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Clinical Bladder Cancer

Outcomes by time to definitive chemoradiation treatment for patients with muscle-invasive bladder cancer

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Abstract

Background: The coronavirus disease 2019 (COVID-19) pandemic has raised concerns about delaying treatment for localized cancer and its impact on long-term outcomes.

Objective: We aimed to investigate the impact of time to chemoradiation (CRT) on recurrence and survival outcomes for patients with muscle-invasive bladder cancer (MIBC).

Methods: In the national Veterans Affairs' database, we identified patients with urothelial histology, MIBC (T2-4a/N0-3/M0) diagnosed between 2000 to 2018 and treated with definitive CRT. Time to treatment was defined as the number of days between date of diagnosis and start date of CRT. The cohort was stratified into < 90 (early) or ≥ 90 days (delayed) groups. Endpoints of locoregional failure (LRF), distant failure (DF), overall survival (OS), and bladder cancer-specific survival (BCS) were evaluated in multivariable Cox and Fine-Gray models.

Results: 305 patients with MIBC underwent CRT − 190 (62.3%) received early CRT, 115 (37.7%) received delayed CRT. Multivariable analysis (including success of transurethral resection of bladder tumor and type of chemotherapy) revealed no difference in recurrence between groups − LRF HR 1.12 (95%CI 0.76-1.67, $P = 0.56$) and DF HR 1.03 (95%CI 0.70-1.53, $P = 0.88$). Similarly, there were no differences in survival outcomes. The lack of association was maintained at both earlier and later time cutoffs (60−120 days).

Conclusions: Our findings suggest that a short-term delay in definitive therapy may not affect long-term outcomes for patients with MIBC undergoing CRT. This study does not endorse delays in therapy, but rather provides information to aid patients and clinicians navigate the unique challenges of MIBC care in both pandemic and non-pandemic times.

Keywords: Muscle-invasive bladder cancer; Chemoradiation; Time to treatment; Veterans affairs (U.S.); COVID-19 pandemic

Abbreviation: MBIC, Muscle-invasive bladder cancer; CRT, Chemoradiation; LRF, Locoregional failure; DF, Distant failure; OS, Overall survival; BCS, Bladder cancer-specific survival

1. Introduction

Timely definitive therapy is a cornerstone in management of localized cancer as prompt treatment prevents local growth and distant spread of the tumor [1−2]. During the coronavirus disease 2019 (COVID-19) pandemic, attention has been drawn to the timing of oncologic treatment given the newfound risk of virus exposure and increased mortality rate in patients with cancer, particularly the elderly [3−6]. For patients with muscle-invasive bladder cancer (MIBC), the benefits of prompt therapy to maximize survival must be weighed against the risks of potential COVID-19 disease and its associated complications.

Contrary to the volume of literature on delay to operative management (radical cystectomy) for MIBC, there is

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limited data on delay to non-operative management (concurrent chemoradiation) [7−8]. Here, we investigate the impact of time to definitive chemoradiation (CRT) on recurrence and survival outcomes for patients with MIBC within the national Veterans Affairs' (VA) database.

2. Materials and methods

VA Informatics and Computing Infrastructure (VINCI) represents a comprehensive informatics platform that enables access to the database comprised of patient-level electronic health records and administrative data throughout the national VA health care system. Our protocol was approved by the San Diego VA Institutional Review Board.

From VINCI, we identified 332 veterans with urothelial histology, localized de novo MIBC (T2-4a/N0-3/M0) diagnosed between 2000 to 2018 who received definitive chemoradiation. Definitive CRT was defined as a radiation regimen lasting at least 4 weeks (or documentation of a radiation dose of at least 55 Gy) in conjunction with at least 1 cycle of chemotherapy administered within 14 days of the radiation start date. Patients were excluded if there were no records of follow up or if cause of death was unknown. The final cohort consisted of 305 veterans.

Covariables of interest included sociodemographic variables, Charlson comorbidity index score, creatinine clearance (estimated by the CKD-EPI equation) [9] prior to CRT, T/N categories, visual success of transurethral resection of bladder tumor (TURBT) according to operative reports prior to CRT, and type of concurrent chemotherapy agent. All covariables and outcomes were manually chart reviewed if not present within database elements. Preferred vs nonpreferred concurrent chemotherapy agents were categorized as per National Comprehensive Cancer Network's (NCCN) 'preferred' regimens (cisplatin alone, cisplatin and fluorouracil, cisplatin and paclitaxel, mitomycin and fluorouracil) [10]. All patients were followed until death or last follow-up with a VA provider before September 1, 2020.

Time to CRT was defined as the number of days between date of diagnosis (via histologic evidence) and start date of radiation. The cohort was stratified into patients who initiated therapy < 90 (early) or ≥ 90 days (delayed). For patients who received delayed CRT, the reasons for delay were identified from chart review. Given that the 90 day cutoff might either be too short or too long to impact outcomes, we repeated the following analyses with separate cutoffs of 60, 75, 105, and 120 days.

Outcomes included locoregional failure (LRF), distant failure (DF), overall survival (OS), and bladder cancer-specific survival (BCS), defined by the date of diagnosis to the specific endpoint of interest. LRF was defined as any recurrence within the bladder (including both non-muscle-invasive and muscle-invasive) or pelvis, whether it be soft tissue or lymph nodes. DF was defined as any recurrence that did not meet LRF criteria [11]. Baseline characteristics were compared between cohorts using Chi Square test and Wilcoxon's rank sum test. LRF, DF, and BCS were defined using a competing risk analysis framework and assessed with cumulative incidence analysis and Fine-Gray regression analysis. OS was assessed with Kaplan-Meier analysis and Cox proportional hazards analysis. All multivariable models were chosen *a priori* with the aforementioned covariables of interest. For all recurrence and survival analysis, hazard ratios (HR) and 95% confidence intervals (CI) were reported. All statistical analyses were performed using SAS

Table 1
Baseline patient, tumor, and treatment characteristics of each time to CRT cohort, stratified by time cutoff of 90 days.

Variable	Early CRT (< 90 days) $n = 190$	Late CRT (≥ 90 days) $n = 115$	*P* value
Age			0.59
Median (range)	76 (53-93)	76 (53-92)	
Gender			0.27
Male	188 (98.9%)	115 (100%)	
Female	2 (1.1%)	0 (0%)	
Race			0.63
White	176 (92.6%)	103 (89.6%)	
Black	11 (5.8%)	9 (7.8%)	
Other	3 (1.6%)	3 (2.6%)	
Charlson Score			0.82
0	49 (25.8%)	31 (27.0%)	
1+	141 (74.2%)	84 (73.0%)	
Smoker at Diagnosis			0.45
Yes	64 (33.7%)	34 (29.6%)	
No	126 (66.3%)	81 (70.4%)	
Married			0.89
Yes	104 (54.7%)	62 (53.9%)	
No	86 (45.3%)	53 (46.1%)	
Median Income in Zip Code			0.39
< 50K	112 (59.0%)	62 (53.9%)	
≥ 50K	78 (41.0%)	53 (46.1%)	
% Population with Bachelor's in Zip Code			0.45
≤ 15%	99 (52.1%)	65 (56.5%)	
> 15%	91 (47.9%)	50 (43.5%)	
Creatinine Clearance			0.20
< 50	75 (39.5%)	37 (32.2%)	
≥ 50	115 (60.5%)	78 (67.8%)	
T Category			0.10
2	157 (82.6%)	103 (89.6%)	
3-4	33 (17.4%)	12 (10.4%)	
N Category			0.68
0	182 (95.8%)	109 (94.8%)	
1-3	8 (4.2%)	6 (5.2%)	
Success of TURBT			0.35
Yes	167 (87.9%)	105 (91.3%)	
No	23 (12.1%)	10 (8.7%)	
Chemotherapy Regimen			**0.03***
Preferred	91 (47.9%)	70 (60.9%)	
Non-preferred	99 (52.1%)	45 (39.1%)	

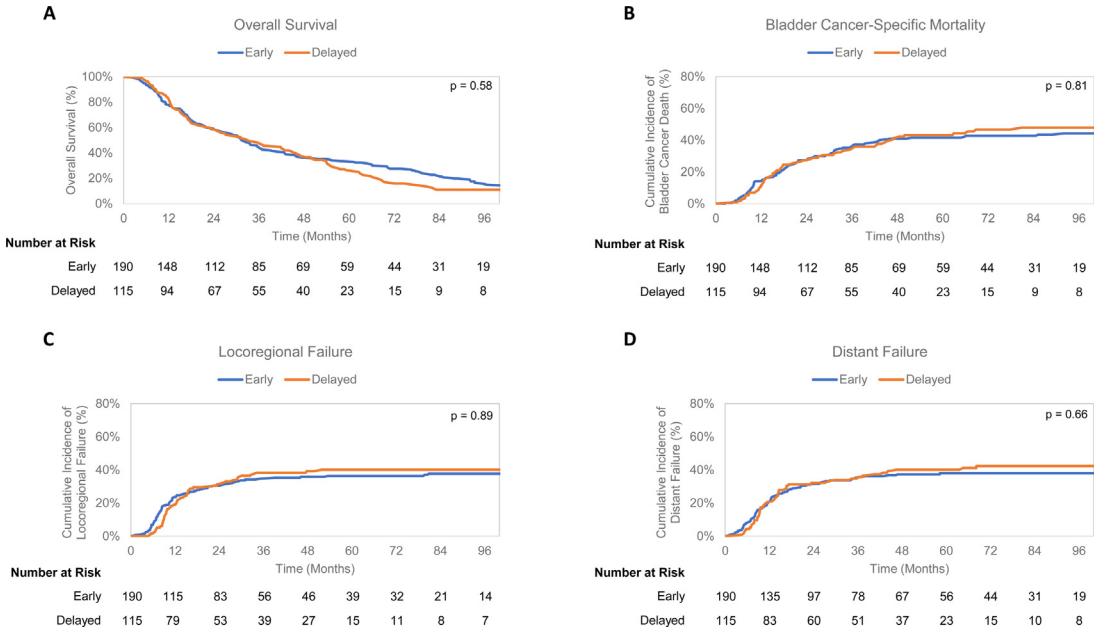

Fig 1. **(A).** Kaplan-Meier curves for overall survival stratified by early (< 90 days) and delayed (≥ 90 days) time to CRT cohorts**, (B).** Cumulative incidence curves for bladder cancer-specific mortality stratified by early (< 90 days) and delayed (≥ 90 days) time to CRT cohorts**, (C).** Cumulative incidence curves for locoregional failure stratified by early (< 90 days) and delayed (≥ 90 days) time to CRT cohorts, **(D).** Cumulative incidence curves for distant failure stratified by early (< 90 days) and delayed (≥ 90 days) time to CRT cohorts.

version 9.4 (SAS Institute, Cary, NC), with two-sided p-values less than 0.05 considered statistically significant.

3. Results

Of the 305 patients in the final cohort, 190 (62.3%) patients received early CRT (median 60, range 8−89 days) and 115 (37.7%) patients received delayed CRT (median 116, range 90−177 days). Most common reason for receiving delayed CRT was additional workup/clearance and associated scheduling delays (47 patients, 41%) − repeat (2−3) TURBTs were performed in 42 patients in the delayed cohort and in 22 patients in the early cohort. There was no significant difference between success of TURBT prior to CRT between the early and delayed cohorts as approximately 90% of patients received a visually successful TURBT (Table 1). Other common reasons were deliberation by patient (39 patients, 34%) and hospitalizations for bladder cancer complications or comorbidities (25 patients, 22%). The only significant difference in baseline characteristics between the cohorts was that a larger proportion of the delayed CRT cohort received a preferred chemotherapy regimen (Table 1).

The median follow up time was 75 months. In the final cohort, there were 118 patients with a LRF, 121 patients with a DF, and 260 deaths (138 attributed to bladder cancer). There was no difference in OS ($P = 0.58$) between early CRT (median OS 31.7 months, 95% CI 25.9-36.8 months) and delayed CRT patients (median OS 33.7 months, 95% CI 23.3-44.7 months) (Fig. 1A). Additionally, time to CRT was not associated with bladder cancer-specific mortality (BCM) ($P = 0.81$), LRF ($P = 0.89$), and DF ($P = 0.66$) (Fig. 1B-1D).

In multivariable analysis, time to CRT was not associated with LRF (HR 1.12, 95% CI 0.76-1.16, $P = 0.56$) or DF (HR 1.03, 95% CI 0.70-1.53, $P = 0.88$). Similarly, time to CRT was not associated with OS (HR 1.12, 95% CI 0.86-1.49, $P = 0.40$) or BCS (HR 1.03, 95% CI 0.72-1.47, $P = 0.87$) (Table 2).

Similar multivariable regression analyses was repeated with 60 days (30.8% early, 69.2% delayed patients), 75 days (48.5% early, 51.5% delayed), 105 days (74.4% early, 25.6% delayed), and 120 days (84.6% early, 15.4% delayed) as the time cutoff. For each cutoff, time to CRT was similarly not associated with any of the endpoints. In sensitivity analysis, time to CRT as a continuous (rather than categorical) variable remained unassociated each endpoint.

4. Discussion

In this study of VA patients with MIBC who underwent definitive CRT, delay to CRT of ≥ 90 days was not associated with inferior recurrence or survival outcomes. Similar findings were observed when the time cutoff was set at 60, 75, 105, and 120 days, suggesting a short delay in definitive therapy may not affect long-term outcomes for MIBC treated with CRT.

Previous literature has reported mixed results on the impact of delay to radical cystectomy with or without neoadjuvant chemotherapy in the treatment of MIBC [12−14]. Fischer-Valuck et al. were the first to investigate the impact

Table 2
Multivariable a priori regressions on overall survival (OS) and bladder cancer-specific survival (BCS).

	OS		BCS	
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Time to CRT				
< 90 days	1.00	0.40	1.00	0.87
≥ 90 days	1.12 (0.86-1.49)		1.03 (0.72-1.47)	
Age	1.00 (0.98-1.01)	0.67	0.97 (0.95-0.99)	0.02*
Gender				
Male	1.00	0.96	1.00	0.51
Female	1.06 (0.13-8.65)		1.86 (0.30-11.63)	
Race				
White	1.00	0.06	1.00	0.46
Black	0.56 (0.30-1.03)	0.14	0.78 (0.39-1.53)	0.04*
Other	2.33 (0.77-7.07)		3.50 (1.09−11.27)	
Charlson Score				
0	1.00	0.50	1.00	0.26
1+	0.91 (0.68-1.21)		0.80 (0.54-1.18)	
Smoker at Diagnosis				
No	1.00	0.96	1.00	0.25
Yes	0.99 (0.73-1.34)		0.77 (0.49-1.20)	
Married				
No	1.00	0.93	1.00	0.67
Yes	0.99 (0.77-1.28)		1.08 (0.75-1.56)	
Median Income in Zip Code				
<50K	1.00	0.12	1.00	0.30
≥50K	1.26 (0.94-1.68)		1.26 (0.81-1.95)	
% Population with Bachelor's in Zip Code				
≤15%	1.00	0.18	1.00	0.24
>15%	0.83 (0.63-1.10)		0.78 (0.51-1.18)	
Creatinine Clearance				
≥50	1.00	0.02*	1.00	0.37
<50	1.42 (1.06-1.90)		1.23 (0.79-1.91)	
T Category				
2	1.00	0.01*	1.00	0.12
3-4	1.68 (1.15-2.44)		1.48 (0.90-2.43)	
N Category				
0	1.00	0.01*	1.00	0.03*
1-3	2.48 (1.30-4.72)		2.34 (1.07-5.15)	
Success of TURBT				
Yes	1.00		1.00	
No	1.37 (0.96-1.95)	0.08	1.16 (0.67-2.01)	0.61
Chemotherapy Regimen				
Preferred	1.00	0.01*	1.00	0.53
Non-preferred	1.43 (1.12-1.83)		0.89 (0.62-1.28)	

of delay to CRT in National Cancer Data Base (NCDB) patients with MIBC [8]. They reported no association between treatment delay of 90 days and OS, but did not investigate the impact on other important endpoints (BCS, recurrence) and were limited by the lack of granularity in NCDB (inability to account for success of TURBT, chemotherapy agents, etc.). Our current study using the VA database allows for these details, and further provides support to the hypothesis that a short delay in definitive treatment is unlikely to have a significant effect on long-term outcomes.

In this real world population of patients with MIBC treated with CRT, the rates of locoregional failure and distant failure appear similar to respective rates within the landmark studies' populations (BC2001, MGH experience, etc.) [15−16]. Due to the study's retrospective design in conjunction with variable documentation across the nationwide centers, we are not able to distinctly report and analyze the types of local recurrences (e.g. muscle-invasive vs non-muscle-invasive). However, given that the rate of locoregional failure in this cohort appears similar to respective rates within prospective cohorts [15−16], we postulate a similar pattern of more non-muscle-invasive recurrences than muscle-invasive recurrences within this cohort. In conjunction with additional retrospective studies demonstrating similar outcomes between MIBC treated with RC and MIBC treated with CRT in appropriately selected individuals [17−18], CRT appears to be an efficacious option for many patients with MIBC. However, during the COVID-19

pandemic, attention has been brought to the impact of delay in oncologic treatment as hospital systems react to the fluctuations in COVID-19 burden to minimize risk of spread and mitigate risk of COVID-19 disease complications in at risk-individuals [1−2]. In pre-pandemic times, 33% to 50% of patients with MIBC do not undergo any definitive treatment [19−20]. With the results of this study, we postulate that treatment of MIBC with CRT should be considered as a feasible, efficacious option even if there is a treatment delay due to reasons such as treatment for concomitant conditions or attempt to obtain access to care. In our cohort, many patients who had a delay to treatment received repeat TURBTs in attempt to achieve visibly complete TURBT, an important prognosticator in the CRT paradigm for MIBC [16,21]. However, given that 12% of patients in the early cohort also received repeat TURBTs, we hypothesize that it is possible and would be prudent for institutions to implement efficient pathways for repeat TURBTs when indicated. In general, many cases of treatment delay in our study were due to workup/clearance with associated scheduling delays or patient deliberation. As such, detailed studies examining hospital-, physician-, and patient-centered factors contributing to these treatment delays are warranted as potential for elucidation of quality improvement avenues.

Limitations of this study include the inherent drawbacks of a retrospective design. We aimed to minimize these by using limited exclusion criteria and thorough multivariable modeling. However, given that a prospective trial to assess time to definitive treatment is unlikely to occur for ethical reasons, the questions of interest will likely rely on retrospective studies. Although the national VA database enables the opportunity to gather relevant variables that are lacking in peer oncologic databases as previously discussed, there remains potentially confounding information that is not accounted for, largely due to variable documentation across the nationwide centers. Namely, the time from initial patient reported symptoms to subsequent workup or treatment is not available in our analysis. This is an interesting variable to investigate in future studies as it holds potential to identify avenues to diagnose bladder malignancy at an earlier stage or to identify bladder cancer disparities, especially in populations that have strained relationships with the healthcare system. Additionally, caution should be applied when considering the implications of our findings for more advanced disease (T3/4 or N1+) given its limited representation in our cohort. Lastly, a greater proportion of patients in the delayed cohort received a preferred chemotherapy regimen which may suggest that the higher proportion of optimal therapy could offset any detriment from delayed time to treatment. However, multivariable analysis demonstrated chemotherapy regimen was associated with OS but not with BCS, suggesting that this variable was associated with a patient population at higher risk for non-bladder cancer-specific mortality rather than inferior treatment for their bladder cancer.

5. Conclusions

In summary, our study suggests that a short-term delay in definitive therapy was not associated with inferior long-term outcomes for patients with MIBC undergoing CRT. Our findings do not endorse delays in therapy, but rather make the clinical observation that a short delay to CRT for MIBC may not significantly affect clinical outcomes. Along with similar studies, our findings should be taken into account as patients and clinicians navigate the unique challenges of oncologic treatment amidst a pandemic, or even navigate the challenges of obtaining definitive treatment during non-pandemic settings.

Conflict of interest

Dr. Rana McKay reports grants from Bayer, Pfizer, Tempus, personal fees from AstraZeneca, Bayer, Bristol Myers Squibb, Calithera, Exelixis, Janssen, Merck, Novartis, Pfizer, Sanofi, Tempus, Dendreon, Vividion, Caris, outside the submitted work. Dr. Tyler Stewart has served as a paid consultant for Seattle Genetics, outside the submitted work. All other authors have no conflicts of interest to report.

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References

[1] Madan A, Siglin J, Khan A. Comprehensive review of implications of COVID-19 on clinical outcomes of cancer patients and management of solid tumors during the pandemic. Cancer Med. 2020. https://doi.org/10.1002/cam4.3534:cam4.3534.

[2] Kutikov A, Weinberg DS, Edelman MJ, Horwitz EM, Uzzo RG, Fisher RI. A war on two fronts: Cancer care in the time of COVID-19. Ann Intern Med 2020;172(11):756–8. https://doi.org/10.7326/M20-1133.

[3] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72314 cases from the Chinese center for disease control and prevention. JAMA - J Am Med Assoc 2020;323(13):1239–42. https://doi.org/10.1001/jama.2020.2648.

[4] Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol 2020;21(3):335–7. https://doi.org/10.1016/S1470-2045(20)30096-6.

[5] Segelov E, Underhill C, Prenen H, et al. Practical considerations for treating patients with cancer in the COVID-19 pandemic. JCO Oncol Pract 2020;16(8):467–82. https://doi.org/10.1200/op.20.00229.

[6] Broom A, Kenny K, Page A, et al. The paradoxical effects of COVID-19 on cancer care: Current context and potential lasting impacts. Clin Cancer Res 2020;26(22):5809–13. https://doi.org/10.1158/1078-0432.ccr-20-2989.

[7] Risks of Delaying Bladder Cancer Diagnosis. Surveillance and surgery during COVID-19. https://www.urotoday.com/library-resources/bladder-cancer/120719-risks-of-delaying-bladder-cancer-treatment-during-covid-19.html. Accessed December 25, 2020.

[8] Fischer-Valuck BW, Michalski JM, Harton JG, et al. Management of muscle-invasive bladder cancer during a pandemic: Impact of treatment delay on survival outcomes for patients treated with definitive

concurrent chemoradiotherapy. Clin Genitourin Cancer 2020. https://doi.org/10.1016/j.clgc.2020.06.005.

[9] Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150(9):604–12. https://doi.org/10.7326/0003-4819-150-9-200905050-00006.

[10] Flaig TW, Spiess PE, Chair V, et al. NCCN Guidelines Version 3.2020 Bladder Cancer NCCN Evidence Blocks TM.; 2020.

[11] Reddy AV, Pariser JJ, Pearce SM, et al. Patterns of failure after radical cystectomy for pT3-4 bladder cancer: Implications for adjuvant radiation therapy this work will be presented at the 12th annual American Society of Clinical Oncology Genitourinary Cancers Symposium, January 7-9, 2016. Int J Radiat Oncol Biol Physics 2016;94:1031–9. https://doi.org/10.1016/j.ijrobp.2015.10.051:Elsevier Inc.;.

[12] Russell B, Liedberg F, Khan MS, et al. A systematic review and meta-analysis of delay in radical cystectomy and the effect on survival in bladder cancer patients. Eur Urol Oncol 2020;3(2):239–49. https://doi.org/10.1016/j.euo.2019.09.008.

[13] 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):880–5. https://doi.org/10.1016/j.juro.2015.11.024.

[14] Chu AT, Holt SK, Wright JL, et al. Delays in radical cystectomy for muscle-invasive bladder cancer. Cancer 2019;125(12):2011–7. https://doi.org/10.1002/cncr.32048.

[15] James ND, Hussain SA, Hall E, et al. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. N Engl J Med 2012;366(16):1477–88. https://doi.org/10.1056/nejmoa1106106.

[16] Giacalone NJ, Shipley WU, Clayman RH, et al. Long-term outcomes after bladder-preserving tri-modality therapy for patients with muscle-invasive bladder cancer: An updated analysis of the massachusetts general hospital experience. Eur Urol 2017;71(6):952–60. https://doi.org/10.1016/J.EURURO.2016.12.020.

[17] Kulkarni GS, Hermanns T, Wei Y, et al. Propensity score analysis of radical cystectomy vs bladder-sparing trimodal therapy in the setting of a multidisciplinary bladder cancer clinic. J Clin Oncol 2017;35(20):2299–305. https://doi.org/10.1200/JCO.2016.69.2327.

[18] Kumar A, Cherry DR, Courtney PT, et al. Outcomes for muscle-invasive bladder cancer with radical cystectomy or trimodal therapy in US veterans. Eur Urol Open Sci 2021;30:1–10. https://doi.org/10.1016/J.EUROS.2021.05.009.

[19] Fletcher SA, Harmouch SS, Krimphove MJ, et al. Characterizing trends in treatment modalities for localized muscle-invasive bladder cancer in the pre-immunotherapy era. World J Urol 2018;36(11):1767–74. https://doi.org/10.1007/s00345-018-2371-y.

[20] Washington SL, Neuhaus J, Meng MV, Porten SP. Social determinants of appropriate treatment for muscle-invasive bladder cancer. Cancer Epidemiol Biomarkers Prev 2019;28(8):1339–44. https://doi.org/10.1158/1055-9965.EPI-18-1280.

[21] Mak RH, Hunt D, Shipley WU, et al. Long-term outcomes in patients with muscle-invasive bladder cancer after selective bladder-preserving combined-modality therapy: A pooled analysis of radiation therapy oncology group protocols 8802, 8903, 9506, 9706, 9906, and 0233. J Clin Oncol 2014;32(34):3801–9. https://doi.org/10.1200/JCO.2014.57.5548.