Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Management of Muscle-Invasive Bladder Cancer During a Pandemic: Impact of Treatment Delay on Survival Outcomes for Patients Treated With Definitive Concurrent Chemoradiotherapy

Benjamin W. Fischer-Valuck,[1] Jeff M. Michalski,[2] Joanna G. Harton,[5] Alison Birtle,[7,8] John P. Christodouleas,[6] Jason A. Efstathiou,[9] Vivek K. Arora,[3] Eric H. Kim,[4] Eric M. Knoche,[3] Russell K. Pachynski,[3] Joel Picus,[3] Yuan James Rao,[10] Melissa Reimers,[3] Bruce J. Roth,[3] Paul Sargos,[11,12] Zachary L. Smith,[4] Mohamed S. Zaghloul,[13,14] Hiram A. Gay,[2] Sagar A. Patel,[1] Brian C. Baumann[2,6]

Abstract

Limited data are available on the effect of treatment delays for initiating chemoradiotherapy (CRT) for muscle-invasive bladder cancer. We used the National Cancer Database and found that 1387 patients had started CRT < 90 days after transurethral resection of bladder tumor (TURBT) compared with 197 with delayed CRT (≥ 90 days after TURBT). On multivariable analysis, delayed CRT was not associated with differences in overall survival. These results suggest that short, strategic treatment delays during a pandemic can be considered based on clinician judgment.

Introduction: During the coronavirus disease 2019 (COVID-19) pandemic, providers and patients must engage in shared decision making to ensure that the benefit of early intervention for muscle-invasive bladder cancer exceeds the risk of contracting COVID-19 in the clinical setting. It is unknown whether treatment delays for patients eligible for curative chemoradiation (CRT) compromise long-term outcomes. **Patients and Methods:** We used the National Cancer Data Base to investigate whether there is an association between a $\geq$ 90-day delay from transurethral resection of bladder tumor (TURBT) in initiating CRT and overall survival. We included patients with cT2-4N0M0 muscle-invasive bladder cancer from 2004 to 2015 who underwent TURBT and curative-intent concurrent CRT. Patients were grouped on the basis of timing of CRT: $\leq$ 89 days after TURBT (earlier) vs. $\geq$ 90 and $<$ 180 days after TURBT (delayed). **Results:** A total of 1387 (87.5%) received earlier CRT (median, 45 days after TURBT; interquartile range, 34-59 days), and 197 (12.5%) received delayed CRT (median, 111 days after TURBT; interquartile range, 98-130 days). Median overall survival was 29.0 months (95% CI, 26.0-32.0) versus 27.0 months (95% CI, 19.75-34.24) for earlier

[1]Department of Radiation Oncology, Winship Cancer Institute of Emory University, Atlanta, GA
[2]Department of Radiation Oncology
[3]Division of Oncology
[4]Division of Urology, Washington University School of Medicine in St Louis, St Louis, MO
[5]Department of Biostatistics, Epidemiology, and Informatics
[6]Department of Radiation Oncology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA
[7]Lancashire Teaching Hospitals NHS Foundation Trust, Preston, UK
[8]University of Manchester, Manchester, UK
[9]Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA
[10]Department of Radiation Oncology, George Washington University, Washington D.C.
[11]Department of Radiation Oncology, Jewish General Hospital, Montreal, QC, Canada
[12]Department of Radiotherapy, Institut Bergonié, Bordeaux, France
[13]Radiation Oncology Department, Children's Cancer Hospital, Cairo, Egypt
[14]Radiation Oncology Department, National Cancer Institute, Cairo University, Cairo, Egypt

Submitted: May 13, 2020; Revised: Jun 15, 2020; Accepted: Jun 15, 2020; Epub: Jun 22, 2020

Address for correspondence: Brian C. Baumann, MD, Department of Radiation Oncology, Washington University School of Medicine in St Louis, 660 S Euclid Ave, Campus Box 8224, St Louis, MO 63110
Fax: (314) 362-7769; E-mail contact: Brian.Baumann@wustl.edu

1558-7673/$ - see frontmatter
https://doi.org/10.1016/j.clgc.2020.06.005

and delayed CRT (P = .94). On multivariable analysis, delayed CRT was not associated with an overall survival difference (hazard ratio, 1.05; 95% CI, 0.87-1.27; P = .60). **Conclusion:** Although these results are limited and require validation, short, strategic treatment delays during a pandemic can be considered on the basis of clinician judgment.

Clinical Genitourinary Cancer, Vol. 19, No. 1, 41-6
Keywords: ChemoRT MIBC, COVID-19 bladder cancer, Delays in chemoRT MIBC, MIBC, Pandemic treatment delays MIBC

Introduction

To mitigate exposure risk during the coronavirus disease 2019 (COVID-19) pandemic, the National Comprehensive Cancer Network and several physician organizations have recommended alternative treatment approaches including hypofractionated radiotherapy (RT) and delaying or omitting daily RT for several cancers, including those of breast, prostate, and skin, with many of these guidelines recommending a 3-month delay for patients who are relatively asymptomatic without rapidly progressive disease.[1-3] To our knowledge, no guidelines have yet been released regarding nonoperative management of muscle-invasive bladder cancer (MIBC). To make informed decisions about whether to delay definitive chemoradiotherapy (CRT) of MIBC during this pandemic, risk assessment of potential COVID-19–associated morbidity and mortality from contracting COVID-19 in the clinic setting versus cancer morbidity and mortality is necessary. Given that most patients with bladder cancer are elderly and/or former smokers, their risk of COVID-19 complications is relatively high.[4] In the recent publication by Kuderer et al,[5] patients with cancer and COVID-19 had high 30-day all-cause mortality; independent factors associated with increased 30-day mortality included increased age, male sex, smoking history, active cancer, multiple comorbidities, and poorer performance status. While several retrospective cystectomy series suggest that 2- to 3-month delays in the setting of neoadjuvant chemotherapy (NAC) are not associated with worse outcomes,[6,7] it is unknown whether delays in CRT for MIBC affects survival. In clinical practice, it has been estimated that the first fraction of definitive RT occurs 82 days (IQR, 62-105) after transurethral resection of bladder tumor (TURBT),[8] and the currently enrolling Southwest Oncology Group (SWOG) 1806 trial of CRT allows delays of up to 77 days.[9] The optimal timing of CRT after TURBT has not been determined.

In this study, we sought to determine if there is an association between the timing of CRT initiation and overall survival (OS). We hypothesized that delays in initiating definitive CRT after TURBT would not be associated with decreased OS.

Patients and Methods

We identified cT2-4N0M0 MIBC patients between 18 and 90 years old in the National Cancer Data Base's most recent bladder cancer participant user file (PUF), which included data from 2004 to 2015, who underwent TURBT and curative-intent concurrent CRT therapy (55 Gy in 20 fractions or ≥ 60 Gy with conventional fractionation). Chemotherapy had to start within 14 days of RT, and patients who received NAC were excluded. All patients underwent TURBT within 30 days of diagnosis (Supplemental Figure 1 in the online version). Patients were grouped by timing of CRT: ≤ 89 days after TURBT (earlier) versus ≥ 90 and < 180 days after TURBT (delayed). Patient and demographic characteristics included: age, sex, race, facility type, facility location, metro/urban/rural population, income, education level, insurance status, distance from treatment center, Charlson-Deyo comorbidity index, year of diagnosis, T stage, number of chemotherapy agents, and earlier CRT versus delayed CRT. Patients with missing demographic, treatment, or survival data were excluded from the analysis.

The chi-square test was used to compare categorical demographic and patient characteristics between the two groups. The Student *t* test was used to compare continuous variables between groups. Multivariable logistic regression was used to identify predictors of delayed CRT. To account for lead-time bias, OS was calculated from time of starting RT until death, censoring at last follow-up for patients who were alive. The Kaplan-Meier method was used to estimate OS probabilities. Variables included in the multivariable Cox proportional hazards model were chosen for their clinical relevance, and the proportional hazards assumption was found to be met. Sensitivity analyses were performed. We repeated the analysis with delay from TURBT to CRT as a continuous, rather than dichotomized, variable. We also repeated the analysis with OS defined as time from diagnosis until death, censoring at last follow-up for patients still alive. $P < .05$ was considered significant. All were 2 sided. Analysis was performed by SPSS version 27 (IBM, Armonk, NY).

Results

Data of 1584 patients were eligible for analysis: 1387 (87.5%) received earlier CRT (median 45 days after TURBT, IQR 34-59 days) and 197 (12.5%) received delayed CRT (median 111 days after TURBT, IQR 98-130 days). Of the delayed CRT cohort, 130 patients (66.0%) were delayed 90-120 days and 24 patients (12.2%) were delayed > 150 days. Baseline patient characteristics are listed in Table 1. Multivariable logistic regression showed that covariables associated with increased likelihood for treatment delays included patients living in rural counties (odds ratio [OR], 2.52; 95% hazard ratio [HR], 1.09-5.80; $P = .030$) and increasing distance (in miles) from residence to treatment facility (OR, 1.01; 95% HR, 1.00-1.01; $P = .008$). Covariables associated with less likelihood of delayed CRT included: younger age (OR, 0.98; 95% HR, 0.96-0.99; $P = .010$) and higher education (7-12.9% rate of not graduating high school: OR, 0.56; 95% HR, 0.32-0.97; $P = .038$; and < 7% rate of not graduating high school: OR, 0.47; 95% HR, 0.24-0.91; $P = .024$).

Median OS calculated from date of starting CRT was 29.0 months (95% confidence interval [CI], 26.0-32.0) for earlier CRT versus 27.0 months (95% CI, 19.75-34.24) for delayed CRT ($P = .94$) (Figure 1). On multivariable analysis, delayed CRT was not associated with an OS difference compared to earlier CRT (HR,

Table 1 Patient Characteristics

Characteristic	Patient Group			Multivariable Analysis	
	Earlier CRT (N = 1387)	Delayed CRT (N = 197)	*P*	HR (95% CI)	*P*
Earlier CRT (days), median [IQR]	45 [34-59]	—	—	Reference	—
Delayed CRT (days), median [IQR]	—	111 [98-130]	—	1.05 (0.87-1.27)	.601
Age (years), mean [SD]	76.3 [9.4]	74.5 [9.4]	.011[a]	1.03 (1.02-1.03)	<.0001[a]
Sex			.825		
Male	1042 (75.1)	150 (76.1)		Reference	—
Female	345 (24.9)	47 (23.9)		1.01 (0.88-1.16)	.670
Race			.254		
White	1286 (92.7)	178 (9.4)		Reference	—
Other	101 (7.3)	19 (9.6)		1.14 (0.91-1.44)	.260
Facility type			.024[a]		
Community CC	177 (12.8)	18 (9.1)		Reference	—
Comprehensive community CC	684 (49.4)	83 (42.1)		0.96 (0.79-1.16)	.670
Academic/research CC	326 (23.5)	63 (32)		1.04 (0.85-1.30)	.696
Integrated network CC	198 (14.3)	33 (16.8)		1.05 (0.83-1.33)	.696
Facility location			.346		
East	638 (46.0)	102 (51.8)		Reference	—
Central	519 (37.4)	65 (33.0)		1.07 (0.93-1.23)	.355
West	230 (16.6)	30 (15.2)		0.92 (0.77-1.11)	.391
Median income			.795		
<$38,000	210 (15.1)	33 (16.8)		Reference	—
$38,000-47,999	339 (24.4)	50 (25.4)		1.00 (0.80-1.23)	.949
$48,000-62,999	397 (28.6)	50 (25.4)		0.95 (0.76-1.18)	.628
$63,000+	442 (31.9)	64 (32.5)		0.99 (0.76-1.29)	.934
Education[a]			.138		
21% or more	180 (13.0)	37 (18.8)		Reference	—
13-20.9%	324 (23.4)	47 (23.9)		1.19 (0.96-1.48)	.109
7-12.9%	505 (36.4)	67 (34.0)		1.11 (0.88-1.39)	.386
<7%	378 (27.3)	46 (23.4)		0.98 (0.75-1.28)	.867
Urban/rural[b]			.097		
Metro counties	1125 (81.1)	155 (78.7)		Reference	—
Urban counties	169 (12.2)	23 (11.7)		1.04 (0.86-1.27)	.688
Rural counties	68 (4.9)	10 (5.1)		0.96 (0.75-1.34)	.994
Unknown	25 (1.8)	9 (4.6)		0.67 (0.42-1.09)	.104
Insurance status			.445		
Private insurance	15 (1.1)	2 (1.0)		Reference	—
Not insured	213 (15.4)	39 (19.8)		0.91 (0.44-1.87)	.790
Medicaid	33 (2.4)	3 (1.5)		1.31 (0.58-2.96)	.517
Medicare	1102 (79.5)	148 (75.1)		1.01 (0.49-2.08)	.981
Other government	24 (1.7)	5 (2.5)		1.25 (0.54-2.92)	.604
Distance from residence to treatment, mean [SD] (miles)	19.4 [67]	46.3 [207.7]	<.0001[a]	1.00 (1.00-1.00)	.884
Charlson-Deyo comorbidity score			.745		
0	911 (65.7)	123 (62.4)		Reference	—
1	318 (22.9)	51 (25.9)		1.26 (1.09-1.46)	.002[a]
2	108 (7.8)	17 (8.6)		1.63 (1.31-2.03)	<.0001[a]
>2	50 (3.6)	6 (3.0)		2.36 (1.73-3.21)	<.0001[a]

Table 1 Continued

Characteristic	Patient Group			Multivariable Analysis	
	Earlier CRT (N = 1387)	Delayed CRT (N = 197)	*P*	HR (95% CI)	*P*
Year of diagnosis			.738		
2004-06	282 (20.3)	37 (18.8)		Reference	—
2007-09	331 (23.9)	51 (25.9)		0.95 (0.80-1.12)	.544
2010-12	318 (22.9)	40 (2.3)		0.97 (0.81-1.16)	.730
2013-15	456 (32.9)	69 (35.0)		1.04 (0.87-1.25)	.652
Clinical T stage			.108		
T2	1150 (82.9)	175 (88.8)		Reference	—
T3	135 (9.7)	12 (6.1)		1.24 (1.01-1.52)	.038[a]
T4	102 (7.4)	10 (5.1)		1.60 (1.28-1.98)	<.0001[a]
Chemotherapy			.004[a]		
Single agent	830 (59.9)	142 (72.1)		Reference	—
Multiagent	458 (33.0)	46 (23.4)		0.96 (0.84-1.09)	.517
No. of agents unknown	99 (7.1)	9 (4.6)		0.97 (0.76-1.22)	.781

Data are presented as n (%) unless otherwise indicated.
Abbreviations: CC = cancer center; CI = confidence interval; CRT = chemoradiotherapy; HR = hazard ratio; IQR = interquartile range; SD = standard deviation.
[a]Education indicates measure of number of adults in patient's zip code who did not graduate from high school.
[b]Urban/rural defined per United States Department of Agriculture Economic Research Service: metro indicates counties in metropolitan areas; urban, counties in urban areas; and rural, counties with less than 2500 population.

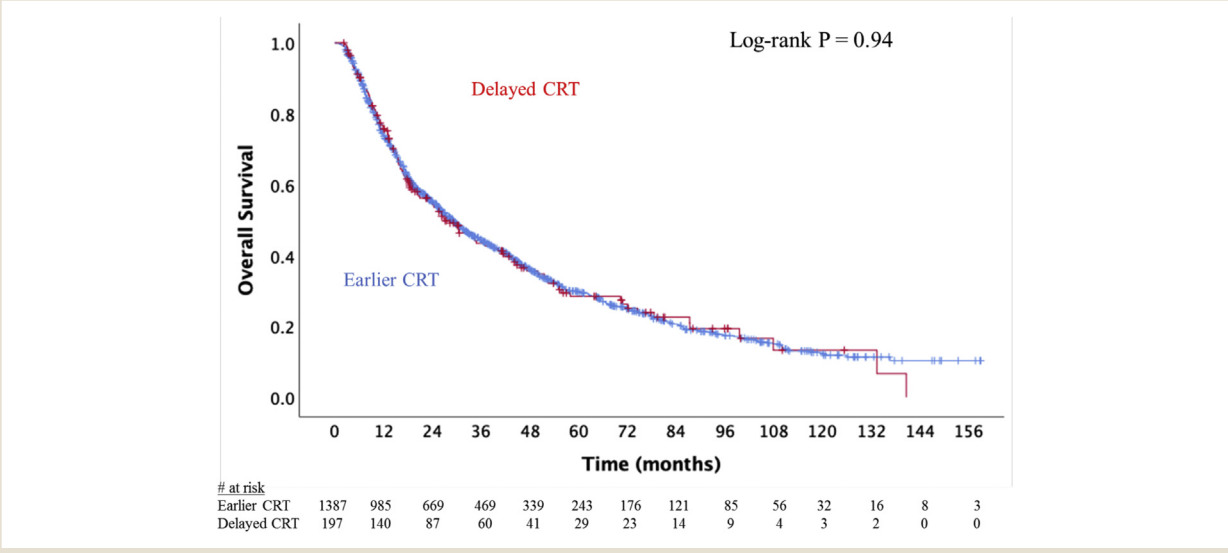
1.05; 95% CI, 0.87-1.27; $P = .60$) (Table 1). Increasing age, higher comorbidity score, and cT3/4 disease were associated with worse OS ($P < .04$ each covariable).

As a sensitivity analysis, earlier CRT and delayed CRT were removed from the model and replaced with days between TURBT and CRT as a continuous variable. In the multivariable model, increasing days from TURBT and CRT was not associated with decreased OS (HR, 1.0; 95% CI, 0.99-1.01; $P = .192$). There was also no difference in OS when calculated from date of diagnosis for earlier CRT versus delayed CRT ($P = .45$). On multivariable analysis using OS calculated from date of diagnosis, results were comparable (delayed CRT: HR, 0.98; 95% CI, 0.80-1.17; $P = .745$).

Discussion

During the COVID-19 pandemic, providers and patients must engage in shared decision making to ensure that the benefit of early

Figure 1 Unadjusted OS for Earlier Versus Delayed CRT for Muscle-Invasive Bladder Cancer. OS was Measured From Start of CRT



Abbreviations: CRT = chemoradiotherapy; OS = overall survival.

intervention for MIBC to prevent tumor progression exceeds the risk of contracting COVID-19 in the clinical setting, especially for patients requiring daily radiotherapy. In our analysis, we were unable to find any differences in OS between earlier CRT for MIBC and delayed CRT $\geq$ 90 days (median, 111 days) despite multiple methods of analyzing the data, suggesting that a moderate delay from TURBT (~ 90 days) may be feasible during the COVID-19 pandemic or during other times when a short delay in treatment is being considered by the patient or provider.

To our knowledge, this is the first study to evaluate the effect of treatment delay on survival for MIBC patients treated with definitive CRT. Our findings are consistent with a number of published series looking at the effect of treatment delay for NAC plus radical cystectomy (RC) patients, although there is not consensus in the cystectomy literature on the effect of treatment delay on survival. Several larger surgical series reported either no association between delay and survival for patients treated with NAC and RC,[6] or no impact when the delay was < 5 months.[7] A Surveillance, Epidemiology, and End Results (SEER) analysis, in contrast, reported that cT2N0 patients who underwent RC more than 11 weeks after NAC had worse OS than patients who underwent earlier RC.[10] For patients treated with RC alone, treatment delays may be associated with worse outcomes, but results in the literature are mixed.[10-14] It may be hypothesized that delays in cystectomy patients who do not receive NAC may lead to tumor progression and higher rates of positive margins or lymph node metastases, which in turn decrease survival, whereas RT with radiosensitizing chemotherapy can effectively treat a larger target volume with less risk for a marginal miss than cystectomy.

This observational study has several limitations, many of which are inherent to the retrospective, nonrandomized nature of the analysis. First, it should be noted that the only method to definitively determine the effect of delays in CRT on OS is a randomized trial powered to detect such a difference. Although we found no difference in OS for patients who had delayed CRT, these data were not prospectively collected, or randomized and powered to detect such a difference. Another notable limitation of the National Cancer Data Base (NCDB) is that there is no reporting on oncologic outcomes such as recurrence-free survival, progression-free survival, or salvage cystectomy rates.[15] It is therefore unclear if patients who were delayed had worse cancer-specific mortality even if their OS did not appear to be affected. Given the retrospective design using a population-based database, analyses are subject to selection biases and imbalances in measured and unmeasured variables. However, multivariable modeling was utilized to address potential confounding. Relatively few patients (12.2%) were delayed > 150 days, so the impact of such a long delay is not well understood. Another limitation is the lack of key variables that are not included in the NCDB, including detailed information regarding extent and outcomes of the TURBT as well as radiation treatment volumes (eg, elective nodal irradiation vs. bladder alone). Comprehensive information on chemotherapeutic agents (eg, cisplatin based vs. non−cisplatin based) and their dosing are also not available in the NCDB. Surveillance schedules are also lacking in the NCDB. Finally, the median OS for patients in our cohort is lower than would be expected for trimodal bladder preservation in cystectomy candidates who have lower competing mortality risk due to other causes. It is unclear whether the results of this study would apply to trimodal bladder preservation patients. Caution should also be taken when applying these findings to more locally advanced disease (cT3/4), given the small number of such patients included in the delayed CRT group (n = 22).

Conclusion

Although a long treatment delay may result in disease upstaging, symptomatic progression, and worse survival, we were unable to show a worse OS for MIBC patients treated with delayed CRT between 90 and 180 days from TURBT (median, 111 days). During pandemics such as COVID-19, both hypofractionated CRT (eg, 55 Gy/20 fractions), when feasible, and short, strategic delays in starting CRT can be considered on a case-by-case basis to reduce the patient's risk of contracting the infection. The clinician's judgment is critical in making these decisions.

Clinical Practice Points

- The global coronavirus disease 2019 (COVID-19) pandemic has led to hospitals caring for affected patients, thus likely exposing unaffected health care workers and other patients. We sought to determine whether there is an association between the timing of chemoradiotherapy (CRT) initiation and overall survival. We hypothesized that delays in initiating definitive CRT after transurethral resection of bladder tumor may not be associated with decreased overall survival.
- In our analysis, 12.5% of patients with muscle-invasive bladder cancer had a delay of over 90 days (median, 111 days) from transurethral resection of bladder tumor to starting definitive-intent CRT.
- Treatment delays over 90 days were more common for patients living in rural communities and those living farther away from the treatment facility.
- We observed no difference in overall survival between patients treated with earlier CRT compared to those with delayed CRT.
- During pandemics such as COVID-19, short, strategic delays in starting CRT can be considered on a case-by-case basis to reduce the patient's risk of contracting the infection. The clinician's judgment is critical in making these decisions.

Disclosure

The authors have stated that they have no conflict of interest.

Supplemental Data

Supplemental figure accompanying this article can be found in the online version at https://doi.org/10.1016/j.clgc.2020.06.005.

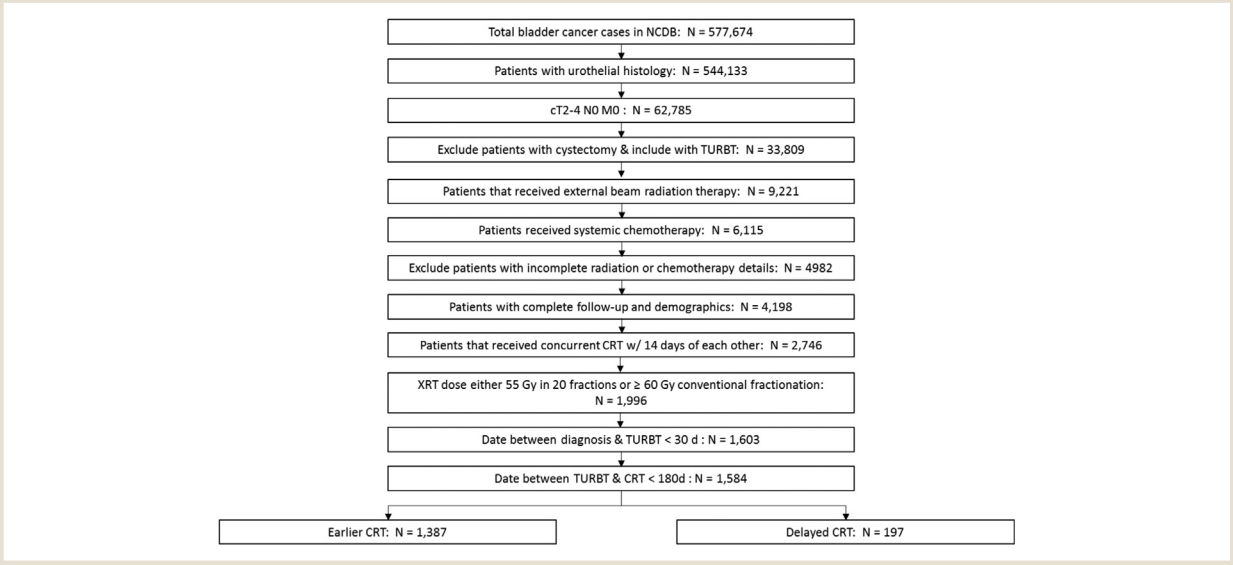
References

1. National Comprehensive Cancer Network. COVID-19 resources, Available at: https://www.nccn.org/covid-19/. Accessed: April 15, 2020.
2. Zaorsky NG, Yu JB, McBride SM, et al. Prostate cancer radiotherapy recommendations in response to COVID-19. *Adv Radiat Oncol* 2020.
3. Braunstein LZ, Gillespie EF, Hong L, et al. Breast radiotherapy under COVID-19 pandemic resource constraints—approaches to defer or shorten treatment from a comprehensive cancer center in the United States. *Adv Radiat Oncol* 2020.

4. Wang R, Pan M, Zhang X, et al. Epidemiological and clinical features of 125 hospitalized patients with COVID-19 in Fuyang, Anhui, China. *Int J Infect Dis* 2020.
5. Kuderer NM, Choueiri TK, Shah DP, et al, Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. *Lancet* 2020.
6. Park JC, Gandhi NM, Carducci MA, et al. A retrospective analysis of the effect on survival of time from diagnosis to neoadjuvant chemotherapy to cystectomy for muscle invasive bladder cancer. *J Urol* 2016; 195(4 part 1):880-5.
7. Alva AS, Tallman CT, He C, et al. Efficient delivery of radical cystectomy after neoadjuvant chemotherapy for muscle-invasive bladder cancer: a multidisciplinary approach. *Cancer* 2012; 118:44-53.
8. Varughese M, Treece S, Drinkwater KJ. Radiotherapy management of muscle invasive bladder cancer: evaluation of a national cohort. *Clin Oncol (R Coll Radiol)* 2019; 31:637-45.
9. Southwest Oncology Group (SWOG). Phase III randomized trial of concurrent chemoradiotherapy with or without atezolizumab in localized muscle invasive bladder cancer, Available at: https://www.swog.org/clinical-trials/s1806. Accessed: April 16, 2020.
10. Chu AT, Holt SK, Wright JL, et al. Delays in radical cystectomy for muscle-invasive bladder cancer. *Cancer* 2019; 125:2011-7.
11. Sanchez-Ortiz RF, Huang WC, Mick R, Van Arsdalen KN, Wein AJ, Malkowicz SB. An interval longer than 12 weeks between the diagnosis of muscle invasion and cystectomy is associated with worse outcome in bladder carcinoma. *J Urol* 2003; 169:110-5.
12. May M, Nitzke T, Helke C, Vogler H, Hoschke B. Significance of the time period between diagnosis of muscle invasion and radical cystectomy with regard to the prognosis of transitional cell carcinoma of the urothelium in the bladder. *Scand J Urol Nephrol* 2004; 38:231-5.
13. Gore JL, Lai J, Setodji CM, Litwin MS, Saigal CS. Mortality increases when radical cystectomy is delayed more than 12 weeks: results from a Surveillance, Epidemiology, and End Results–Medicare analysis. *Cancer* 2009; 115:988-96.
14. Nielsen ME, Palapattu GS, Karakiewicz PI, et al. A delay in radical cystectomy of $>$ 3 months is not associated with a worse clinical outcome. *BJU Int* 2007; 100: 1015-20.
15. Fischer-Valuck BW, Michalski JM, Contreras JA, et al. A propensity analysis comparing definitive chemo-radiotherapy for muscle-invasive squamous cell carcinoma of the bladder vs. urothelial carcinoma of the bladder using the National Cancer Database. *Clin Transl Radiat Oncol* 2019; 15:38-41.

Supplemental Data

Supplemental Figure 1 CONSORT Diagram



Abbreviation: CONSORT = Consolidated Standards of Reporting Trials.