESULTS

A total of 9107 patients with pT3-T4 and/or pN+ disease underwent RC for locally invasive bladder cancer between 2006 and 2013. Of these patients, 3590 met inclusion criteria: 1009 (28%) received AC and 2581 (72%) underwent RC alone. Among those treated with AC, the median time to chemotherapy was 58 days (interquartile range, 46-77 days; range, 31-172 days). The characteristics of the 4 groups are shown in Table 1. Significant differences in baseline characteristics between the AC-treated patients include age, median household income, facility location (data not shown), and pathologic nodal staging. Patients who did not receive AC were more likely to be older, have increasing comorbidity, have Medicare, and have negative margins with no nodal involvement.

Effect of Timing of AC on Overall Survival

The median survival of patients who underwent RC alone was 26.9 months compared with 35.8 months among all AC-treated patients. Median survival in patients receiving AC 31-60 days post-RC was 33.5 months, for 61-90 days post-RC, 37.8 months, and for those 91-180 days post-RC, 36.1 months (Fig. 1). Using those who did not receive AC as reference, the multivariable Cox regression model showed a decrease in overall mortality in patients receiving AC 31-60 days post-RC (HR, 0.60; 95% confidence interval [CI] = 0.52-0.69; P <.001), 61-90 days post-RC (HR, 0.62; 95% CI, 0.53-0.74; P <.001) and 91-180 days post-RC (HR, 0.69; 95% CI, 0.55-0.87; P = .002) (Table 2). Covariate analysis was notable for increased mortality in black patients (HR, 1.26; 95% CI, 1.05-1.52; P = .011) and decreased mortality in patients living in areas with higher levels of education (HR, 0.80; 95% CI, 0.66-0.96; P = .020).

Factors Associated With Early AC

For our logistic regression model to assess factors associated with early AC, 538 (53%) of all AC patients received treatment between 31 and 60 days post-RC and 471 (47%) received AC 61-180 days post-RC. Factors associated with an increased likelihood of early AC initiation include median income >$62,999 (odds ratio [OR], 1.83; 95% CI, 1.06-3.14; P = .028), and lymphatic invasion with pN1 (OR, 1.58, 95% CI, 1.11-2.25, P = .011) and pN2+ disease (OR, 1.53; 95% CI, 1.13-2.09; P = .006). Factors associated with a decreased likelihood of early AC initiation include age (OR, 0.98; 95% CI, 0.96-0.99; P = .036), Comorbidity Score of 1 (OR, 0.70, 95% CI, 0.51-0.97; P = .032), and treatment at an Academic or Research institute (OR, 0.43; 95% CI, 0.20-0.92; P = .030) (Table 3).

Comments

The aim of this study was to determine if delaying AC post-RC in patients with high-risk disease who do not receive NAC

Table 1. Patient demographics, social factors, and pathologic findings

Characteristic	Number (%) AC 31-60 (n = 538)	AC 61-90 (n = 321)	AC 91-180 (n = 150)	*P* Value	No AC (n = 2,581)	P Value
Age (mean)	64.2	65.8	65.1	.028	70.5	<.0001
Sex				.7		.5
Male	414 (77)	241 (75)	111 (74)		1,906 (74)	
Female	124 (23)	80 (25)	39 (26)		675 (26)	
Race				.056		.13
White	500 (93.0)	283 (88.2)	135 (90.0)		2,360 (91.4)	
Black	26 (4.8)	27 (8.4)	7 (4.7)		142 (5.5)	
Other	12 (2.2)	11 (3.4)	8 (5.3)		79 (3.1)	
Charlson-Deyo score				.17		<.001
0	396 (73.6)	218 (67.9)	103 (68.7)		1,659 (64.3)	
1	108 (20.1)	87 (27.1)	38 (25.3)		666 (25.8)	
≥2	34 (6.3)	16 (5.0)	9 (6.0)		256 (9.9)	
Insurance				.4		<.001
Not Insured	22 (4.1)	12 (3.7)	8 (5.3)		69 (2.7)	
Private	235 (43.7)	115 (35.8)	60 (40.0)		646 (25.0)	
Medicare	247 (45.9)	173 (53.9)	71 (47.3)		1,734 (67.2)	
Medicaid/government	34 (6.3)	21 (6.6)	11 (7.4)		132 (5.1)	
Median household income				.017		.054
< $38,000	78 (14)	64 (20)	18 (12)		449 (18)	
$38,000 - $47,999	141 (26)	81 (25)	49 (33)		701 (27)	
$48,000 - $62,999	148 (28)	85 (27)	52 (34)		707 (27)	
> $62,999	171 (32)	91 (28)	31 (21)		724 (28)	
% High school educated				.15		.082
< 79%	70 (13)	50 (16)	21 (14)		411 (16)	
79.1% - 87%	125 (23)	82 (25)	47 (31)		713 (28)	
87.1% - 93%	210 (39)	102 (32)	53 (35)		866 (33)	
> 93%	133 (25)	87 (27)	29 (20)		591 (23)	
Home location				.7		.12
Metro	435 (80.8)	268 (83.5)	124 (82.7)		2,003 (77.6)	
Urban	88 (16.4)	47 (14.6)	24 (16.0)		510 (19.8)	
Rural	15 (2.8)	6 (1.9)	2 (1.3)		68 (2.6)	
Facility type				.050		.078
Community cancer Center	24 (4.5)	8 (2.5)	4 (2.6)		127 (4.9)	
Comprehensive cancer community	206 (38.3)	110 (34.3)	49 (32.7)		899 (34.8)	
Academic/research	254 (47.2)	181 (56.4)	88 (58.7)		1,324 (51.3)	
Integrated network	54 (10.0)	22 (6.8)	9 (6.0)		231 (9.0)	
pT stage				.3		<.001
≤2	54 (10)	43 (13)	13 (8.7)		151 (5.9)	
3	341 (63)	208 (65)	99 (66.0)		1,937 (75.0)	
4	143 (27)	70 (22)	38 (25.3)		493 (19.1)	
pN stage				.009		<.001
0	183 (34)	135 (42)	70 (47)		1,860 (72)	
1	141 (26)	68 (21)	39 (26)		335 (13)	
≥2	214 (40)	118 (37)	41 (27)		386 (15)	
Margins				.080		<.001
Negative	429 (80)	270 (84)	130 (87)		2,291 (89)	
Positive	109 (20)	51 (16)	20 (13)		290 (11)	

affects survival since patients will frequently require delayed initiation of AC due to postoperative morbidity. We found a persistent improvement in overall survival with delayed initiation of AC more than 60 days after RC and up to 180 days following RC. Often, clinical trials require AC be started within 8 weeks of surgery, though we observed up to half of patients receiving AC will be treated further out from surgery.[21] Previous studies demonstrating a benefit with AC defined treatment as occurring within 90 days of cystectomy, though our data suggest patients may still benefit if treatment is delayed twice that period.[10]

Although we found a persistent benefit with AC following RC up to 6 months after surgery, our secondary objective, determining risk factors for delayed initiation of AC, is still important in counseling patients about their postoperative treatment course and its effect on their long-term prognosis. Unsurprisingly, increasing age and increasing comorbidity were both associated with a decreased likelihood of early initiation of AC. Treatment at an academic or research institution was also associated with a decreased likelihood of early initiation of AC, though we hypothesize this may be related to the medical complexity of patients often referred to these institutions. In contrast, patients with node-positive disease were more likely to begin AC earlier, which is consistent with reports that those in the highest risk categories were most likely to benefit from AC.[23,24]

While no prior studies have directly addressed how the timing of AC affects overall survival, studies assessing the use of AC

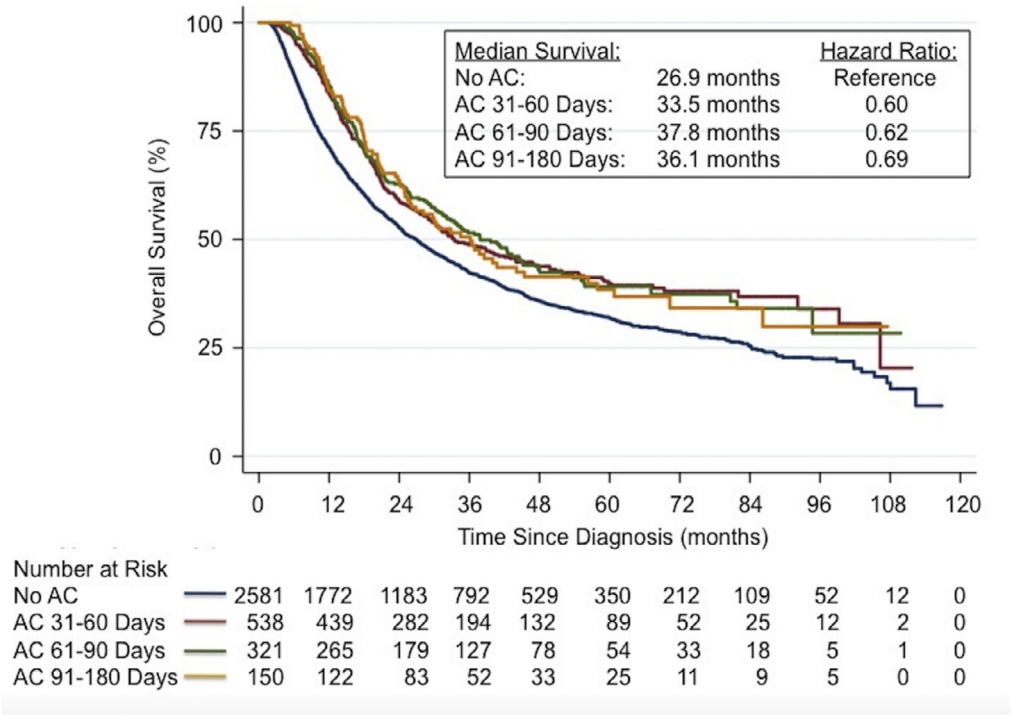

Figure 1. Kaplan-Meier survival curves with median survival and hazard ratios. AC, adjuvant chemotherapy. (Color version available online.)

have found similar factors associated with increased odds of undergoing AC, regardless of whether a patient received NAC. First, in the study by Galsky et al, patients were less likely to receive AC if they were older or had increasing comorbidity, and more likely if they had node-positive disease or positive margins.[10] The same study showed a decreased odds of AC in the lowest income cohort, displaying a similar trend as our study, where those in the highest income group were more likely to undergo early AC initiation.[10] In addition, in 2 studies assessing the efficacy of AC in patients who also received NAC, patients were more likely to receive AC if they were treated at a nonacademic institution or had node-positive disease, and less likely if they were older.[25,26] Across all of these studies, variables associated with increased odds of undergoing AC were also associated with an increased likelihood of early AC initiation in our cohort. Of note, the increased use of AC at nonacademic institutions suggests factors beyond patient complexity may affect the use of AC.

The use of AC for the treatment of MIBC has been notoriously difficult to study in a prospective manner due to poor accrual that ultimately results in underpowered studies.[23,27] Although current studies demonstrating the survival benefit of AC are largely retrospective and caution must be used when drawing any conclusions, it would be unethical to delay the administration of a treatment with a known survival benefit to conduct a randomized trial to address whether timing of AC alters its efficacy. In contrast, retrospective studies also face limitations, including missing data and an inability to control for confounding variables, though we have attempted to control for confounding variables using our Cox regression model.

Finally, despite the large dataset contained within the NCDB, it has several limitations that should be considered when interpreting these findings. First, we cannot determine if patients in the delayed group had disease recurrence, as this information is not recorded within the NCDB. However, the findings of one study assessing outcomes following RC were notable for an earliest recurrence noted at 0.3 years in patients with lymph-node positive disease.[28] Another study found that in patients undergoing RC, approximately 10% will have disease recurrence within 1 year; the median time to recurrence in this group was 7 months, suggesting less than 5% of patients recur within 6 months following RC.[29] Additionally, the AUA guidelines recommend imaging at 6-12 month intervals following treatment for nonmetastatic, muscle-invasive bladder cancer.[2] Consequently, we suspect the likelihood of disease recurrence being the indication for initiation of AC within our cohort to be very low.

The chemotherapy regimen and the underlying cause of mortality are also not included in the NCDB. Without information on the specific chemotherapy regimen, it is difficult to assess if patients underwent a full treatment regimen and its overall impact on survival. However, in the recent study by Vetterlein et al, they approximated an intention-to-treat population by including patients who received at least one cycle of AC and still found an overall and cancer-specific survival benefit.[12] Additionally, patients who received only a partial course of AC may have even better outcomes if they had received a full course of treatment, suggesting our findings may underestimate the benefit of AC. Cancer-specific and recurrence-free survival are also not recorded in the NCDB. Though tumor grade is available in the NCDB, only 2% of our cohort had well- or moderately differentiated disease, so it was not included in our multivariable Cox regression model. Beyond these readily identifiable variables that could affect patient outcomes and the generalizability of our findings, other variables that might reveal significant differences between our cohorts may exist that are not captured by the

Table 2. Select variables associated with decreased overall survival

Characteristic	Hazard Ratio	95% Confidence Interval	P Value
Adjuvant chemotherapy initiation			
No adjuvant chemotherapy (Ref.)	–	–	–
31–60 d	0.60	0.52–0.69	<.001
61–90 d	0.62	0.53–0.74	<.001
91–180 d	0.69	0.55–0.87	.002
Age	1.01	1.00–1.02	<.001
Sex			
Male (ref.)	–	–	–
Female	0.97	0.88–1.07	.6
Race			
White (ref.)	–	–	–
Black	1.26	1.05–1.52	.011
Other	1.11	0.86–1.42	.4
Charlson–Deyo score			
0 (ref.)	–	–	–
1	1.36	1.23–1.50	<.001
≥2	1.54	1.33–1.78	<.001
Insurance			
Private (ref.)	–	–	–
Medicare	1.03	0.92–1.16	.5
Medicaid/government	1.15	0.93–1.41	.17
Not insured	0.81	0.60–1.08	.16
Median household income			
<$38,000 (ref.)	–	–	–
$38,000–$47,999	1.00	0.87–1.15	>.9
$48,000–$62,999	0.96	0.82–1.12	.7
>$62,999	0.97	0.81–1.16	.8
% High school educated			
<79% (ref.)	–	–	–
79.1%–87%	0.91	0.79–1.05	.2
87.1%–93%	0.92	0.79–1.07	.3
>93%	0.80	0.66–0.96	.020
Home location			
Metro (ref.)	–	–	–
Urban	0.95	0.84–1.07	.5
Rural	1.09	0.83–1.43	.5
Facility type			
Community cancer center (ref.)	–	–	–
Comprehensive cancer community	0.90	0.73–1.10	.3
Academic/research	0.90	0.73–1.10	.3
Integrated network	0.95	0.75–1.21	.7
pT stage			
≤2 (ref.)	–	–	–
3	1.82	1.50–2.20	<.001
4	2.48	2.02–3.04	<.001
pN stage			
0 (ref.)	–	–	–
1	1.61	1.41–1.83	<.001
≥2	2.13	1.91–2.39	<.001
Margins			
Negative (ref.)	–	–	–
Positive	1.60	1.42–1.81	<.001

NCDB. For example, while overall comorbidity is reported, specific secondary diagnoses that may alter patient management, such as renal function, are not available. Patient performance status is also not included in the NCDB, but we believe the comorbidity score may serve a similar purpose in approximating overall health, and was included in our multivariable Cox regression model.

Future, prospective studies could address these limitations and control for these potential confounding variables. Additionally, prospective studies could also address whether significant differences in survival exist for those undergoing delayed AC compared with those undergoing early salvage treatment following documented recurrence. However, as previously noted, prospective studies in this patient population are difficult to conduct due to ethical considerations in delaying potentially beneficial treatment, though randomized controlled trials may be considered if other types of prospective studies were to suggest that AC may not have a definite benefit.

Table 3. Variables associated with early adjuvant chemotherapy

Characteristic	Odds Ratio	95% Confidence Interval	P Value
Age	0.98	0.96-0.99	.036
Sex			
Male (ref.)	–	–	–
Female	0.84	0.61–1.14	.3
Race			
White (ref.)	–	–	–
Black	0.69	0.39–1.24	.2
Other	0.66	0.30–1.46	.3
Charlson–Deyo score			
0 (ref.)	–	–	–
1	0.70	0.51–0.97	.032
≥2	1.05	0.59–1.86	.9
Insurance			
Private (ref.)	–	–	–
Medicare	0.87	0.62–1.22	.4
Medicaid/government	0.77	0.43–1.36	.4
Not insured	0.65	0.33–1.29	.2
Median household income			
<$38,000 (ref.)	–	–	–
$38,000–$47,999	1.08	0.70–1.67	.7
$48,000–$62,999	1.14	0.72–1.81	.6
>$62,999	1.83	1.06–3.14	.028
% High school educated			
<79% (ref.)	–	–	–
79.1%–87%	0.93	0.59–1.46	.8
87.1%–93%	1.12	0.69–1.79	.6
>93%	0.75	0.42–1.32	.3
Home location			
Metro (ref.)	–	–	–
Urban	1.15	0.78–1.69	.5
Rural	1.52	0.60–3.86	.4
Facility type			
Community cancer center (ref.)	–	–	–
Comprehensive cancer community	0.56	0.26–1.19	.13
Academic/research	0.43	0.20–0.92	.030
Integrated network	0.91	0.39–2.14	.8
pT stage			
≤2 (ref.)	–	–	–
3	1.29	0.82–2.03	.3
4	1.56	0.94–2.58	.084
pN stage			
0 (ref.)	–	–	–
1	1.58	1.11–2.25	.011
≥2	1.53	1.13–2.09	.006
Margins			
Negative (ref.)	–	–	–
Positive	1.32	0.92–1.90	.13

CONCLUSION

While NAC followed by RC remains the preferred treatment for MIBC, AC has a known survival benefit in patients with high-risk disease who do not receive NAC. Our findings suggest this benefit persists even if AC is delayed up to 6 months post-RC. Although we must use caution when drawing conclusions given the retrospective design and limited data provided within the NCDB, conducting prospective randomized controlled trials to further address these differences would be unethical. Instead, prospective cohort studies can better address the limitations of this study without requiring patients to unnecessarily delay postsurgical AC. Additionally, our findings suggest that AC should not be deferred due solely to delayed initiation which may increase the population of patients receiving AC, which would ultimately facilitate enrollment in future prospective trials.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2019.05.038.

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