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Trimodality therapy with or without neoadjuvant chemotherapy for muscle invasive bladder cancer

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Abstract

Introduction—Bladder-sparing chemoradiation therapy is a definitive first-line treatment option for muscle-invasive bladder cancer. Randomized trials have demonstrated that the addition of neoadjuvant chemotherapy to radical cystectomy or radiation monotherapy results in a survival benefit. Whether neoadjuvant chemotherapy improves outcomes when used with definitive chemoradiation is unknown.

Patients and Methods—We identified 2,566 patients in the National Cancer Data Base with cT2–4N0M0 urothelial cell carcinoma of the bladder treated with definitive intent concurrent chemoradiation from 2004–2015. The exposure of interest was receipt of neoadjuvant chemotherapy (versus those without neoadjuvant chemotherapy). The primary outcome was overall survival defined from the time of diagnosis. Kaplan Meier and multivariable Cox proportional hazards were used to compare survival between groups. Sensitivity analyses tested 1) an interaction term for clinical T stage and 2) defining survival from start of radiation (opposed to time of diagnosis) to address potential leading time bias.

Results—We identified 462 patients treated with neoadjuvant chemotherapy followed by chemoradiation and 2104 patients treated with chemoradiation alone. With a median follow up of 6.2 years, we found no difference in survival between groups (5-year or 10-year overall survival of 30.6% [95%CI: 28.4–32.9%] in the neoadjuvant group versus 31.8% [27.0–36.8%] in the standard chemoradiation therapy group and 13.3% [11.2–15.5%] versus 13.0% [8.4–18.7%], respectively; log-rank p-value 0.19). On multivariable analysis we found no association between receipt of neoadjuvant chemotherpay and overall survival (HR 1.01, 95%CI: 0.88–1.15; p=0.921).

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On sensitivity analyses we found no differential effect by clinical T stage nor by defining survival from start of radiation.

Conclusion—These results do not support the routine addition of neoadjuvant chemotherapy to definitive chemoradiation for bladder cancer, and optimizing the chemotherapy sequencing and regimens for bladder-preserving approaches to muscle invasive bladder cancer should continue to be studied under prospective clinical trials.

Microabstract:

The benefit of adding neoadjuvant chemotherapy to bladder-sparing chemoradiation for muscle invasive bladder cancer remains unclear. This retrospective large database study of 2,566 patients found no survival benefit with the addition of neoadjuvant chemotherapy to definitive chemoradiation. These results do not support the routine addition of neoadjuvant chemotherapy to definitive chemoradiation for bladder cancer, which should be investigated under trial.

Keywords

muscle invasive bladder cancer; radiation; chemotherapy; radical cystectomy; trimodality therapy

Introduction

Bladder cancer is the sixth most common cancer in the United States and accounts for nearly 81,000 new cases and 18,000 deaths per year.[1] Nearly 25% of new cases are muscle-invasive bladder cancer (MIBC) (T2-T4 disease), which has a 5-year survival of <15% without treatment.[2] Both bladder-removing radical cystectomy (RC) and bladder-sparing tri-modality therapy (TMT) are definitive, first-line treatment options for MIBC recommended by professional society guidelines.[3–5] TMT is a multidisciplinary, organ-preserving approach involving transurethral resection of the bladder tumor followed by concurrent chemoradiation. Chemotherapy is an important component of TMT, with the randomized BC2001 trial showing that chemoradiation provides superior locoregional disease free survival compared to radiation alone.[6]

Randomized controlled trials and meta-analyses have shown the addition of neoadjuvant chemotherapy (NAC) to RC improves outcomes with an estimated 5% overall survival benefit.[7–9] Further, the addition of NAC to definitive radiation-alone provides a 6% overall survival benefit.[10] However, the impact of NAC to bladder-sparing TMT (i.e. definitive chemoradiation) is unknown, but there is increasing interest that the addition of NAC could further improve outcomes for these patients.[11,12] The RTOG 88–02 trial was a single-arm phase II study that demonstrated the feasibility of TMT with a NAC component.[13,14] The RTOG 89–03 trial further attempted to answer this question by randomizing patients to TMT with or without NAC, but it closed prematurely due to unexpected high rates of neutropenia.[15] Therefore, the purpose of this study is to evaluate whether the addition of NAC to TMT improves outcomes in a contemporary cohort of patients with MIBC.

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Patients and Methods

Data Source

The National Cancer Data Base (NCDB) is a national hospital-based registry jointly sponsored by the American College of Surgeons and the American Cancer Society. It captures the first course of cancer treatment[16] and collects data from more than 1,500 Commission on Cancer-accredited facilities and captures approximately 70% of incident cancers in the United States, annually. The data accuracy and quality is continually validated via data quality reviews, site surveys, and internal monitoring.[17] Methods regarding data coding have been described elsewhere.[18] This study received institutional review board exemption.

Study population

We identified patients aged ≥18 with a diagnosis of cT2–4N0M0 urothelial cell carcinoma of the bladder treated with definitive intent concurrent chemoradiation from 2004–2015. Patients had to receive a transurethral resection of bladder tumor (TURBT) prior to chemoradiation. Patient were included if they had a total radiation dose ≥40 Gy. We excluded those who were post-cystectomy, node positive (N1+), metastatic (M1), had unknown stage, non-urothelial cell carcinoma (i.e. non-transitional cell carcinoma, or variant histologies[19]), a history of prior malignancy, or received palliative intent therapy. These criteria left 2,566 patients for analysis. Detailed patient selection schema is shown in the Appendix (eTable 1).

Measurements

The exposure of interest was receipt of NAC (versus those without NAC). The NAC group was defined as chemotherapy that was started 31–120 days prior to concurrent chemoradiation; concurrent chemoradiation was defined as chemotherapy and radiation starting within 30 days of each other.[20] The primary outcome of interest was overall survival from date of diagnosis, censoring at last follow up for patients still alive.

Statistical analyses

Descriptive statistics presented the baseline characteristics between groups: TMT versus NAC+TMT. Categorical variables were evaluated via Chi-square tests and continuous variables by ANOVA. Patients were stratified by variables of interest including age, T-stage, diagnosis year, race/ethnicity, hospital setting, Charlson-Deyo comorbidity index, insurance status, US region, residence type, education level, household income, and distance to treatment facility. Kaplan-Meier and multivariable Cox proportional hazards were used to assess the association with overall survival (OS). For the multivariable model, backward selection with an alpha level of removal of 0.2 was used, eliminating the following variables from the model: travel distance, facility, residence, and time to radiation.

Two sensitivity analyses were performed. The first, by running the multivariable Cox proportional hazards model and adding an interaction term with clinical T stage subgroup (cT2 versus cT3–4) to test the subgroup interaction by T-stage, hypothesizing that perhaps there may be a benefit to the addition of NAC in more advanced cancers (i.e. clinical

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T3-T4). The second, to account for potential lead-time bias, we evaluated overall survival defined as start of radiation until death (opposed to from date of diagnosis until death). Analyses used SAS 9.4 (SAS Institute Inc., Cary, NC) and SAS macros.[21] Tests were 2-sided with a 0.05 level of significance.

Results

We identified 462 patients in the NAC+TMT group and 2104 patients in the TMT group. The NAC+TMT cohort was younger with 33.8% aged 80+ years versus 42.4% in the TMT group (p=0.001). There were no other differences identified between baseline characteristics of groups including sociodemographic variables (Table 1). Mean time from diagnosis to TURBT was not found to be different between groups (1.8–1.9 weeks; p=0.704). Mean time from diagnosis to radiation start for NAC+TMT versus TMT was 14.7 versus 9.4 weeks, respectively (p<0.001).

Median follow up time was 6.2 years. There was no difference between those who received TMT versus NAC+TMT in estimated 5-year or 10-year OS (30.6% [95%CI: 28.4–32.9%] versus 31.8% [27.0–36.8%] and 13.3% [11.2–15.5%] versus 13.0% [8.4–18.7%], respectively; log-rank p-value 0.19; Figure 1). Further, on multivariable analysis we found no association between overall survival and receipt of NAC (HR 1.01, 95%CI: 0.88–1.15; p=0.921). Age at diagnosis, year of diagnosis, comorbidity, T2 stage, insurance status, education, were all independent predictors of survival (Table 2).

On the first sensitivity analysis we found no association between overall survival and receipt of NAC using an interaction term for clinical T stage subgroup with a HR 0.96 (95%CI: 0.83–1.10; p=0.50) for cT2 and 1.19 (0.88–1.61; p=0.30) cT3–4 patients (Table 3).

On the second sensitivity analysis, we again found no association between overall survival and receipt of NAC when, to account for potential lead-time bias, we evaluated overall survival defined as start of radiation until death (opposed to from date of diagnosis until death) (Table 4, Figure 2).

Discussion

In this study, we consistently found no survival benefit with the addition of NAC to TMT. Our analysis included 2,566 patients with a median follow up of 6.2 years, and these findings held true when looking at both 5-year and 10-year survival rates, and also on multivariable analysis. Further, on sensitivity analysis, when we included an interaction term for the clinic T stage subgroup, hypothesizing that perhaps there may be a benefit to the addition of NAC in more advanced cancers (i.e. clinical T3-T4), we again found no difference. Finally, to account for the potential of lead time bias, a sensitivity result measuring survival from start of radiation (opposed to from diagnosis) we again found no benefit with the addition of NAC.

The clinical significance of these findings are that they do not support the hypothesis that adding NAC to TMT would improve outcomes.[12] This finding stands in contrast to the

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known benefit, observed via prospective randomized trials, of adding NAC to RC[7–9] or to radiation alone.[10]

These results are important in that they fill an existing gap in the literature regarding the question of whether there is an added benefit with NAC to chemoradiation. While the optimal approach to evaluate this question is in the form of a prospective randomized trial, these have been conducted with mixed success. The RTOG 89–03 randomized trial compared a course of neoadjuvant methotrexate, cisplatin, and vinblastine chemotherapy followed by radiation with concurrent cisplatin to a course of radiation with concurrent cisplatin alone. Although the study closed prematurely due to unexpected high rate of neutropenia, they found no impact on 5-year overall survival with the addition of NAC to chemoradiation.[15] Additionally, the BC2001 randomized trial of 360 patients was designed to evaluate the impact of the addition of concurrent chemotherapy to radiation therapy, and a recent post hoc analysis revealed a small subset of 56 patients who received NAC followed by chemoradiation;[11] this analysis was also underpowered to adequately evaluate a benefit of NAC in the chemoradiation group. Finally, the results of our study are supported by two smaller retrospective or post hoc single-institutional series that have demonstrated no clear benefit with the addition of NAC to chemoradiation.[22,23]

A limitation of the study is the possibility that some of the NAC+TMT patients did not receive chemotherapy concurrently with radiation (i.e. received NAC followed by radiation alone), but this is likely uncommon given the known advantage of concurrent chemo in addition to radiation as shown in the BC2001 trial.[6] Additional limitations include its retrospective nature and the lack of other oncologic endpoints available in the registry database, such as progression-free survival or salvage cystectomy rates, which would be clinically relevant outcomes. The dataset also lacks important data regarding adverse events (e.g. neutropenia) or patient reported outcomes. Finally, our dataset lacks granularity regarding the extent of TURBT or regarding specific types of chemotherapy regimens (e.g. cisplatin versus non-cisplatin-based regimens). For example, it is plausible an inability to discriminate between cisplatin-based versus carboplatin-based chemotherapy could reduce the power of the survival analysis, given the lack of known survival benefit from carboplatin-based chemotherapy. Further, lack of granular lab data limits the ability to control for certain confounders, for example using kidney function a surrogate for receipt of carboplatin. An additional open question is what role, if any, adjuvant chemotherapy may have in MIBC; these results do not speak to that.

Conclusions

Our study found no survival benefit with the addition NAC to a definitive course of TMT for MIBC. These results do not support the routine addition of neoadjuvant chemotherapy to definitive chemoradiation for bladder cancer, and optimizing the chemotherapy sequencing and regimens for bladder-preserving approaches to muscle invasive bladder cancer should continue to be studied under prospective clinical trials.

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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

TMT	trimodality therapy
RC	radical cystectomy
NAC	neoadjuvant chemotherapy

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Clinical Practice Points:

Definitive chemoradiation therapy is a first-line treatment option for muscle invasive bladder cancer. Neoadjuvant chemotherapy improves survival when muscle invasive bladder cancer is treated with surgery or radiation. However, how neoadjuvant chemotherapy improves outcomes for those treated with definitive chemoradiation therapy is unknown. This retrospective large database study of 2,566 patients found no survival benefit with the addition of neoadjuvant chemotherapy to definitive chemoradiation. These results do not support the routine addition of neoadjuvant chemotherapy to definitive chemoradiation for bladder cancer, and optimizing the chemotherapy sequencing and regimens for bladder-preserving approaches for muscle invasive bladder cancer should continue to be studied under prospective clinical trials.

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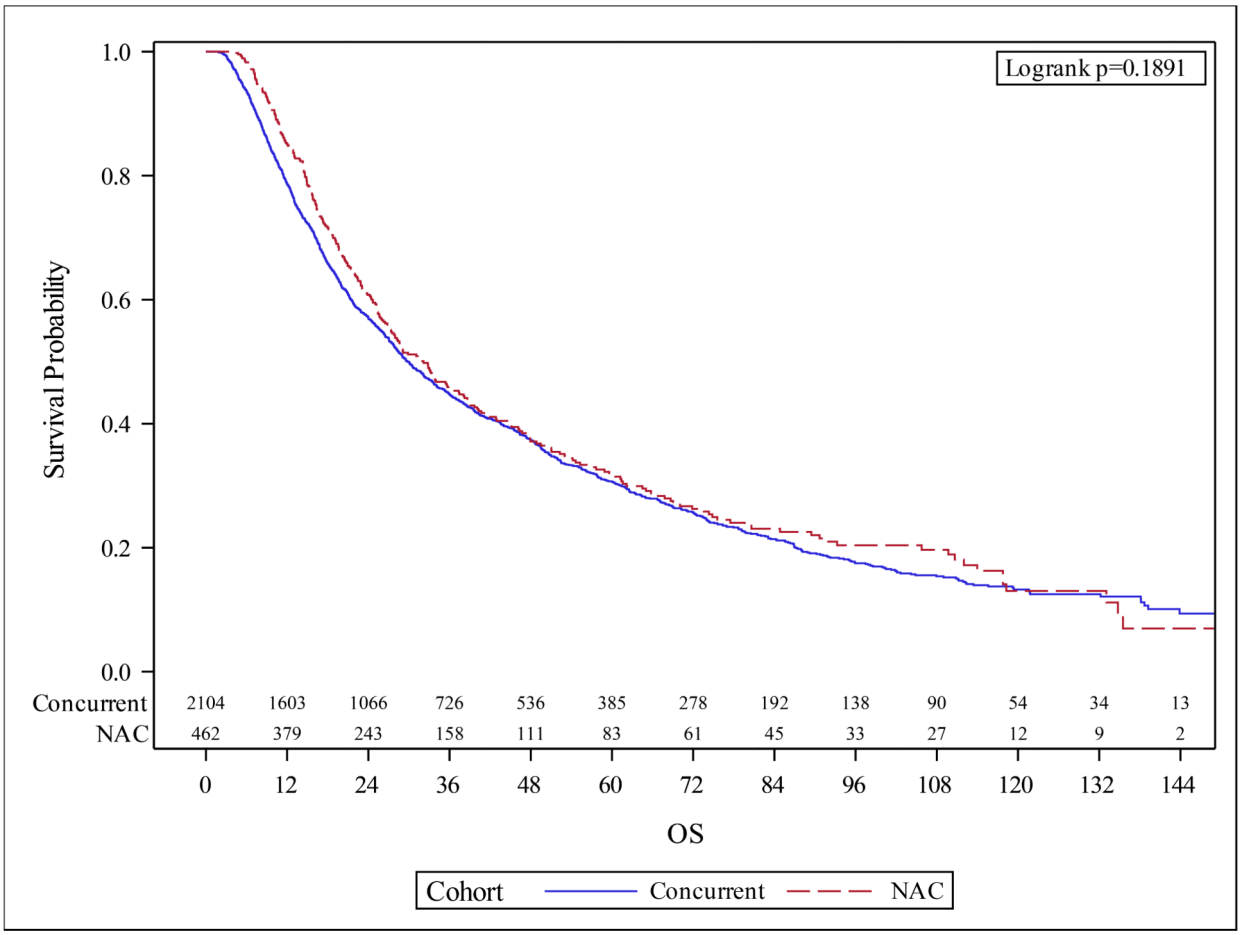

Cohort	No. of Subject	Event	Censored	Median Survival (95% CI)	60 Mo Survival	120 Mo Survival
Concurrent	2104	1459 (69%)	645 (31%)	29.8 (28, 32.2)	30.6% (28.4%, 32.9%)	13.3% (11.2%, 15.5%)
NAC	462	308 (67%)	154 (33%)	32.2 (27.5, 37.4)	31.8% (27.0%, 36.8%)	13.0% (8.4%, 18.7%)

Figure 1.

Kaplan-Meier survival estimates for patients treated with trimodality therapy (TMT) with or without neoadjuvant chemotherapy (NAC) for muscle invasive bladder cancer, with overall survival defined from date of diagnosis.

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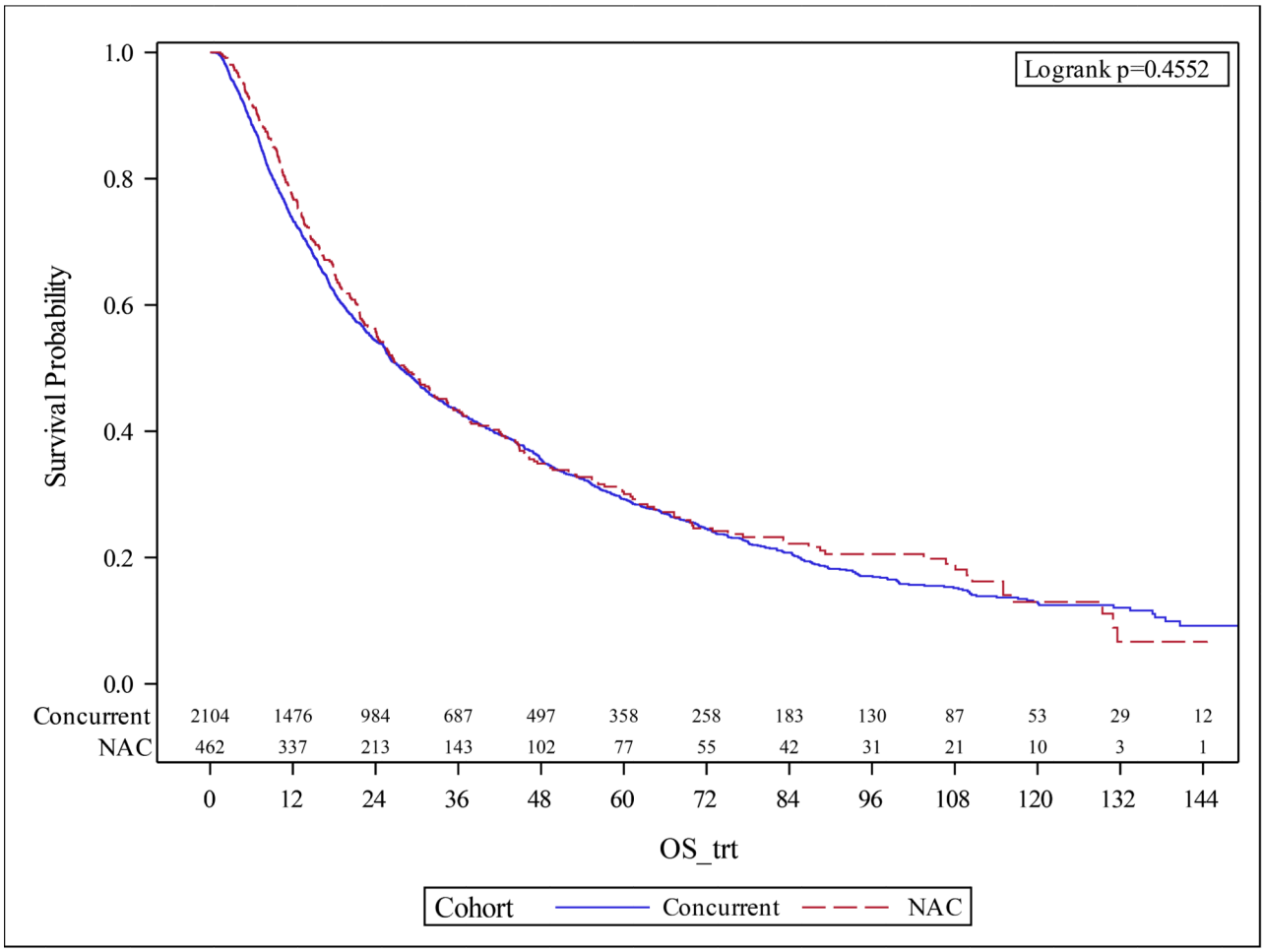

Cohort	No. of Subject	Event	Censored	Median Survival (95% CI)	60 Mo Survival	120 Mo Survival
Concurrent	2104	1459 (69%)	645 (31%)	27.6 (25.8, 30)	29.3% (27.1%, 31.5%)	13.0% (10.9%, 15.3%)
NAC	462	308 (67%)	154 (33%)	28.3 (24.4, 32.9)	30.4% (25.6%, 35.4%)	13.0% (8.3%, 18.7%)

Figure 2.

Kaplan-Meier survival estimates for patients treated with trimodality therapy (TMT) with or without neoadjuvant chemotherapy (NAC) for muscle invasive bladder cancer, with overall survival defined from start date of radiation.

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Table 1.

Cohort characteristics among patients who received trimodality therapy (TMT) for muscle invasive bladder cancer, stratified by receipt of neoadjuvant chemotherapy (NAC).

		TMT N=2104		NAC+TMT N=462		
Variable	**Level**	**N**	**%**	**N**	**%**	**P-value***
Age at Diagnosis	<60	147	7.0	48	10.4	0.001
	60–69	362	17.2	97	21.0	
	70–79	703	33.4	160	34.6	
	80+	892	42.4	157	34.0	
Race	White	1876	89.2	413	89.4	0.700
	Black	128	6.1	29	6.3	
	Asian-Indian-Pacific	30	1.4	9	1.9	
	Hispanic	43	2.0	8	1.7	
	Other/unknown	27	1.3	3	0.6	
Year	2004–2006	447	21.2	84	18.2	0.315
	2007–2009	514	24.4	107	23.2	
	2010–2012	457	21.7	113	24.5	
	2013–2015	686	32.6	158	34.2	
Charlson-Deyo Score	0	1340	63.7	300	64.9	0.613
	1+	764	36.3	162	35.1	
Clinical T stage	T2	1728	82.1	389	84.2	0.289
	T3–4	376	17.9	73	15.8	
Residence	Metro	1698	80.7	360	77.9	0.591
	Urban	310	14.7	79	17.1	
	Rural	41	1.9	10	2.2	
	Unknown	55	2.6	13	2.8	
Insurance	Other	151	7.2	28	6.1	0.099
	Private	344	16.3	94	20.3	
	Medicare	1609	76.5	340	73.6	
Median income	< $38,000	335	16.0	67	14.6	0.325
	$38,000-$47,999	510	24.4	124	27.0	
	$48,000-$62,999	597	28.6	141	30.7	
	>=$63,000	647	31.0	127	27.7	
No high school degree (%)	≥21.0%	304	14.5	62	13.4	0.318
	13.0–20.9%	503	24.1	127	27.5	
	7.0–12.9%	769	36.8	172	37.3	
	<7.0%	514	24.6	100	21.7	
Facility	Non-academic	1536	73.1	328	71.1	0.401
	Academic	566	26.9	133	28.9	
Region	Northeast	531	25.3	99	21.5	0.190
	South	662	31.5	142	30.8	

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Variable	Level	TMT N=2104		NAC+TMT N=462		P-value*
		N	%	N	%	
	Midwest	571	27.2	145	31.5	
	West	338	16.1	75	16.3	
Travel distance (miles)	<25	1740	83.3	378	82.0	0.650
	25–50	210	10.0	53	11.5	
	>50	140	6.7	30	6.5	
TURBT (weeks from dx)	Median (IQR)	0.0	0.0–2.0	0.0	0.0–2.0	0.593
Chemo start (weeks from dx)	Median (IQR)	8.1	5.7–12	4.0	0.0–7.4	<0.001
Radiation start (weeks from dx)	Median (IQR)	8.1	5.9–12	14.6	9.7–18.9	<0.001
Total radiation dose	Median (IQR)	64.5	59.4–64.8	64.8	59.4–64.8	0.796

*P-value by ANOVA for numerical covariates and chi-square test for categorical covariates

Abbreviations: TURBT, transurethral resection of bladder tumor; DX, diagnosis; IQR, intraquartile range

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Table 2.

Multivariate overall survival (OS) analysis among patients who received trimodality therapy (TMT) for muscle invasive bladder.

Variable	Level	N	Hazard Ratio (95% CI)	P-value*
Cohort	TMT	2108	-	
	NAC+TMT	463	1.01 (0.88–1.15)	0.921
Age at Diagnosis	<60	192	-	-
	60–69	456	1.30 (1.02–1.66)	0.035
	70–79	857	1.75 (1.38–2.23)	<0.001
	80+	1040	2.13 (1.67–2.70)	<0.001
Race	White	2270	-	-
	Black	155	1.17 (0.95–1.43)	0.132
	Asian-Indian-Pacific	39	0.66 (0.42–1.04)	0.075
	Hispanic	51	0.76 (0.51–1.12)	0.165
	Other/unknown	30	1.12 (0.80–1.83)	0.372
Year	2004–2006	522	-	-
	2007–2009	615	1.13 (0.99–1.29)	0.074
	2010–2012	567	1.06 (0.92–1.22)	0.395
	2013–2015	841	1.16 (1.01–1.34)	0.037
Charlson-Deyo Score	0	1624	-	-
	1+	921	1.27 (1.15–1.40)	<0.001
Clinical T stage	T2	2099	-	-
	T3–4	446	1.43 (1.27–1.61)	<0.001
Insurance	Private	435	-	-
	Medicare	1933	1.14 (0.98–1.32)	0.079
	Other	177	1.34 (1.07–1.68)	0.010
Median income	>=$63,000	782	-	-
	< $38,000	402	0.92 (0.76–1.12)	0.423
	$38,000–$47,999	632	1.10 (0.94–1.28)	0.248
	$48,000–$62,999	738	0.96 (0.83–1.10)	0.523
No high school degree (%)	<7.0%	621	-	-
	7.0–12.9%	939	1.06 (0.92–1.22)	0.441
	13.0–20.9%	630	1.12 (1.02–1.44)	0.025
	≥21.0%	365	1.12 (0.91–1.37)	0.293
Region	West	409	-	-
	Northeast	623	0.90 (0.77–1.06)	0.206
	South	799	0.97 (0.83–1.14)	0.732
	Midwest	714	1.14 (0.98–1.33)	0.087

Abbreviation: CI, confidence interval

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Table 3.

Multivariate overall survival (OS) analysis among patients who received trimodality therapy (TMT) with or without neoadjuvant chemo (NAC) for muscle invasive bladder sensitivity analysis using an interaction term with clinical T stage subgroup.

Variable	Level	N	Hazard Ratio (95% CI)	P-value*
T2	TMT	1713	-	-
	NAC+TMT	386	1.05 (0.91–1.21)	0.536
T3–4	TMT	374	-	-
	NAC+TMT	72	0.84 (0.62–1.13)	0.253

The estimated stratified treatment effect was controlled by: age, comorbidity, facility, income, education, insurance, race, and year.

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Table 4.

Multivariate overall survival (OS) analysis among patients who received trimodality therapy (TMT) with or without neoadjuvant chemo (NAC) for muscle invasive bladder sensitivity analysis using overall survival defined from start date of radiation.

Variable	Level	N	Hazard Ratio (95% CI)	P-value*
Cohort	TMT	2087	-	
	NAC+TMT	458	0.97 (0.86–1.10)	0.618

The estimated stratified treatment effect was controlled by: age, comorbidity, facility, income, education, insurance, race, region, T stage, and year.