

## Research Report

# The Role of Adjuvant Radiation Therapy in Locally Advanced Bladder Cancer

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### Abstract.

**Background:** The standard of care for locally advanced bladder cancer (LABC) is neoadjuvant chemotherapy followed by cystectomy. However, the role of adjuvant therapy for locally advanced bladder cancer is unclear.

**Objective:** The purpose of this study was to evaluate the outcomes of adjuvant radiation therapy (RT) for patients with LABC, and to determine which risk factors best predict for patients who may best benefit from adjuvant RT.

**Methods:** The National Cancer Data Base (NCDB) was queried (2004–2013) for patients with newly-diagnosed pT3-4N0-3M0 urothelial carcinoma of the bladder that received neoadjuvant chemotherapy and cystectomy. Patients were divided into two groups based on the adjuvant therapy they received: RT or observation. Statistics included multivariable logistic regression to determine factors predictive of receiving adjuvant RT, Kaplan-Meier analysis to evaluate overall survival (OS), and Cox proportional hazards modeling to determine variables associated with OS.

**Results:** Altogether, 1,646 patients met inclusion criteria; 59 (3.6%) patients received adjuvant RT, while 1,587 (96.4%) were observed. Patients treated with adjuvant RT were more likely to be female, have positive surgical margins, and receive treatment at a non-academic facility. There was no difference in median overall survival (OS) between patients treated with RT when compared to patients observed (17.7 months vs. 23.5 months;  $p=0.085$ ). However, an improvement in median OS with the use of adjuvant RT was observed among patients with positive surgical margins (20.3 months vs. 13.1 months;  $p=0.032$ ). On multivariate analysis, advancing age, pT4 stage, positive N stage, positive margins, and lower socioeconomic status were associated with worse OS.

**Conclusions:** In the largest study to date evaluating efficacy of adjuvant radiotherapy in patients with locally advanced bladder cancer, use of RT was not associated with OS in all patients, while RT was associated with improved OS among patients with positive surgical margins. Prospective studies are recommended to confirm these findings.

Keywords: Bladder cancer, cystectomy, radiotherapy

## INTRODUCTION

After prostate cancer, bladder cancer is the most common neoplasm of the genitourinary tract in the United States and results in the deaths of approxi-

mately 15,000 patients per year [1]. Of all bladder cancer patients, 25% present with muscle-invasive disease, for which radical cystectomy has long been the cornerstone of definitive management and is currently a standard of care [2, 3]. Although survival outcomes are reasonable (60% at 5 years) for organ-confined, muscle-invasive disease (pT2), survival outcomes are worse (10–50% at 5 years for >pT3 disease) for patients with more advanced disease,

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with a high rate of distant metastasis [4]. Consequently, systemic chemotherapy has been used to improve outcomes for these patients, with level one evidence supporting its use in the neoadjuvant setting [3, 5].

However, there is growing concern about the importance of locoregional control for locally advanced bladder cancer (LABC). Historically, the rate of pelvic failure for LABC after radical cystectomy was thought to be low; early surgical literature reported locoregional recurrence rates on the order of 7–13% [6–8]. These low reported rates are likely due to the absence of routine use of advanced imaging of the pelvis during follow-up [6, 7] as well as the lack of reporting pelvic failure if they were synchronous with distant metastases [9, 10]. More recent data suggests that the rate of locoregional recurrence for patients undergoing cystectomy can be as high as 58%, with local failure rates of up to 72% for patients with pT4pN1 disease [11, 12]. Other studies have demonstrated that that locoregional recurrence independently predicts for distant metastasis and worse disease-specific survival, leading authors to advocate for adjuvant therapy in patients with high risk bladder cancer at high risk for local failure [13, 14].

As a result, there may be a role for local therapy with adjuvant radiotherapy (RT) to improve local control, consequently enhancing survival outcomes [15]. A randomized trial by Zaghoul et al. comparing postoperative radiotherapy to observation after cystectomy for patients with LABC in Egypt reported both a disease-free survival benefit and local control benefit with radiotherapy, albeit in the setting of no systemic therapy [16]. A follow-up phase II trial by the same group demonstrated a substantial local control benefit and marginal disease free survival benefit with the addition of radiation therapy (RT) to adjuvant chemotherapy following cystectomy [17]. To further elucidate the role of adjuvant RT for patients with LABC, clinical trials addressing this question are either currently accruing or in development in France (GETUG-AFU), the United Kingdom (NCRI), National Cancer Institution (NCI) Cairo, Belgium (University of Ghent), and India (Tata Memorial Hospital) [15]. Given this interest, we aimed to examine if post-operative radiotherapy is associated with improved survival outcomes in patients with LABC urothelial carcinoma of the bladder who received neoadjuvant chemotherapy and underwent radical cystectomy using the National Cancer Data Base (NCDB).

## MATERIALS AND METHODS

This investigation 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 [18–20]. 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 age  $\geq 18$  with urothelial carcinoma of the bladder treated with neoadjuvant chemotherapy and cystectomy and found to have pT3/4pN0–3M0 disease. We opted to include solely patients with pT3/4pN0–3M0 disease based on inclusion criteria similar to randomized trials attempting to address the role of adjuvant RT for LABC [15]. Additionally, for inclusion, patients required histological diagnostic confirmation, definitive treatment with neoadjuvant chemotherapy and cystectomy (surgical procedure of the primary site codes 50, 60–64, 70–74, 80), and a recorded vital status. Patients treated with adjuvant chemotherapy or neoadjuvant RT were excluded from this analysis, because based on current national guidelines, there is no solid indication for neoadjuvant RT for adjuvant chemotherapy if neoadjuvant chemotherapy is given [21]. Patients were divided into two cohorts: those receiving adjuvant RT and those observed following surgery. Using a classification scheme from other published studies utilizing the NCDB, an academic facility was defined as an institution with both an accession of more than 500 newly diagnosed cancer cases per year and one that provided postgraduate medical education in at least four program areas, including internal medicine and general surgery [22]. All other facilities, including Comprehensive Community Cancer Programs, Community Cancer Programs, and Integrated Network Programs, were categorized as non-academic,

as none of these institutions require graduate medical education.

Information collected on each patient included demographic data, comorbidity information, clinico-pathologic tumor parameters, and treatment facility characteristics. 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  $\chi^2$  test analyzed categorical proportions between groups in the non-parametric and parametric settings, respectively. Univariable and multivariable logistic regression modeling was utilized to determine characteristics that were predictive for receipt of RT. Factors for inclusion in the multivariate analysis were those found to be statistically significant on univariate analysis. The Kaplan-Meier method was used for survival analysis while performing a landmark analysis, in which patients dying within 6 months of diagnosis were excluded to account for immortal time bias, and comparisons between the two treatment paradigms were performed with the log-rank test for all patients. Subset analysis was performed while stratifying patients by T stage, N stage, and surgical margin status, based on data demonstrating that these factors were predictive of local recurrence for patients with urothelial carcinoma following cystectomy [23]. Overall survival (OS) was defined as the interval between the date of diagnosis and the date of death or last contact. Multivariate Cox proportional hazards modeling was additionally used to identify

variables associated with OS in the entire cohort. Patients included in the multivariate analysis were those found to be statistically significant on univariate analysis. Multivariate cox proportional hazards modeling was subsequently performed on the subset of patients with positive margins.

## RESULTS

A complete flow diagram of patient selection is provided in Fig. 1. In total, 1,646 patients met inclusion criteria. Of these, 59 (3.6%) patients received adjuvant RT, while 1,587 (96.4%) patients were observed. A greater proportion of patients that received adjuvant RT had pT4 disease, positive margins, and received treatment at a non-academic facility. Table 1 displays the demographic and clinical characteristics of the analyzed patients. The majority of patients were male, Caucasian, and had a Charlson-Deyo comorbidity score of 0.

Multivariable logistic regression analysis was performed to evaluate factors independently associated with receiving adjuvant RT. Patients treated with adjuvant RT were more likely to be female, have positive surgical margins, and receive treatment at a non-academic facility. These factors are summarized in Table 2.

The median follow up time was 19.5 months (interquartile range, 11.7–32.9 months) Kaplan-Meier curves are displayed in Fig. 2. In the whole

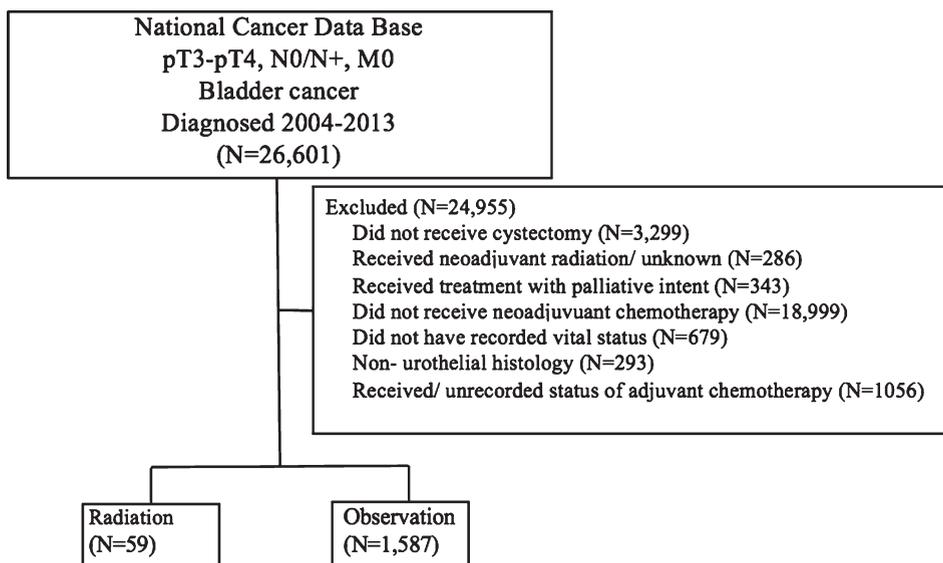


Fig. 1. Patient selection diagram.

Table 1  
Baseline characteristics of patients in each of the four cohorts

Characteristic	Adjuvant radiation; <i>n</i> = 59 (%)	Observation; <i>n</i> = 1587 (%)	<i>P</i> value
Age			
<65	25 (42.4%)	656 (41.3%)	0.953
65–74	23 (39.0%)	609 (38.4%)	
75+	11 (18.6%)	322 (20.3%)	
Sex			
Male	37 (62.7%)	1196 (75.4%)	0.028
Female	22 (37.3%)	391 (24.6%)	
Race			
White	51 (86.4%)	1409 (88.9%)	0.024
African American	3 (5.1%)	96 (6.1%)	
Hispanic	5 (8.5%)	39 (2.5%)	
Other	0 (0.0%)	43 (2.7%)	
pT Stage			
T3	27 (45.8%)	1112 (70.1%)	<0.0001
T4	32 (54.2%)	475 (29.9%)	
pN Stage			
N0	26 (44.1%)	907 (57.2%)	0.086
N1	10 (17.0%)	263 (16.6%)	
N2	18 (30.5%)	358 (22.6%)	
N3	5 (8.5%)	59 (3.7%)	
Margin status			
Negative	26 (44.1%)	1284 (80.9%)	<0.0001
Positive	30 (50.9%)	244 (15.4%)	
Not recorded	3 (5.1%)	59 (3.7%)	
Charlson Deyo Score			
0	46 (78.0%)	1138 (71.7%)	0.390
1	9 (15.3%)	361 (22.8%)	
2	4 (6.8%)	88 (5.6%)	
Facility Type			
Academic	23 (39.0%)	952 (60.0%)	0.004
Non academic	36 (61.0%)	626 (39.5%)	
Not recorded	0 (0.0%)	(0.6%)	
Insurance			
Medicaid	3 (5.1%)	73 (4.6%)	0.697
Private	22 (37.3%)	581 (36.6%)	
Medicare	33 (55.9%)	839 (52.9%)	
Not insured	1 (1.7%)	46 (2.9%)	
Other	0 (0.0%)	48 (3.0%)	
Income			
<\$47999	26 (44.1%)	600 (37.8%)	0.247
\$48000+	31 (52.5%)	965 (60.8%)	
Not recorded	2 (3.4%)	22 (1.4%)	

cohort, there was no difference in median overall survival (OS) between patients treated with RT when compared to patients observed (17.7 months vs. 23.4 months;  $p = 0.085$ ). However, on subset analysis, an improvement in median OS with adjuvant RT was observed among patients with positive surgical margins (20.3 months vs. 13.1 months;  $p = 0.032$ ), though there was no difference in OS with adjuvant RT use for patients with N2–N3 disease (16.6 months vs. 15.1 months,  $p = 0.205$ ) or pT4 disease (18.5 months vs. 16.7 months,  $p = 0.5728$ ).

On multivariate analysis (Table 3), advancing age, pT4 stage, positive N stage, positive surgical margins,

receipt of treatment at a non-academic facility, and lower socioeconomic status were associated with worse OS. Multivariate analysis amongst patients specifically with positive margins confirmed (supplemental Table 1) that adjuvant RT was associated with improved OS when accounting for confounding variables (Hazard ratio = 0.474, 95% confidence interval 0.281–0.801,  $p = 0.005$ ).

## DISCUSSION

Given the lack of clear evidence to guide adjuvant management for LABC, the current study provides

Table 2  
Characteristics predictive for receipt of radiation therapy on multivariable logistic regression analysis

Characteristic	Odds Ratio	95% Confidence Interval	P value
Age			
<65		1 (reference)	
65–74	0.693	0.294–1.630	0.400
75+	0.522	0.190–1.435	0.208
Sex			
Male		1 (reference)	
Female	1.785	1.010–3.154	0.046
Race			
White		1 (reference)	
African American	0.741	0.216–2.536	0.633
Hispanic	3.331	1.109–10.007	0.032
Other	–	–	–
pT Stage			
T3		1 (reference)	
T4	1.723	0.958–3.099	0.069
pN Stage			
N0		1 (reference)	
N1	1.263	0.584–2.730	0.553
N2	1.256	0.650–2.427	0.499
N3	1.858	0.632–5.462	0.260
Margin status			
Negative		1 (reference)	
Positive	4.671	2.537–8.602	<0.0001
Not recorded	2.325	0.648–8.349	0.196
Charlson Deyo Score			
0		1 (reference)	
1	0.629	0.296–1.338	0.229
2	0.994	0.333–2.963	0.991
Facility Type			
Academic		1 (reference)	
Non academic	2.259	1.286–3.968	0.005
Not recorded	–	–	–
Insurance			
Medicaid		1 (reference)	
Private	1.242	0.328–4.698	0.750
Medicare	1.968	0.446–8.675	0.371
Not insured	0.540	0.049–5.990	0.616
Other	–	–	–
Income			
<\$47999		1 (reference)	
\$48000+	0.813	0.463–1.427	0.470
Not recorded	1.455	0.284–7.469	0.653

important information regarding the utility of adjuvant RT for patients in this patient population. To our knowledge, this is the largest study to date examining the use, role, and benefit of adjuvant RT for patients with LABC undergoing treatment with neoadjuvant chemotherapy and radical cystectomy in which some of the patients received adjuvant therapy. Several observations can be made from our analysis. First, in accordance with the existing literature, observation is the most common management strategy after neoadjuvant chemotherapy and cystectomy. Second, adjuvant RT was more likely to be in the setting of positive margins and in patients treated at non-academic centers. Third, though there were no differences in OS

with adjuvant RT, an improvement in OS was observed among patients with positive margins.

As noted earlier, the randomized controlled trial by Zaghoul et al. found an improvement in disease-free survival and local control with radiotherapy as compared to cystectomy alone [16]. However, since the trial was conducted in Egypt, the majority of patients in the study had squamous cell carcinoma histology, and its results may not be applicable to patients with bladder cancer in the U.S., who have primarily urothelial carcinoma. A second randomized trial by the same group compared adjuvant chemotherapy and RT to adjuvant chemotherapy alone in patients with high-risk bladder cancer following cystectomy

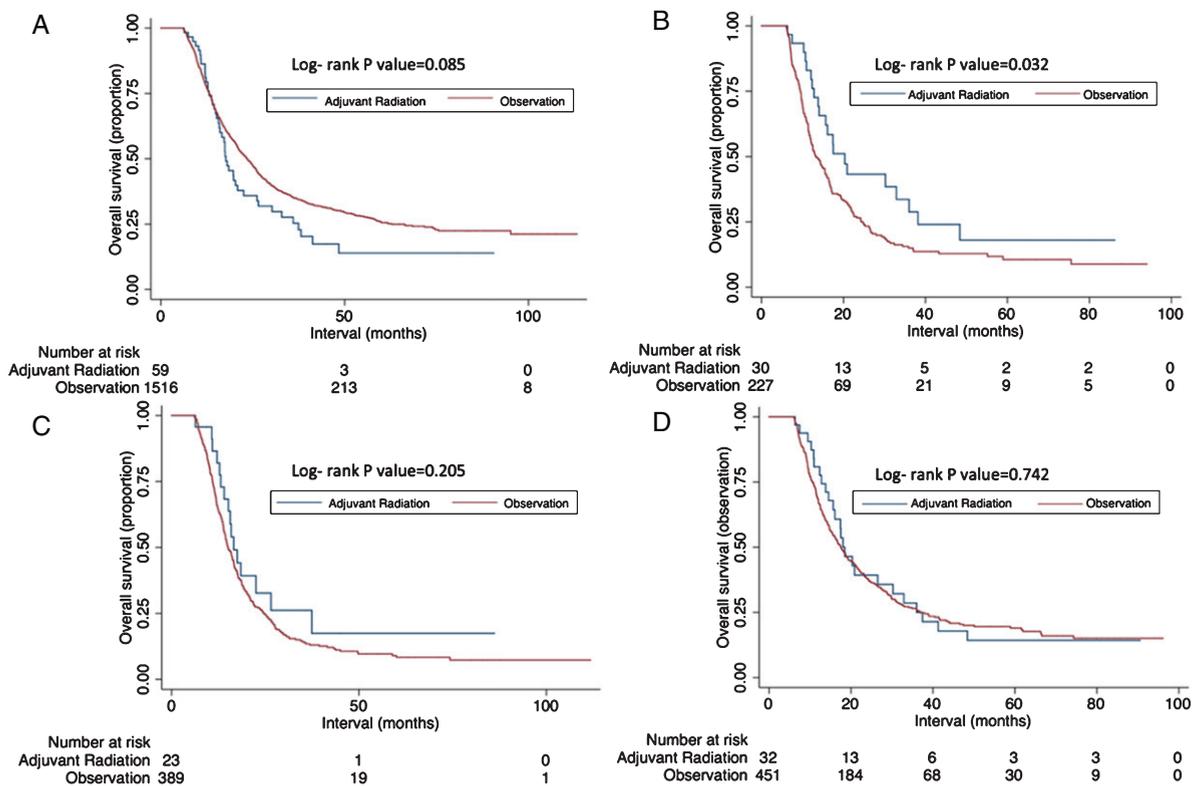


Fig. 2. Kaplan-Meier overall survival curves comparing those receiving chemoradiation versus observation for all patients (A); among surgical margin positive patients (B); among pN2-3 patients (C); among pT4 patients (D).

and demonstrated improved local control and disease free survival with the use of RT [17]. Only 47% of the patients in this study had squamous cell carcinoma, whereas 53% had urothelial carcinoma, so these results may be applicable to patients with bladder cancer in the U.S. However, in each of the aforementioned trials, patients did not receive neoadjuvant chemotherapy, so the efficacy of RT may have been partially due to the lack of systemic therapy. To eliminate these confounding factors in our study, we focused specifically on patients with urothelial carcinoma who received standard of care therapy with neoadjuvant chemotherapy followed by radical cystectomy.

The present results suggest patients with positive surgical margins may have an OS benefit with the use of adjuvant RT. This may be since the goal of adjuvant RT is to eradicate residual disease. The importance of adjuvant RT in patients with positive surgical margins appears to be relatively well understood; while only 3.6% of all patients included in the present study received adjuvant RT, among patients with positive surgical margins, the proportion of patients receiving RT increased to 10.9%.

Although RT may not be necessary for all patients in adjuvant setting, there are likely to be high-risk patients that do derive a benefit. In an attempt to better select patients who may benefit most from adjuvant RT, researchers have attempted to determine risk factors for pelvic recurrence. Baumann et al. developed a risk stratification model based on a cohort of 442 consecutive cystectomy patients and found that  $\geq pT3$  stage, number of nodes excised ( $<10$  vs.  $\geq 10$ ), and surgical margin status were significant independent predictors of local failure [23]. However, other investigators have determined that only pT-stage and pN-stage are significant predictors of local failure [12]. In the present study, we opted not to examine number of nodes excised as this has not been validated in multiple studies and since a significant proportion of these values were missing in the NCDB.

Our analysis did not find an OS benefit with adjuvant RT in pN2-3 disease or higher T-stage (pT4) disease. This is may be due to the relatively small number of patients receiving radiotherapy in our analysis. Though a trend to an OS benefit with the addition of adjuvant RT in patients with N2-N3 disease was observed in the present investigation (16.6 months vs

Table 3  
Cox univariate and multivariate analysis of factors predictive of overall survival in the entire cohort

Characteristic	Hazard Ratio- Univariate analysis	95% Confidence Interval	P value	Hazard Ratio- Multivariate analysis	95% Confidence Interval	P value
Treatment						
Observation	1 (reference)			–	–	–
Adjuvant radiation	1.222	0.906–1.647	0.180	–	–	–
Age						
<65	1 (reference)			1 (reference)		
65–74	1.142	0.998–1.306	0.053	1.130	0.987–1.294	0.077
75+	1.289	1.100–1.511	0.002	1.247	1.02–1.463	0.007
Sex						
Male	1 (reference)			–	–	–
Female	1.023	0.892–1.173	0.743	–	–	–
Race						
White	1 (reference)			–	–	–
African American	1.118	0.880–1.420	0.363	–	–	–
Hispanic	0.996	0.605–1.399	0.538	–	–	–
Other	0.704	0.466–1.065	0.097	–	–	–
pT Stage						
T3	1 (reference)			1 (reference)		
T4	1.508	0.330–1.708	<0.0001	1.245	1.091–1.421	0.001
pN Stage						
N0	1 (reference)			1 (reference)		
N1	1.422	1.204–1.681	<0.0001	1.447	1.223–1.711	<0.0001
N2	2.332	2.025–2.684	<0.0001	2.112	1.825–2.444	<0.0001
N3	2.785	2.085–3.729	<0.0001	2.602	1.941–3.488	<0.0001
Margin status						
Negative	1 (reference)			1 (reference)		
Positive	2.005	1.729–2.326	<0.0001	1.553	1.27–1.817	<0.0001
Not recorded	1.085	0.95–1.479	0.608	0.933	0.682–1.276	0.664
Charlson Deyo Score						
0	1 (reference)			–	–	–
1	1.139	0.989–1.311	0.070	–	–	–
2	1.205	0.934–1.556	0.152	–	–	–
Facility Type						
Academic	1 (reference)			1 (reference)		
Non academic	1.210	1.073–2.364	0.002	1.258	1.113–1.421	<0.0001
Not recorded	0.917	0.380–2.212	0.847	0.792	0.36–1.930	0.609
Insurance						
Medicaid	1 (reference)			–	–	–
Private	0.808	0.602–1.085	0.157	–	–	–
Medicare	0.937	0.70–1.251	0.660	–	–	–
Not insured	0.726	0.457–1.153	0.175	–	–	–
Other	0.868	0.557–1.353	0.531	–	–	–
Income						
<\$47999	1 (reference)			1 (reference)		
\$48000+	0.810	0.716–0.915	0.001	0.820	0.725–0.927	0.001
Not recorded	2.204	1.422–3.417	<0.0001	2.197	1.413–3.417	<0.0001

14.5 months,  $p=0.1283$ ), this did not achieve statistical significance. Given that only 23 patients with N2–N3 disease received RT, as well as the significant imbalance in terms of negative prognostic factors in the two treatment arms, it is possible that with greater patient numbers, an OS would have been statistically significant. A survey of US radiation oncologists found nearly half (46%) had used adjuvant RT, so the low numbers of patients receiving RT in our study are somewhat surprising [24]. On the other hand, the US-based NRG-GU001 trial investigating the role of

adjuvant RT closed due to poor accrual, suggesting a lack of robust referral patterns. Our study also did not have information on the radiation fields for the patients receiving adjuvant RT. Patterns of failure studies indicate that the iliac/obturator nodal beds common sites of pelvic recurrence in patients with negative margins and the presacral nodes and cystectomy are more common failure sites in patients with positive margins [25]. Another possible explanation for the lack of survival benefit seen in our study for patients with pN2–3 disease or T4 disease

may be inadequate RT coverage of regions most at risk for recurrence. A recently published consensus contouring atlas for adjuvant bladder RT may help with standardization of target delineation for management of future patients and may lead to further improvements in patients treated with adjuvant RT [26]. A multi-institutional study from France has demonstrated good local control for patients with bladder cancer treated with adjuvant RT [27]. The authors reported using the Radiation Therapy Oncology Group (RTOG) atlas as a guide to define the Clinical Target Volume, suggesting that using published guidelines for target delineation can result in good clinical outcomes.

There are several limitations in our study due to its reliance on the NCDB. First, the retrospective nature of the study and all associated inherent biases must be acknowledged. Second, the NCDB does not keep track of several noteworthy variables, such as reasons for a particular treatment, radiation treatment fields, receipt of targeted therapies, and salvage treatments. In addition, the NCDB does not record other endpoints such as tolerance of therapy, cancer-specific survival, and local/regional control, which are important variables when assessing the utility of additional therapy. Moreover, patients treated with adjuvant chemotherapy were excluded from this study, suggesting that we do not know the role of adjuvant radiotherapy in patients in addition to adjuvant concurrent/sequential chemotherapy. While this study was not designed to determine the efficacy of adjuvant chemotherapy after neoadjuvant chemotherapy and cystectomy, there may be potential benefits for high risk patients [28, 29]; additional research is needed to further explore this question. Overall, these limitations do not diminish the need for further investigations of the role of adjuvant therapy for LABC.

## CONCLUSIONS

Adjuvant RT following neoadjuvant chemotherapy and radical cystectomy was not associated with improved OS in a general LABC cohort. However, an improvement in OS was observed among patients with positive margins. On multivariate analysis, advancing age, pT4 stage, positive N stage, positive margins, and lower socioeconomic status were associated with worse overall survival. This study is the largest study of adjuvant radiotherapy to date, and our findings highlight the need for

additional prospective data; we eagerly await the results of the currently ongoing clinical trials on this topic.

## DECLARATION

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## DISCLAIMERS

None. This has never been presented/published before in any form. All authors declare that conflicts of interest do not exist.

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## SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: <http://dx.doi.org/10.3233/BLC-180163>.

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