Comparative real-world survival outcomes of muscle-invasive bladder cancer treated with bladder-only vs. whole-pelvis concurrent chemoradiation

Carlos Riveros[1], Sanjana Ranganathan[1], Waqar Haque[2], Emily Huang[1], Jiaqiong Xu[3], Girish S. Kulkarni[4,5], Michael Geng[6], Maryam Anis[1], Taliah Muhammad[1], Keith Syson Chan[1,7], Andrew Farach[2], Bin S. Teh[2], Brian J. Miles[1], Zachary Klaassen[8], Guru P. Sonpavde[9], Christopher J.D. Wallis[4,5,10], Raj Satkunasivam[1]

[1]Department of Urology, Houston Methodist Hospital, Houston, TX, United States; [2]Department of Radiation Oncology, Houston Methodist Hospital, Houston, TX, United States; [3]Center for Health Data Science and Analytics, Houston Methodist Hospital, Houston, TX, United States; [4]Division of Urology and Surgical Oncology, Department of Surgery, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; [5]Division of Urology, University of Toronto, Toronto, ON, Canada; [6]School of Engineering Medicine, Texas A&M University, Houston, TX, United States; [7]Center for TME Spatial Profiling in GU Oncology, Houston Methodist Research Institute, Houston, TX, United States; [8]Division of Urology, Medical College of Georgia, Augusta University, Augusta, GA, United States; [9]Genitourinary Oncology Program, AdventHealth Cancer Institute, Orlando, FL, United States; [10]Division of Urology, Mount Sinai Hospital, Toronto, ON, Canada

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ABSTRACT

INTRODUCTION: Elective pelvic nodal irradiation for patients with muscle-invasive bladder cancer (MIBC) undergoing trimodal therapy (TMT) is controversial. In patients with node-negative (N0) MIBC, the benefit of elective whole-pelvis concurrent chemoradiation (WP-CCR) compared to bladder-only (BO)-CCR has not been demonstrated. Using real-world data from the National Cancer Database (NCDB), we sought to compare the overall survival (OS) between BO-CCR and WP-CCR for MIBC.

METHODS: Using the 2020 NCDB Participant User File, we identified cases of MIBC diagnosed between 2017 and 2019. We selected patients with clinical T2–T4aN0M0 disease receiving CCR as first-line treatment. CCR was defined as transurethral resection of bladder tumor followed by ≥40 Gy radiation to the bladder with concurrent single- or multiple-agent chemotherapy. Based on elective nodal irradiation status, patients were stratified as having received BO-CCR vs. WP-CCR. OS analysis was performed using summary three-month conditional landmark, inverse probability treatment weighting (IPTW)-adjusted Kaplan-Meier estimates, and Cox regression.

RESULTS: A total of 604 patients receiving CCR for MIBC were identified: 367 (60.8%) BO-CCR and 237 (39.2%) WP-CCR. Before IPTW, the groups were imbalanced in terms of baseline characteristics. The median followup of the weighted population was 42.3 months (interquartile range 18.1–49.1 months). In IPTW-adjusted Cox proportional hazards regression analysis, WP-CCR was associated with a significant OS benefit compared to BO-CCR (adjusted hazard ratio 0.72, 95% confidence interval 0.54–0.96, p=0.026).

CONCLUSIONS: In the setting of CCR for N0 MIBC, this retrospective NCDB analysis revealed that WP-CCR was associated with a benefit in OS compared to BO-CCR.

INTRODUCTION

Bladder cancer is the 10th most frequently diagnosed cancer worldwide, with approximately 573 000 new cases and 213 000 deaths in 2020.[1] Almost 25% of patients will have muscle-invasive bladder cancer (MIBC) at the time of diagnosis and often undergo radical cystectomy (RC), trimodal therapy (TMT), or palliation. TMT entails maximal transurethral resection of bladder tumor (TURBT) followed by concurrent chemoradiation (CCR). Historically, TMT is generally reserved for patients who desire bladder preservation and for those with significant comorbidities for whom RC is not an option.[2] Several single-arm phase 2 and phase 3 trials have provided evidence for the efficacy of TMT.[3] We and others have previously shown TMT as a viable alternative strategy to RC using prospective, propensity score-matched data from single and multiple institutions.[4,5]

In the absence of neoadjuvant chemotherapy, up to 25% of patients with clinically node-negative (cN0) MIBC are found to have nodal involvement at the time of pelvic lymphadenectomy.[6] The rationale for pelvic lymph node dissection in the setting of RC is supported by multiple studies examining node count and density, all showing reproducibility and consistency.[7,8] Extrapolating the need to deliver radiation to the nodes is, however, unclear. Elective pelvic nodal irradiation in the setting of TMT for cN0 MIBC remains controversial.[9,10] Radiotherapy to the bladder

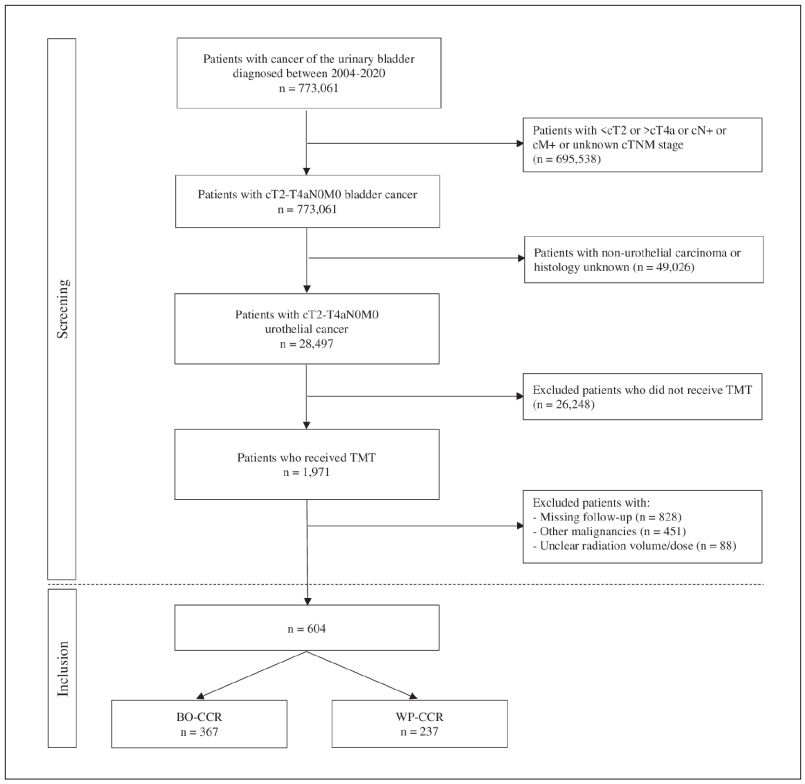

Figure 1. Flowchart for patient selection. TMT: trimodal therapy.

alone already results in significant incidental doses to peripheral lymph nodes.[11] Whole-pelvis (WP)-CCR has also been associated with higher radiation toxicity and side effects.[12] The role of prophylactic and therapeutic nodal irradiation has been explored in other pelvic malignancies, such as prostate and cervical carcinoma.[13,14] Few studies have compared oncologic outcomes between WP- and bladder-only (BO)-CCR in the setting of TMT for MIBC.[15] Thus, we sought to explore differences in overall survival (OS) between WP- and BO-CCR among patients with cN0 MIBC using real-world data.

METHODS

Data source

The National Cancer Database (NCDB) is a nationwide, facility-based, comprehensive oncology dataset that captures over 70% of all newly diagnosed malignancies in the U.S. annually.[16] Since the data are de-identified, the study was exempt from approval by our institutional review board. This study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[17]

Study population

Using the 2020 Urinary Bladder NCDB Participant User File, we identified patients with clinical T2–T4aN0M0 bladder cancer between 2017 and 2019. Based on the International Classification of Diseases for Oncology Third Edition (ICD-O-3) histology codes, we identified patients with urothelial carcinoma (8120/8130).[18] We selected 2017 as the earliest year for inclusion, as it was the year when reporting of "radiation to draining lymph nodes" began.[19] The upper bound was 2019, as it was the latest year for which survival data was available. We excluded patients with unclear radiation volume/dose and those with other malignancies (as they could have received previous radiation or chemotherapy).

Exposure and covariates

Receipt of TMT was defined as having undergone TURBT followed by CCR. Concurrent chemoradiation was defined as radiation to the bladder ≥40 Gy,[20] in addition to single- or multi-agent chemotherapy. To be considered concurrent, the maximum time interval between the beginning of radiation and chemotherapy was set at 30 days. Radiation could have been delivered in one or two phases. Whole-pelvis radiation was defined as having received concomitant radiation to the bladder and draining pelvic lymph nodes during at least one phase. The following covariates were included: age at diagnosis, sex, race, insurance status, income level, education level, degree of rurality, Charlson-Deyo score, clinical tumor (cT) stage, facility type, and distance to facility (miles).

Outcomes

The primary endpoint of interest was OS. To account for immortal time bias in starting CCR, a three-month landmark was used.[21]

Statistical analysis

Patients were stratified into the type of CCR received. Baseline characteristics were abstracted and reported. Continuous variables were expressed as mean with standard deviation (SD) or median with interquartile range [IQR], while categorical variables were reported as proportions and frequencies. Multiple imputation using chained equations was performed to handle missing data assumed to be missing at random for all covariates.[22] The continuous variable for distance to facility was imputed using predictive mean matching with the number of nearest neighbors (k=5).[23] As the recommended number of imputed data sets should be at least as large as the percentage of subjects with any

Table 1. Baseline characteristics

	Unweighted population			Weighted population		
	BO-CCR n=367	WP-CCR n=237	ASD	BO-CCR	WP-CCR	ASD
Age at diagnosis, mean [SD]	76.47 [8.92]	74.89 [8.51]	0.181	75.84 [9.23]	75.79 [8.14]	0.005
Sex (%)			0.056			0.001
Male	281 (76.57)	187 (78.90)		77.08	77.12	
Female	86 (23.43)	50 (21.10)		22.92	23.88	
Race (%)			0.061			0.005
White	338 (92.10)	220 (92.83)		92.47	92.73	
Black	21 (5.72)	15 (6.33)		5.84	5.49	
Other	8 (2.18)	2 (0.84)		1.69	1.78	
Insurance status (%)			0.278			0.003
Private insurance	30 (8.17)	37 (15.61)		10.85	10.84	
Medicaid/other government	22 (5.99)	23 (9.70)		7.41	7.26	
Medicare	315 (85.83)	177 (74.68)		81.74	81.9	
Income level (%)			0.001			0.004
Low	147 (40.05)	95 (40.08)		39.56	39.35	
High	220 (59.95)	142 (59.92)		60.44	60.65	
Education level (%)			0.029			0.012
Low	162 (44.14)	108 (45.57)		43.85	43.27	
High	205 (55.86)	129 (54.43)		56.15	56.73	
Rurality (%)			0.103			0.001
Metro	291 (79.29)	197 (83.12)		80.61	80.56	
Urban	73 (19.89)	39 (16.46)		18.73	18.79	
Rural	3 (0.82)	1 (0.42)		0.65	0.65	
Charlson-Deyo score (%)			0.044			0.002
0	214 (58.31)	135 (56.96)		58.29	58.82	
1	65 (17.71)	44 (18.57)		17.55	16.88	
2	43 (11.72)	22 (9.28)		10.90	10.87	
≥3	45 (12.26)	36 (15.19)		13.26	13.43	
Clinical T stage (%)			0.073			0.005
cT2	341 (92.92)	216 (91.14)		91.85	91.63	
cT3	20 (5.45)	15 (6.33)		6.21	6.46	
cT4a	6 (1.63)	6 (2.53)		1.94	1.91	

ASD: absolute standardized differences; BO-CCR: bladder-only concurrent chemoradiation; IQR: interquartile range; SD: standard deviation; WP-CCR: whole-pelvis concurrent chemoradiation.

Table 1 (cont'd). Baseline characteristics

	Unweighted population			Weighted population		
	BO-CCR n=367	WP-CCR n=237	ASD	BO-CCR	WP-CCR	ASD
Facility type (%)			0.16			0.008
Academic	106 (28.88)	52 (21.94)		26.49	26.86	
Non-academic	261 (71.12)	185 (78.06)		73.51	73.14	
Distance to facility in miles, median [IQR]	11.3 [4.9, 28.0]	10.4 [3.3, 24.6]	0.110	10.5 [4.8, 22.1]	10.2 [4.3, 21.9]	0.008

ASD: absolute standardized differences; BO-CCR: bladder-only concurrent chemoradiation; IQR: interquartile range; SD: standard deviation; WP-CCR: whole-pelvis concurrent chemoradiation.

missing data,[24] we generated 15 imputed data sets using a sequential regression method. Rubin's rules were used to summarize the effect estimates and variances from the 15 different analyses across imputed data sets.[25] We performed multivariable logistic regression analysis to determine predictors of WP-CCR vs. BO-CCR receipt.

To account for selection bias, we controlled for observed differences in baseline characteristics between the two treatment groups using inverse probability of treatment weighting (IPTW)-adjusted analyses.[26] Absolute standardized differences (ASD) were reported to assess for baseline differences between the groups and evaluate covariate balance following IPTW. An ASD >0.1 was used to define meaningful imbalance in covariates between treatment groups.[27]

Since the median time between diagnosis of MIBC and initiation of CCR was 61 days (IQR 47–86), summary three-month conditional landmark, IPTW-adjusted Kaplan-Meier estimates were calculated to compare OS between the two groups. Overall median followup with IQR was reported for the weighted population. Median IPTW-adjusted OS with corresponding IQR in months were reported for both treatment groups, along with three-year survival rates. An IPTW-adjusted Cox proportional hazards regression model was computed to evaluate the association between type of CCR treatment and OS. The adjusted hazard ratio (aHR), with its corresponding confidence intervals (CI), was reported. The proportional hazards assumption was assessed globally using a test of weighted Schoenfeld residuals.

Using the IPTW-adjusted Cox proportional hazards regression model, we performed interaction analyses to examine treatment heterogeneity based on age (<65 vs. ≥65 years old), sex (male vs. female), insurance status (private vs. government-sponsored [Medicare/Medicaid/other]), income level (low vs. high), education level (low vs. high), Charlson-Deyo score (0 vs. ≥1), cT stage (cT2 vs. cT3–4a), facility type (academic vs. non-academic), and distance to facility (continuous). Sensitivity analysis with multivariable Cox regression after listwise deletion was performed to assess the robustness of results. All analyses were performed with STATA version 17 (StataCorp 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC). Statistical significance was defined as two-tailed $p < 0.05$ for all tests.

RESULTS

A total of 604 patients who received TMT for cT2–4aN0M0 urothelial carcinoma of the bladder were identified; 367 (60.76%) received BO-CCR and 237 (39.24%) received WP-CCR (Figure 1). Unweighted and weighted baseline characteristics of both groups are reported in Table 1. ASD between the unweighted groups indicated imbalance with respect to age, insurance status, rurality, facility type, and distance to facility. Before IPTW, patients in the BO-CCR group were older (mean years [SD]: 76.5 [8.9] vs. 74.9 [8.5]), less likely to have private insurance (8.17% vs. 15.61%) and live in metropolitan areas (79.29% vs. 83.12%), and more likely to be treated in academic facilities (28.88% vs. 21.94%). In multivariable logistic regression analysis (Table 2), treatment at a non-academic facility was an independent predictor of WP-CCR receipt (odds radio [OR] 1.83, 95% CI 1.15–2.93), while Medicare insurance was independently associated with non-receipt of WP-CCR (OR 0.50, 95% CI 0.26–0.94).

After IPTW-adjustment, all ASDs were <0.1, indicating adequate balance between the two treatment groups. The median followup of the weighted popu-

Table 2. Multivariable logistic regression analysis determining receipt of WP-CCR vs. BO-CCR

Variable	OR (95% CI)	P
Age at diagnosis	0.99 (0.97–1.01)	0.4
Sex		
Male	1 [reference]	NA
Female	0.89 (0.56–1.41)	0.6
Race		
White	1 [reference]	NA
Black	0.81 (0.36–1.82)	0.6
Other	0.55 (0.10–3.15)	0.5
Insurance status		
Private insurance	1 [reference]	NA
Medicaid/other government	0.99 (0.42–2.33)	1
Medicare	0.50 (0.26–0.94)	0.032
Income level		
Low	1 [reference]	NA
High	0.92 (0.58–1.45)	0.7
Education level		
Low	1 [reference]	NA
High	1.10 (0.70–1.75)	0.7
Rurality		
Metro	1 [reference]	NA
Urban	0.70 (0.41–1.19)	0.19
Rural	0.78 (0.05–13.44)	0.9
Charlson-Deyo score		
0	1 [reference]	NA
1	1.14 (0.68–1.90)	0.6
2	0.80 (0.43–1.51)	0.5
≥3	1.46 (0.83–2.57)	0.19
Clinical T stage		
cT2	1 [reference]	NA
cT3	1.28 (0.68–2.81)	0.5
cT4a	1.49 (0.40–5.48)	0.5
Facility type		
Academic	1 [reference]	NA
Nonacademic	1.83 (1.15–2.93)	0.011
Distance to facility	1.00 (0.99–1.01)	0.7

CI: confidence interval; BO-CCR: bladder-only concurrent chemoradiation; OR: odds ratio; NA: not applicable; WP-CCR: whole-pelvis concurrent chemoradiation.

lation was 42.3 months (IQR 18.1–49.1). The three-month conditional landmark, IPTW-adjusted Kaplan-Meier curves (Figure 2) showed that median OS was significantly better for WP-CCR (49.1 months, IQR 20.8 months–not reached) vs. BO-CCR (38.9 months, IQR 16.7 months–not reached). The three-year IPTW-adjusted OS rates were 62.2% for WP-CCR vs. 50.0% for BO-CCR. In IPTW-adjusted Cox proportional hazards regression analysis, WP-CCR was associated with a significant OS benefit compared to BO-CCR (aHR 0.72, 95% CI 0.54–0.96, p=0.026). Exploratory interaction term analyses demonstrated that the OS benefit of WP-CCR increased significantly with government-sponsored insurance (HR 0.17, 95% CI 0.03–0.86, p=0.032). No significant interaction was observed with age (p=0.9), sex (p=0.5), income (p=0.16) or education (p=0.6) level, Charlson-Deyo score (p=0.6), cT stage (p=0.8), facility type (p=0.2), or distance to facility (p=0.3). Given the age of eligibility for Medicare, we explored the interaction between age (≥65 years old) and insurance status (Medicare) post-hoc; however, it was not significant (p=0.70). Sensitivity analysis yielded a similar OS benefit for WP-CCR (aHR 0.66, 95% CI 0.47–0.93, p=0.018).

DISCUSSION

In the setting of patients receiving TMT for cN0 MIBC, no clear recommendation exists regarding concomitant pelvic nodal irradiation during CCR.[10] As such, we sought to investigate differences in OS between WP- and BO-CCR using real-world data from more than 600 patients.

Treatment at a non-academic facility was associated with receipt of WP-CCR. After a median followup of 42 months, our IPTW-adjusted analysis showed a significant OS benefit for WP-CCR. Specifically, patients who received WP-CCR were 28% less likely to die of any

cause compared with patients who received BO-CCR. Although not mature, receipt of WP-CCR translated into a 10-month OS benefit. Interaction analyses revealed that government-sponsored insurance further improved the OS benefit of WP-CCR. Sensitivity analysis demonstrated the robustness of the primary analysis.

Occult nodal involvement despite negative imaging is a common problem among patients with solid tumors. Prophylactic nodal irradiation has shown a benefit in survival outcomes for prostate,[28] cervical,[29] and breast cancer.[30] In MIBC, despite the absence of randomized data demonstrating the superiority of surgery over TMT,[31] radiation with or without concomitant chemotherapy accounts for 8% of treatments in the U.S.[32] Current guidelines state that CCR is most suitable for patients with solitary tumors, negative nodes, no extensive carcinoma in situ, no tumor-related hydronephrosis, and adequate baseline bladder function.[10]

Elective pelvic nodal irradiation during CCR is currently optional for patients with cN0 MIBC, as previous trials have not shown a survival benefit.[9] As academic hospitals are more likely to provide guideline-based treatment,[33] we hypothesize that this could be why receipt of WP-CCR was less common in these hospitals. Regionalization of care could also explain why treatment at a non-academic facility was associated with receipt of WP-CCR. Sicker patients generally get referred to academic hospitals;[34] however, they would be less likely to receive WP-CCR due to the greater toxicity associated with larger radiation fields.

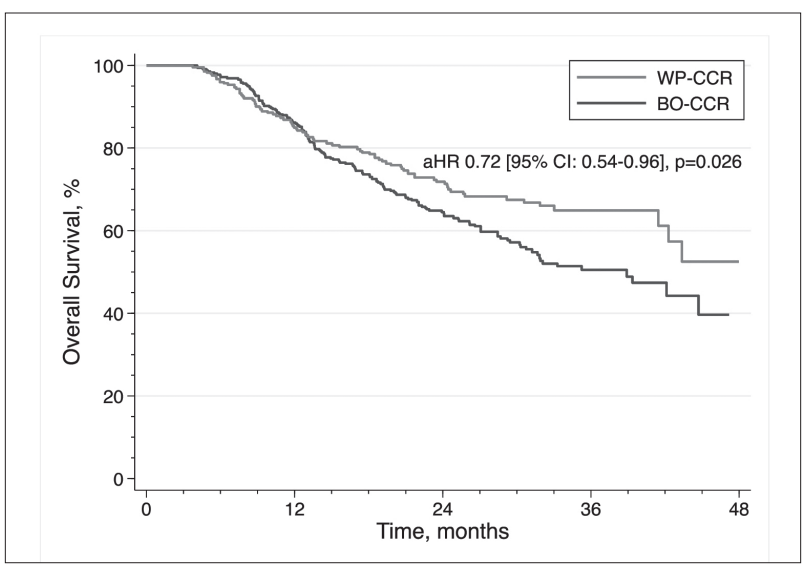

Figure 2. Three-month conditional landmark inverse probability of treatment weighting-adjusted Kaplan-Meier estimates of overall survival for patients who received bladder-only concurrent chemoradiation vs. whole-pelvis concurrent chemoradiation in the setting of trimodal therapy for bladder cancer. Risk tables are not shown as data are weighted proportions and not absolute numbers. aHR: adjusted hazard ratio; CI: confidence interval; BO: bladder-only; WP: whole-pelvis; CCR: concurrent chemoradiation.

A randomized, single center trial including 230 patients with cN0 MIBC compared elective WP-CCR (full pelvic volume extending to the L5/S1 interspace superiorly) vs. BO-CCR (bladder with 2 cm margins). At a median follow up of five years, there were no significant differences in disease-free survival, bladder preservation rates, or OS. In terms of side effects, the overall incidence of grade 3 or 4 acute toxicity was 17.6% in the WP-CCR group vs. 13.3% in the BO-CCR group (p=0.05). The treatment protocol completion rate was 93.1% in the WP-CCR group vs. 95.9% in the BO-CCR group (p=0.05). There were no significant differences in late toxicities between the groups during the five-year followup.[15] Compared to our study, the patients in this randomized trial were overall younger, had higher cT stage, and up to 23% did not undergo maximal TURBT prior to CCR.

Approximately 54% of patients in the trial by Tunio et al had ≥cT3 disease,[15] while our cohort only had 7.8% of patients with ≥cT3 disease. Given that cT stage is a predictor of lymph node metastasis,[35] it is likely that many patients in the trial had occult lymph node metastasis. Intuitively, this would make BO-CCR a less efficacious option, compared to WP-CCR. This is further supported by the rates of locoregional recurrence reported at five years. The number of patients who experienced regional lymphadenopathy was 42.9% and 45.7% in the WP-CCR and BO-CCR groups, respectively; however, the trial failed to find a significant difference in OS rates between the two groups. The same radiation dose of 65 Gy was used in both groups and there was significant overlap in the radiation fields (≤2 cm), which could possibly explain the findings.

Although the results of our study are encouraging, increased toxicity is a major concern in WP-CCR, as previously mentioned. Intensity-modulated radiotherapy (IMRT) may provide better sparing of organs at risk and reduce toxicity rates associated with conventional 3D conformal radiation. The single-center, phase 2 Intensity-Modulated Pelvic Node and Bladder Radiotherapy (IMPART) trial assessed the feasibility and efficacy of delivering IMRT to the bladder and pelvic nodes. A total of 38 patients (58% and 42% with clinical node positive [cN+] and N0 MIBC, respectively) were recruited, with up to 63% having >cT2 disease.

The majority of grade 1 or 2 side effects were gastrointestinal (72%), while most grade 3 side effects were genitourinary (21%). The authors attributed the high gastrointestinal toxicity to the concomitant che-

motherapy use in 50% of their cohort. At two years, there was no reported grade 3 or 4 toxicity. In terms of efficacy, the median OS was 1.9 years, with two- and five-year OS rates of 50% and 34%, respectively. An exploratory analysis comparing OS in patients with cN+ and cN0 disease showed no significant difference (p=0.62).[36] Predictors of occult lymph node involvement might prove useful when deciding between BO- and WP-CCR. A recent study identified lymphovascular invasion as an independent predictor of nodal upstaging (OR 10.1, 95% CI 2.9–34.9).[37]

Our results are corroborated by a recent Canadian, academic, multicenter, retrospective, inverse probability treatment-weighted analysis of 599 cT2-4aN0-2M0 patients, which reported a survival benefit for WP vs. BO radiotherapy; however, this Canadian study was not exclusive to patients receiving TMT and was performed in select academic centers in contrast to our real-world NCDB study.[38] Finally, the randomized, three-arm, phase 2 RAIDER trial enrolled 345 patients and compared whole bladder RT (WBRT), standard-dose adaptive tumor focused RT (SART), and dose-escalated adaptive tumor boost RT (DART) for unifocal muscle-invasive, node-negative bladder cancer. This trial did not evaluate WP radiotherapy but demonstrated promise for image-guided DART.[39]

Although Medicare insurance was associated with decreased odds of WP-CCR receipt, government-sponsored insurance was associated with an increase in the OS benefit of WP-CCR. Previous research suggests that Medicare beneficiaries experience fewer problems getting access to care compared to those with private insurance.[40] It is possible that WP-CCR might be more beneficial for the typical Medicare patient.[41] Nonetheless, in our exploratory interaction analyses, we did not find age or comorbidity burden to affect the OS benefit of WP-CCR.

Limitations

The present study is not without limitations. First, it is retrospective in nature. Second, while higher risk features may lead to selection for WP-CCR, fitter or less frail patients may receive WP-CCR. Third, we could not adjust for relevant covariates, such as the specific chemotherapeutic agents used, the specific radiotherapy dosing and fractionation schedules administered, the presence of hydronephrosis, or the completeness of baseline TURBT, as these are not reported in NCDB. Fourth, we did not have toxicity data or CCR completion rate. Fifth, the OS was not mature, given the recency of the variable that was used to identify patients who received pelvic nodal irradiation. Sixth, there could still be confounding bias despite having adjusted for all available relevant covariates. Seventh, we could not evaluate the impact of not having insurance, as we did not have uninsured patients in our cohort.

CONCLUSIONS

Compared with BO-CCR, the use of WP-CCR for patients with N0 MIBC is associated with an OS benefit; however, these findings must be interpreted with caution, as toxicities could not be abstracted, and they may significantly impact quality of life. Further work is required to fully evaluate and select patients for the role of elective nodal irradiation in MIBC.

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This paper has been peer-reviewed.

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CORRESPONDENCE: Dr. Raj Satkunasivam, Department of Urology, Houston Methodist Hospital, Houston, TX, United States; raj.satkunasivam@gmail.com