VOLUME 34 · NUMBER 29 · OCTOBER 10, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Efficacy of High-Intensity Local Treatment for Metastatic Urothelial Carcinoma of the Bladder: A Propensity Score–Weighted Analysis From the National Cancer Data Base

Thomas Seisen, Maxine Sun, Jeffrey J. Leow, Mark A. Preston, Alexander P. Cole, Francisco Gelpi-Hammerschmidt, Nawar Hanna, Christian P. Meyer, Adam S. Kibel, Stuart R. Lipsitz, Paul L. Nguyen, Joaquim Bellmunt, Toni K. Choueiri, and Quoc-Dien Trinh

See accompanying article on page 3495

Thomas Seisen, Maxine Sun, Jeffrey J. Leow, Mark A. Preston, Alexander P. Cole, Francisco Gelpi-Hammerschmidt, Nawar Hanna, Christian P. Meyer, Adam S. Kibel, Stuart R. Lipsitz, Paul L. Nguyen, and Quoc-Dien Trinh, Brigham and Women's Hospital; and Joaquim Bellmunt and Toni K. Choueiri, Dana-Farber Cancer Institute, Boston, MA.

Published online ahead of print at www.jco.org on June 6, 2016.

Supported by an unrestricted educational grant from the Vattikuti Urology Institute.

The data used in the study were derived from a deidentified National Cancer Data Base file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology used or the conclusions drawn from these data by the investigators.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

Corresponding author: Quoc-Dien Trinh, MD, Division of Urologic Surgery/Center for Surgery and Public Health, Brigham and Women's Hospital, 45 Francis St, ASB II-3, Boston, MA, 02115; e-mail: qtrinh@bwh.harvard.edu.

0732-183X/16/3429w-3529w/$20.00

DOI: 10.1200/JCO.2016.66.7352

ABSTRACT

Purpose

Evidence from studies of other malignancies has indicated that aggressive local treatment (LT), even in the presence of metastatic disease, is beneficial. Against a backdrop of stagnant mortality rates for metastatic urothelial carcinoma of the bladder (mUCB) at presentation, we hypothesized that high-intensity LT of primary tumor burden, defined as the receipt of radical cystectomy or ≥ 50 Gy of radiation therapy delivered to the bladder, affects overall survival (OS).

Patients and Methods

We identified 3,753 patients within the National Cancer Data Base who received multiagent systemic chemotherapy combined with high-intensity versus conservative LT for primary mUCB. Patients who received no LT, transurethral resection of the bladder tumor alone, or < 50 Gy of radiation therapy delivered to the bladder were included in the conservative LT group. Inverse probability of treatment weighting (IPTW) –adjusted Kaplan-Meier curves and Cox regression analyses were used to compare OS of patients who received high-intensity versus conservative LT.

Results

Overall, 297 (7.91%) and 3,456 (92.09%) patients with mUCB received high-intensity and conservative LT, respectively. IPTW-adjusted Kaplan-Meier curves showed that median OS was significantly longer in the high-intensity LT group than in the conservative LT group (14.92 [interquartile range, 9.82 to 30.72] *v* 9.95 [interquartile range, 5.29 to 17.08] months, respectively; $P < .001$). Furthermore, in IPTW-adjusted Cox regression analysis, high-intensity LT was associated with a significant OS benefit (hazard ratio, 0.56; 95% CI, 0.48 to 0.65; $P < .001$).

Conclusion

We report an OS benefit for individuals with mUCB treated with high-intensity versus conservative LT. Although the findings are subject to the usual biases related to the observational study design, these preliminary data warrant further consideration in randomized controlled trials, particularly given the poor prognosis associated with mUCB.

J Clin Oncol 34:3529-3536. © 2016 by American Society of Clinical Oncology

INTRODUCTION

With an estimated 74,000 new cases and 16,000 deaths for the year 2015, urothelial carcinoma of the bladder (UCB) is a leading cause of cancer-related mortality in the United States.[1] Although studies have identified several novel therapeutic targets for the development of systemic therapies[2] and immune checkpoint inhibitors,[3] there has been little to no change in the mortality rates of metastatic disease since the introduction of cisplatin-based combination chemotherapy in the early 1990s.[4]

Despite the growing interest in local treatment (LT) for a broad range of solid tumors, even when the disease has spread to other parts of the body,[5] the potential benefit of controlling primary tumor burden has never been comprehensively explored for metastatic UCB (mUCB).

Nonetheless, the underlying rationale for considering such an approach is manifold. First, treatment of the primary focus may affect further metastatic progression by limiting the secretion of factors that promote cancer cell engraftment in distant organs.[6] Second, local progression of UCB is frequently associated with significant adverse effects, including hematuria, pain, sepsis, and renal failure. These events impede patient quality of life, incur significant costs, and may result in precipitated death in an undesirable setting.[7]

Evidence from studies of other metastatic urologic malignancies has indicated potential benefits of aggressive LT. For example, randomized controlled trials (RCTs) have shown that overall survival (OS) may be prolonged by ≥ 6 months with cytoreductive nephrectomy in addition to cytokines in the context of metastatic renal cell carcinoma.[8,9] This benefit seems to extend to patients treated in the targeted therapy era.[10] Similarly, a preliminary study of SEER data revealed > 5-year OS and cancer-specific survival in men with metastatic prostate cancer who underwent radical prostatectomy or brachytherapy.[11] As a result, several RCTs are currently accruing men with metastatic prostate cancer to receive surgery or radiation therapy (RT) in addition to standard-of-care management (NCT00268476, NCT01751438).

Against a backdrop of stagnant mortality rates for mUCB at presentation, we hypothesized that high-intensity LT of primary tumor burden (herein defined as the receipt of radical cystectomy [RC] or ≥ 50 Gy of RT delivered to the bladder) affects patient survival. We assessed the comparative effectiveness of high-intensity LT versus conservative LT for mUCB by using the National Cancer Data Base (NCDB).

PATIENTS AND METHODS

Data Source

Established in 1989 by the Commission on Cancer (CoC) of the American Cancer Society and American College of Surgeons, the NCDB registry includes all patients seen at one of 1,500 participating CoC-accredited hospitals for any portion of their treatment or diagnosis. The data set captures > 70% of incident cancers in the United States and comprises > 29 million unique cases. Trained data abstractors use a standardized methodology[12] to collect demographic and clinical data, such as tumor type, stage, grade, and treatments.

Study Population

From a population of 603,298 men and women with bladder cancer diagnosed between 1998 and 2012 (International Classification of Diseases for Oncology, Third Edition, codes C67.0 to C67.9), we identified 4,313 adult individuals who received multiagent systemic chemotherapy for high-grade mUCB at presentation. mUCB, per the clinical American Joint Committee on Cancer staging system, was defined as the presence of extrapelvic positive lymph nodes as well as bone or visceral involvement. Only individuals with missing LT modality information or follow-up data were excluded (n = 560). The final study population included 3,753 patients (Fig 1).

Definition of High-Intensity Versus Conservative LT

Among this population of individuals who received systemic chemotherapy for mUCB, patients were further dichotomized into high-intensity versus conservative LT groups. Given the established benefits of RC and ≥ 50 Gy of RT delivered to the bladder[13] in localized UCB, patients who received these modalities were included in the high-intensity LT group. Alternatively, patients who received no LT, transurethral resection of the bladder tumor (TURBT) alone, or < 50 Gy of RT delivered to the bladder[13] were included in the conservative LT group.

Other Covariates

In addition to the treatment modalities, we abstracted patient-level variables, which included age at diagnosis, sex, race, baseline Charlson comorbidity index, and insurance status. Socioeconomic variables were estimated by using household income and education level from county of residence. Hospital location and type as well as UCB characteristics, including clinical tumor (cT) and clinical nodal (cN) stage, were also abstracted.

End Point

The primary analytic end point was OS from initial diagnosis to the date of death or censor at last follow-up. Specifically, we compared patients treated with multiagent chemotherapy combined with high-intensity versus conservative LT for mUCB at diagnosis.

Statistical Analyses

Means and standard deviations or median and interquartile ranges (IQRs) were reported for normally or nonnormally distributed continuous variables, respectively. Categorical variables were presented as frequencies and proportions.

We used the standardized differences approach (as opposed to two-sample t test and χ^2 test) to compare covariates between patients who received high-intensity versus conservative LT to facilitate assessment for possible confounding.[14] This quantitative method allowed us to assess the balance in baseline characteristics between treatment groups. A standardized difference ≥ 10% for a given covariate indicated a significant imbalance. Multivariable Cox regression analyses were performed to identify independent predictors of OS in the unweighted population.

To account for selection bias, observed differences in baseline characteristics between patients who received high-intensity versus conservative LT were controlled for with a weighted propensity score analysis. The propensity (or probability) of being in the two treatment groups was estimated from a logistic regression model that included all available covariates and that allowed us to determine the independent predictors of receiving high-intensity LT. The goodness-of-fit statistic of the propensity score model was assessed by the method proposed by Lemeshow and Hosmer.[15] Each patient was weighted by the inverse probability of being in the high-intensity versus conservative LT group, with the goal of balancing observable characteristics between the two groups; this approach is known as the inverse probability of treatment weighting (IPTW).[16] Balance between covariates in weighted groups was also assessed by using the standardized differences approach and by comparing their distribution with unweighted data.

IPTW-adjusted Kaplan-Meier curves were calculated to compare OS between patients who received high-intensity and those who received conservative LT. To test for equality of survival in the two groups, an IPTW-adjusted log-rank test was used.[17] In addition, we performed a univariable Cox regression analysis to calculate the IPTW-adjusted hazard ratio (HR) of the high-intensity LT effect.[16]

Given that propensity score weighting balances only the observed covariates between treatment groups, we performed additional sensitivity analyses without assumptions using the method described by Ding and VanderWeele[18] to assess the impact of unmeasured confounders on the findings by estimating the magnitudes of the joint bounding factor for various combinations of the odds of receiving high-intensity LT in the presence of unmeasured confounders ($OR_{LT\text{-}U}$) and the likelihood of OS in the presence of unmeasured confounders ($HR_{OS\text{-}U}$).

Finally, we performed an exploratory analysis to compare the OS of high-intensity LT after systemic chemotherapy (ie, consolidative strategy) versus high-intensity LT before systemic chemotherapy

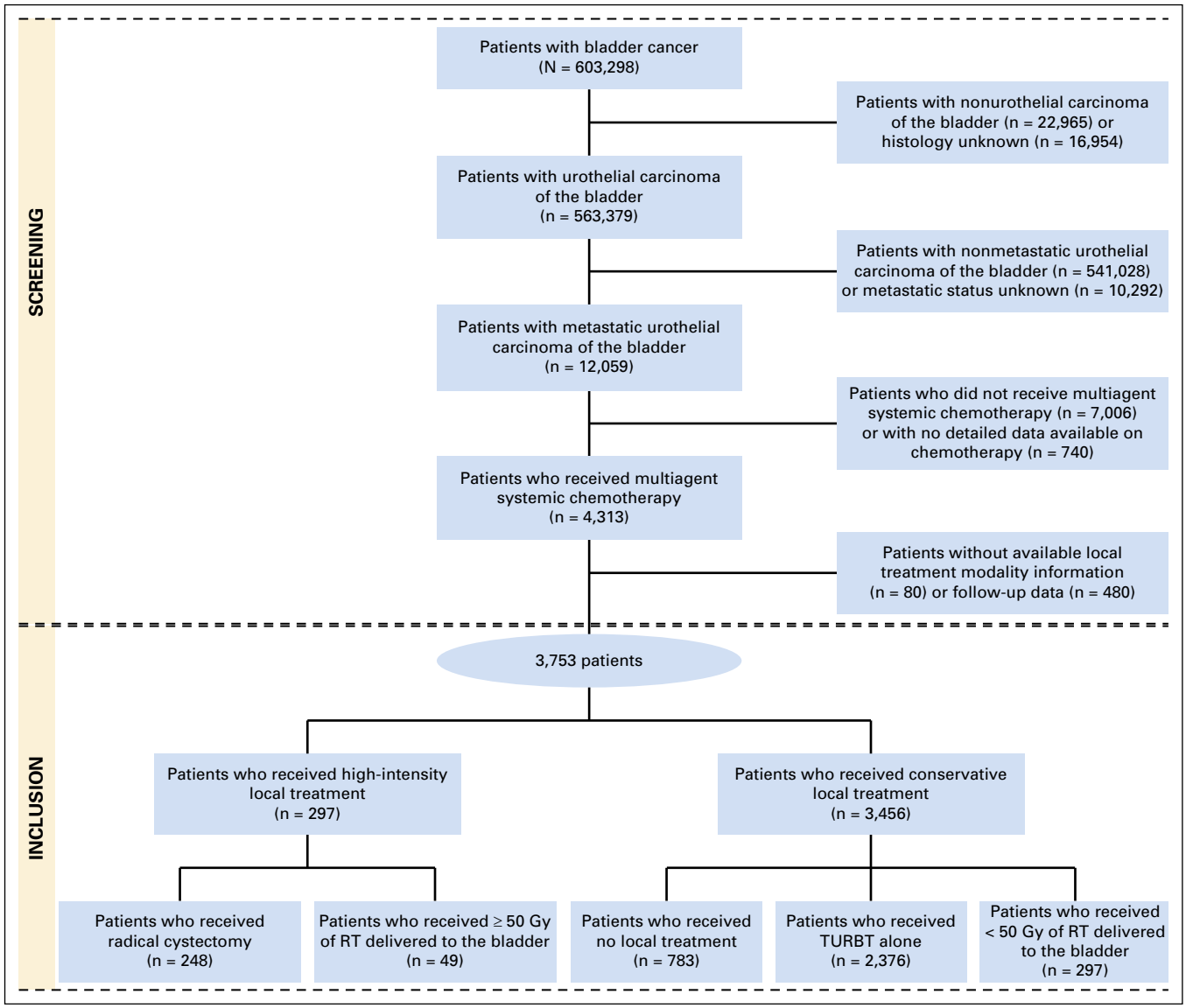

Fig 1. Flowchart that describes the selection of patients who received multiagent systemic chemotherapy combined with high-intensity versus conservative local treatment for metastatic urothelial carcinoma of the bladder in the National Cancer Data Base, 1998 to 2012. RT, radiation therapy; TURBT, transurethral resection of the bladder tumor.

(ie, cytoreductive strategy). After rebalancing all baseline characteristics of patients with available start dates of treatments in the high-intensity LT group by using the previously described methodology, we calculated the IPTW-adjusted HR of consolidative versus cytoreductive strategy for mUCB.

All statistical analyses were performed with Stata 13.0 (StataCorp, College Station, TX) and SAS 9.3 (SAS Institute, Cary, NC) software. Two-sided statistical significance was defined as $P < .05$. An institutional review board waiver was obtained before the study was conducted in accordance with institutional regulation when dealing with deidentified, previously collected data.

RESULTS

Overall, 297 (7.91%) and 3,456 (92.09%) patients with mUCB underwent high-intensity and conservative LT, respectively. In the high-intensity LT group, 248 (83.50%) and 49 (16.50%) patients received RC or ≥ 50 Gy of RT delivered to the bladder (median dose, 59.40 Gy; IQR, 50.40 to 64.80 Gy), respectively. In the conservative LT group, 783 (22.66%), 2,376 (68.75%), and 297 (8.59%) patients received no LT, TURBT alone, and < 50 Gy of RT delivered to the bladder, respectively (Fig 1).

Patient Characteristics and Predictors of OS in the Unweighted Population

Unweighted baseline characteristics of eligible patients, stratified according to high-intensity versus conservative LT are reported in Table 1. Several standardized differences of unweighted comparisons were ≥ 10%, which indicated that both treatment groups differed significantly with respect to clinical, socioeconomic, demographic, and tumor characteristics. The median follow-up in the unweighted population was

Table 1. Baseline Characteristics of Patients Treated With Multiagent Chemotherapy Combined With High-Intensity Versus Conservative LT for Metastatic Urothelial Carcinoma of the Bladder in Unweighted and Weighted Study Populations

Characteristic	Unweighted Population, No. (%)				Weighted Population, %			
	Overall (N = 3,753 [100%])	High-Intensity LT (n = 297 [7.91])	Conservative LT (n = 3,456 [92.09])	Standardized Difference, %	Overall	High-Intensity LT	Conservative LT	Standardized Difference, %
Mean (SD) age, years	66.04 (11.28)	63.70 (11.01)	66.25 (11.28)	−22.88	65.92 (10.89)	65.77 (10.43)	66.07 (11.34)	−2.75
Sex								
Male	2,733 (72.82)	215 (72.39)	2,518 (72.86)	−1.05	73.49	74.25	72.73	3.44
Female	1,020 (27.18)	82 (27.61)	938 (27.14)	1.05	26.51	25.75	27.27	−3.44
Race								
White	3,335 (88.86)	274 (92.26)	3,061 (88.57)	12.56	90.05	90.61	89.49	3.74
Black	302 (8.05)	17 (5.72)	285 (8.25)	−9.94	7.64	7.17	8.12	−3.58
Other	89 (2.37)	6 (2.02)	83 (2.40)	−2.58	2.31	2.22	2.39	−1.13
Unknown	27 (0.72)	0 (0.00)	27 (0.78)	−12.54	—	—	—	—
Charlson comorbidity index								
0	2,119 (56.46)	180 (60.61)	1,939 (56.11)	9.14	57.08	57.53	56.61	1.86
1	490 (13.06)	48 (16.16)	442 (12.79)	9.59	12.68	12.23	13.14	−2.73
≥ 2	167 (4.45)	18 (6.06)	149 (4.31)	7.90	4.44	4.44	4.44	0.00
Unknown	977 (26.03)	51 (17.17)	926 (26.79)	−23.39	25.80	25.80	25.81	−0.02
Insurance type								
Private	1,260 (33.57)	115 (38.72)	1,145 (33.13)	11.67	33.07	32.68	33.45	−1.64
Government	2,220 (59.15)	164 (55.22)	2,056 (59.49)	−8.64	59.06	58.87	59.25	−0.77
No insurance	177 (4.72)	14 (4.71)	163 (4.72)	−0.05	5.00	5.23	4.76	2.16
Unknown	96 (2.56)	4 (1.35)	92 (2.66)	−9.36	2.88	3.22	2.53	4.13
Income level								
High	2,075 (55.29)	169 (56.90)	1,906 (55.15)	3.53	56.49	57.81	55.15	5.37
Low	1,518 (40.45)	118 (39.73)	1,400 (40.51)	−1.59	39.47	38.41	40.54	−4.36
Unknown	160 (4.26)	10 (3.37)	150 (4.34)	−5.04	4.04	3.78	4.30	−2.64
Education level								
High	2,057 (54.81)	166 (55.89)	1,891 (54.72)	2.35	56.93	59.13	54.73	8.89
Low	1,538 (40.98)	121 (40.74)	1,417 (41.00)	−0.53	39.05	37.09	41.02	−8.06
Unknown	158 (4.21)	10 (3.37)	148 (4.28)	−4.75	4.02	3.78	4.25	−2.39
Facility type								
Academic	1,320 (35.17)	132 (44.44)	1,188 (34.38)	20.70	33.77	32.39	35.15	−5.84
Nonacademic	2,425 (65.61)	165 (55.56)	2,260 (65.39)	−20.21	66.23	67.61	64.85	5.84
Unknown	8 (0.21)	0 (0.00)	8 (0.23)	−6.79	—	—	—	—
Facility location								
East	1,642 (43.75)	138 (46.46)	1,504 (43.52)	5.91	44.51	45.05	43.97	2.17
Center	1,480 (39.44)	119 (40.07)	1,361 (39.38)	1.41	38.67	37.98	39.36	2.83
West	631 (16.81)	40 (13.47)	591 (17.10)	−10.10	16.82	16.96	16.67	0.77
County type								
Metropolitan	2,961 (78.90)	239 (80.47)	2,722 (78.76)	4.25	78.97	79.12	78.83	0.71
Urban	518 (13.80)	40 (13.47)	478 (13.83)	−1.05	13.95	14.07	13.83	0.69
Rural	70 (1.87)	3 (1.01)	67 (1.94)	−7.72	1.64	1.40	1.88	−3.78
Unknown	204 (5.44)	15 (5.05)	189 (5.47)	−1.88	5.43	5.41	5.46	−0.22
Clinical T stage								
≤ cT2	1,645 (43.83)	101 (34.01)	1,544 (44.68)	−21.97	43.97	44.10	43.84	0.52
≥ cT3	1,182 (31.49)	125 (42.09)	1,057 (30.58)	24.10	30.88	30.24	31.52	−2.77
Unknown	926 (24.67)	71 (23.91)	855 (24.74)	−1.93	25.15	25.66	24.64	2.35
Clinical N stage								
cN0	1,286 (34.27)	111 (37.37)	1,175 (34.00)	7.04	33.21	32.07	34.34	−4.82
cN+	1,307 (34.83)	113 (38.05)	1,194 (34.55)	7.28	34.95	35.03	34.88	0.31
Unknown	1,160 (30.91)	73 (24.58)	1,087 (31.45)	−15.34	31.84	32.90	30.78	4.55

Abbreviations: LT, local treatment; SD, standard deviation.

60.98 months (IQR, 35.35 to 96.33 months). In multivariable Cox regression analyses, high-intensity LT (HR, 0.61; 95% CI, 0.53 to 0.70; $P < .001$) was associated with a significant OS benefit. Other factors associated with OS in multivariable Cox regression analyses are shown in Table 2. In particular, locally advanced primary tumor (≥ cT3) was an independent predictor of decreased OS (HR, 1.15; 95% CI, 1.06 to 1.25; $P < .001$).

Predictors of Receiving High-Intensity LT

In multivariable logistic regression analysis, the independent predictors associated with the receipt of high-intensity LT were age at initial diagnosis (OR, 0.98; 95% CI, 0.97 to 0.99; $P = .001$), race (black versus white: OR, 0.56; 95% CI, 0.33 to 0.94; $P = .028$), facility type (nonacademic versus academic cancer center: OR, 0.68; 95% CI, 0.53 to 0.87; $P = .003$), and clinical T stage (≥ cT3 versus ≤ cT2: OR, 1.96; 95% CI, 1.48 to 2.60; $P < .001$; Table 3).

Table 2. Multivariable Cox Regression Model That Predicts Overall Survival in the Unweighted Study Population of Patients Treated With Multiagent Chemotherapy for Metastatic Urothelial Carcinoma of the Bladder

Variable	Hazard Ratio (95% CI)	*P*
Age at initial diagnosis	1.00 (0.99 to 1.01)	.324
Sex		
Male	1.00 (reference)	
Female	0.99 (0.93 to 1.08)	.971
Race		
White	1.00 (reference)	
Black	1.12 (0.98 to 1.27)	.091
Other	0.86 (0.68 to 1.09)	.203
Unknown	1.27 (0.85 to 1.90)	.251
Charlson comorbidity index		
0	1.00 (reference)	
1	1.13 (1.02 to 1.26)	**.017**
≥ 2	1.32 (1.12 to 1.56)	**.001**
Unknown	1.08 (0.99 to 1.18)	.060
Insurance type		
Private	1.00 (reference)	
Government	1.08 (0.99 to 1.17)	.080
No insurance	1.32 (1.12 to 1.56)	**.001**
Unknown	0.95 (0.76 to 1.19)	.672
Income level		
High	1.00 (reference)	
Low	1.09 (1.00 to 1.19)	**.039**
Unknown	1.35 (0.34 to 5.42)	.674
Education level		
High	1.00 (reference)	
Low	0.95 (0.88 to 1.03)	.234
Unknown	1.05 (0.25 to 4.35)	.947
Facility type		
Academic	1.00 (reference)	
Nonacademic	1.10 (1.02 to 1.18)	**.011**
Unknown	1.08 (0.51 to 2.26)	.849
Facility location		
East	1.00 (reference)	
Center	1.01 (0.93 to 1.09)	.896
West	0.99 (0.90 to 1.10)	.905
County type		
Metropolitan	1.00 (reference)	
Urban	0.98 (0.89 to 1.09)	.769
Rural	1.08 (0.84 to 1.39)	.536
Unknown	0.79 (0.61 to 1.02)	.068
Clinical T stage		
≤ cT2	1.00 (reference)	
≥ cT3	1.15 (1.06 to 1.25)	**< .001**
Unknown	1.05 (0.96 to 1.15)	.260
Clinical N stage		
cN0	1.00 (reference)	
cN+	0.98 (0.90 to 1.06)	.555
Unknown	1.20 (1.09 to 1.30)	**< .001**
Local treatment		
Conservative	1.00 (reference)	
High intensity	0.61 (0.53 to 0.70)	**< .001**

NOTE. Boldface indicates significance at $P < .05$.

Table 3. Multivariable Logistic Regression Model That Predicts the Receipt of High-Intensity Local Treatment for Metastatic Urothelial Carcinoma of the Bladder in the Unweighted Study Population

Variable	Odds Ratio (95% CI)	*P*
Age at initial diagnosis	0.98 (0.97 to 0.99)	**.001**
Sex		
Male	1.00 (reference)	
Female	1.06 (0.81 to 1.39)	.680
Race		
White	1.00 (reference)	
Black	0.56 (0.33 to 0.94)	**.028**
Other	0.76 (0.32 to 1.78)	.523
Unknown	1 (empty)	—
Charlson comorbidity index		
0	1.00 (reference)	
1	1.29 (0.92 to 1.82)	.143
≥ 2	1.46 (0.86 to 2.46)	.157
Unknown	0.60 (0.43 to 0.84)	**.003**
Insurance type		
Private	1.00 (reference)	
Government	0.96 (0.72 to 1.27)	.761
No insurance	0.80 (0.44 to 1.44)	.460
Unknown	0.47 (0.17 to 1.32)	.151
Income level		
High	1.00 (reference)	
Low	0.97 (0.72 to 1.31)	.850
Unknown	3.80e-06 (0 to .)	.990
Education level		
High	1.00 (reference)	
Low	0.99 (0.74 to 1.33)	.967
Unknown	152258 (0 to .)	.990
Facility type		
Academic	1.00 (reference)	
Nonacademic	0.68 (0.53 to 0.87)	**.003**
Unknown	1 (empty)	—
Facility location		
East	1.00 (reference)	
Center	0.98 (0.75 to 1.28)	.910
West	0.79 (0.55 to 1.15)	.227
County type		
Metropolitan	1.00 (reference)	
Urban	0.96 (0.66 to 1.39)	.827
Rural	0.53 (0.16 to 1.74)	.299
Unknown	1.29 (0.54 to 3.08)	.573
Clinical T stage		
≤ cT2	1.00 (reference)	
≥ cT3	1.96 (1.48 to 2.60)	**< .001**
Unknown	1.44 (1.03 to 2.01)	**.030**
Clinical N stage		
cN0	1.00 (reference)	
cN+	0.85 (0.64 to 1.13)	.275
Unknown	0.74 (0.53 to 1.03)	.071

NOTE. Boldface indicates significance at $P < .05$.

The odds of receiving high-intensity LT significantly increased over time (OR, 1.06; 95% CI, 1.03 to 1.09; $P < .001$; Appendix Fig A1, online only).

Patient Characteristics and High-Intensity LT Effect in the Weighted Population

After IPTW adjustment, all standardized differences of weighted comparisons were < 10%, which indicated that the distribution of baseline patient and tumor characteristics was similar between the high-intensity and conservative LT groups (Table 1). The effect of IPTW adjustment on baseline characteristic distribution is depicted in Appendix Figure A2 (online only).

The median follow-up in the weighted population was 64.72 months (IQR, 37.59 to 117.75 months). IPTW-adjusted Kaplan-Meier curves (Fig 2) show that median OS was significantly longer in the high-intensity LT group versus the conservative LT group (14.92 [IQR, 9.82 to 30.72] *v* 9.95 [IQR, 5.29 to 17.08] months; $P < .001$ by IPTW-adjusted log-rank test). In IPTW-adjusted Cox regression analysis, high-intensity LT was associated with a significant OS benefit (HR, 0.56; 95% CI, 0.48 to 0.65; $P < .001$).

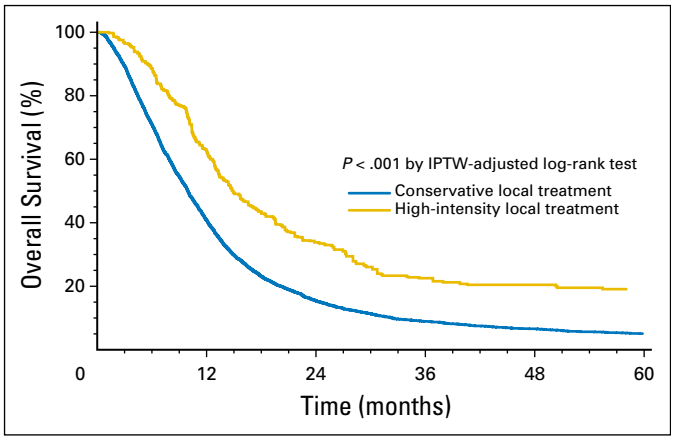

Fig 2. Inverse probability of treatment weighting (IPTW) –adjusted Kaplan-Meier analysis of overall survival in patients who received multiagent systemic chemotherapy combined with high-intensity versus conservative local treatment for metastatic urothelial carcinoma of the bladder.

Sensitivity Analyses

Magnitudes of the joint bounding factor for various combinations of $OR_{LT\text{-}U}$ and $HR_{OS\text{-}U}$ are reported in Appendix Figure A3 (online only). For the OS benefit of high-intensity LT to be explained solely by unmeasured confounders, $OR_{LT\text{-}U}$ and $HR_{OS\text{-}U}$ would need to meet specific estimates where the joint bounding factor would suggest the opposite (red area) or nonsignificant (gold area) treatment effect. Specifically, the odds of receiving high-intensity LT in the presence of a given confounder (eg, nonvisceral *v* visceral metastases) would have to increase with decreasing likelihood of OS in the presence of the same confounder.

Consolidative Versus Cytoreductive Strategy

Start dates of surgery, RT, and chemotherapy were available for 227 (76.43%) patients who received consolidative (n = 108 [47.58%]) or cytoreductive (n = 119 [52.42%]) strategy. For patients who received consolidative strategy, median time from diagnosis to chemotherapy before RC and RT was 34.5 days (IQR, 18.5 to 61.5 days) and 42.0 days (IQR, 29.5 to 62.0 days), respectively. In addition, median time from chemotherapy to RC and RT was 129.0 days (IQR, 100.0 to 166.5 days) and 85.0 days (IQR, 19.0 to 112.0 days), respectively. For patients who received the cytoreductive strategy, median time from diagnosis to RC and RT was 33.5 days (IQR, 13.0 to 58.0 days) and 32.0 days (IQR, 21.0 to 50.0 days), respectively. In addition, median time from RC and RT to chemotherapy was 60.0 days (IQR, 40.0 to 89.0 days) and 7.0 days (IQR, 1.0 to 16.0 days), respectively.

IPTW-adjusted Kaplan-Meier curves (Fig 3) show that median OS was significantly longer in the consolidative strategy group than in the high-intensity LT group (17.71 [IQR, 10.41 to not estimable] *v* 12.42 [IQR, 7.06 to 20.37] months; $P < .001$ by IPTW-adjusted log-rank test). In IPTW-adjusted Cox regression analysis, consolidative strategy was associated with a significant OS benefit (HR, 0.52; 95% CI, 0.38 to 0.73; $P < .001$).

DISCUSSION

Increasing evidence suggests or supports the use of aggressive or high-intensity LT for metastatic solid organ malignancies, yet no study has comprehensively examined the survival benefit of this approach in the context of mUCB. Given the lack of improvement in mUCB mortality rates over the past decade, we assessed the potential benefit of high-intensity LT in these patients. With a median follow-up of approximately 60 months, we found a significant benefit for high-intensity LT in IPTW-adjusted analyses. Specifically, individuals who received high-intensity LT were nearly one-half as likely to die after presentation with mUCB, which translates to a 5-month OS benefit. Previous reports have documented the outcomes of palliative RC or RT to control local symptoms,[19-22] whereas others have demonstrated the relative benefit of high-intensity LT for individuals with pelvic or, occasionally, lumboaortic nodal metastases at diagnosis.[23-26] However, to our knowledge, the present study constitutes the first sizeable comparative effectiveness assessment of the impact of high-intensity versus conservative LT in patients with distant metastases at initial diagnosis.

The seed-and-soil theory provides a biologic rationale for high-intensity LT of the primary tumor in patients with mUCB at presentation.[6] According to this theory, soluble growth factors produced by the primary tumor may promote clustering of hematopoietic progenitor cells and macrophages to create an environment conducive to dissemination of malignant clones and formation of metastases.[27,28] Under such assumption, the development of new metastases depends on an intact primary lesion; consequently, high-intensity LT that targets the index lesion would presumably affect metastatic progression and cancer death. Of note, in multivariable Cox regression analyses, we found that higher T stage (≥ cT3) is associated with worse OS, even in the presence of mUCB. These results suggest that the burden of primary disease continues to play an important role, even when the cancer has already spread throughout the body.

Regardless, the concept of cytoreduction or treatment of the primary site before delivering systemic therapy is a mainstay of management for several metastatic urologic malignancies. For example, on the basis of data from the immunotherapy era,[7,8] patients with metastatic renal cell carcinoma and excellent functional status are recommended to undergo immediate

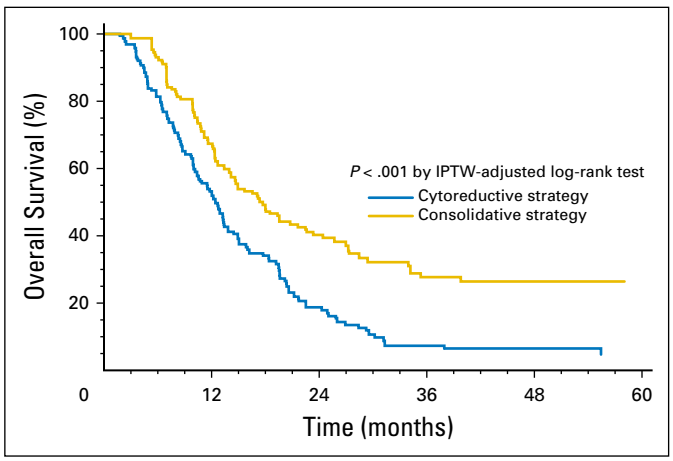

Fig 3. Inverse probability of treatment weighting (IPTW) –adjusted Kaplan-Meier analysis of overall survival in patients who received consolidative versus cytoreductive local treatment strategy for metastatic urothelial carcinoma of the bladder.

cytoreductive nephrectomy before the administration of vascular endothelial growth factor inhibitors.[29] In addition, preliminary data have suggested the feasibility[30] and potential benefit[11] of upfront radical prostatectomy associated with systemic treatment of metastatic prostate cancer, although this remains an uncommon practice. Examples of such practices also exist outside urologic oncology; notably, a meta-analysis of 6,885 women with advanced ovarian carcinoma found an OS benefit of nearly 12 months in those treated with $>$ 75% versus $<$ 25% maximal cytoreductive surgery.[5] Similarly, the OS of patients with colorectal cancer and peritoneal carcinomatosis who received cytoreduction followed by hyperthermic intraperitoneal and systemic chemotherapy was prolonged by approximately 10 months compared with those treated with systemic chemotherapy only.[31] The alternative concept of consolidative surgery or RT after clinical response to induction chemotherapy has also been reported for metastatic solid malignancies. Specifically, patients with advanced-stage small-cell carcinoma of the lung who received thoracic RT after responding to upfront chemotherapy were demonstrated to be 0.84-fold less likely to die than those treated with systemic chemotherapy alone.[32] Of note, our exploratory analysis showed that patients treated with the consolidative strategy were almost one-half as likely to die after presentation with mUCB compared with those treated with the cytoreductive strategy.

The present findings need to be interpreted within the limitations of the observational study design. The analyses are subject to selection bias, which we attempted to correct by using propensity scores to approximate randomization. However, we cannot account for many unmeasured confounders, particularly the severity and burden of disease. Although we know that all selected patients had metastatic disease at presentation, one would expect a patient with a single resectable nonvisceral metastasis to evolve differently from a patient with disseminated disease throughout the body. As such, prospective trials designed to address the present findings should focus on select groups of individuals with mUCB, for example, patients with oligometastatic disease and, preferentially, those with isolated extrapelvic lymph node involvement.

Other potential confounders include body mass index as well as renal function and cardiovascular disease (which may preclude the use of life-prolonging systemic treatments), although the present results were adjusted for Charlson comorbidity index status. Moreover, the NCDB provides little information on the use of systemic treatments after the initial diagnosis period, which would presumably affect survival. In addition, although we selected only patients who received multiagent chemotherapy to prevent the inclusion of those who received single-agent noncisplatin-based chemotherapy, the regimen type remained unknown. However, our sensitivity analyses suggest that it is implausible that the benefit recorded for high-intensity LT is entirely attributable to the aforementioned unmeasured confounders, as under most reasonable scenarios, the OS benefit of high-intensity LT remains statistically significant. Nonetheless, the exploratory analysis comparing the consolidative versus cytoreductive strategy may be subject to additional confounding. For example, selection bias for patients who experienced a favorable clinical response to chemotherapy was likely to exist in the consolidative group.

Finally, the present study focused on OS, but many other important considerations exist when dealing with advanced or metastatic disease (eg, quality of life). Although high-intensity LT may improve OS, one must weigh the potential harms of aggressive management to tailor treatments to the individual patient. Whereas the short-term morbidity of pelvic RT may be acceptable from a quality-of-life perspective,[33] complications after RC may be life threatening or at the very least, distressful. That said, local progression of mUCB left untreated is associated with undesirable symptoms, such as pain and hematuria, that can markedly affect quality of life.[34]

To summarize, we report a net OS benefit for individuals with mUCB treated with high-intensity LT (ie, aggressive treatment of the primary tumor burden in the setting of metastatic disease) relative to their counterparts treated with conservative LT. Although the findings are subject to the usual biases related to the observational study design, these preliminary data warrant RCTs to explore this question, particularly given the poor prognosis associated with mUCB.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Thomas Seisen, Maxine Sun, Jeffrey J. Leow, Alexander P. Cole, Francisco Gelpi-Hammerschmidt, Nawar Hanna, Joaquim Bellmunt, Toni K. Choueiri, Quoc-Dien Trinh
Financial support: Toni K. Choueiri
Administrative support: Toni K. Choueiri
Collection and assembly of data: Thomas Seisen, Maxine Sun, Jeffrey J. Leow, Francisco Gelpi-Hammerschmidt, Christian P. Meyer, Quoc-Dien Trinh
Data analysis and interpretation: Thomas Seisen, Maxine Sun, Jeffrey J. Leow, Mark A. Preston, Alexander P. Cole, Francisco Gelpi-Hammerschmidt, Nawar Hanna, Adam S. Kibel, Stuart R. Lipsitz, Paul L. Nguyen, Joaquim Bellmunt, Toni K. Choueiri, Quoc-Dien Trinh
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2015. CA Cancer J Clin 65:5-29, 2015
2. Cancer Genome Atlas Research Network: Comprehensive molecular characterization of urothelial bladder carcinoma. Nature 507:315-322, 2014
3. Powles T, Eder JP, Fine GD, et al: MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature 515: 558-562, 2014
4. Loehrer PJ Sr, Einhorn LH, Elson PJ, et al: A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: A cooperative group study. J Clin Oncol 10:1066-1073, 1992
5. Bristow RE, Tomacruz RS, Armstrong DK, et al: Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: A meta-analysis. J Clin Oncol 20: 1248-1259, 2002
6. Paget S: The distribution of secondary growths in cancer of the breast. 1889. Cancer Metastasis Rev 8:98-101, 1989
7. Roychowdhury DF, Hayden A, Liepa AM: Health-related quality-of-life parameters as independent prognostic factors in advanced or metastatic bladder cancer. J Clin Oncol 21:673-678, 2003

8. Flanigan RC, Salmon SE, Blumenstein BA, et al: Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. N Engl J Med 345:1655-1659, 2001

9. Mickisch GH, Garin A, van Poppel H, et al: Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: A randomised trial. Lancet 358:966-970, 2001

10. Choueiri TK, Xie W, Kollmannsberger C, et al: The impact of cytoreductive nephrectomy on survival of patients with metastatic renal cell carcinoma receiving vascular endothelial growth factor targeted therapy. J Urol 185:60-66, 2011

11. Culp SH, Schellhammer PF, Williams MB: Might men diagnosed with metastatic prostate cancer benefit from definitive treatment of the primary tumor? A SEER-based study. Eur Urol 65: 1058-1066, 2014

12. American College of Surgeons: Facility Oncology Registry Data Standards (FORDS): Revised for 2016. www.facs.org/cancer/coc/fordsmanual.html

13. Gray PJ, Fedewa SA, Shipley WU, et al: Use of potentially curative therapies for muscle-invasive bladder cancer in the United States: Results from the National Cancer Data Base. Eur Urol 63:823-829, 2013

14. Austin PC: Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 28:3083-3107, 2009

15. Lemeshow S, Hosmer DW Jr: A review of goodness of fit statistics for use in the development of logistic regression models. Am J Epidemiol 115: 92-106, 1982

16. Austin PC: The use of propensity score methods with survival or time-to-event outcomes: Reporting measures of effect similar to those used in randomized experiments. Stat Med 33:1242-1258, 2014

17. Cole SR, Hernán MA: Adjusted survival curves with inverse probability weights. Comput Methods Programs Biomed 75:45-49, 2004

18. Ding P, VanderWeele TJ: Sensitivity analysis without assumptions. Epidemiology 27:368-377, 2016

19. Ghahestani SM, Shakhssalim N: Palliative treatment of intractable hematuria in context of advanced bladder cancer: A systematic review. Urol J 6: 149-156, 2009

20. Ok J-H, Meyers FJ, Evans CP: Medical and surgical palliative care of patients with urological malignancies. J Urol 174:1177-1182, 2005

21. Zebic N, Weinknecht S, Kroepfl D: Radical cystectomy in patients aged > or = 75 years: An updated review of patients treated with curative and palliative intent. BJU Int 95:1211-1214, 2005

22. Konski A, Feigenberg S, Chow E: Palliative radiation therapy. Semin Oncol 32:156-164, 2005

23. Dodd PM, McCaffrey JA, Herr H, et al: Outcome of postchemotherapy surgery after treatment with methotrexate, vinblastine, doxorubicin, and cisplatin in patients with unresectable or metastatic transitional cell carcinoma. J Clin Oncol 17: 2546-2552, 1999

24. Herr HW, Donat SM, Bajorin DF: Post-chemotherapy surgery in patients with unresectable or regionally metastatic bladder cancer. J Urol 165:811-814, 2001

25. de Vries RR, Nieuwenhuijzen JA, Meinhardt W, et al: Long-term survival after combined modality treatment in metastatic bladder cancer patients presenting with supra-regional tumor positive lymph nodes only. Eur J Surg Oncol 35:352-355, 2009

26. Ho PL, Willis DL, Patil J, et al: Outcome of patients with clinically node-positive bladder cancer undergoing consolidative surgery after preoperative chemotherapy: The M.D. Anderson Cancer Center Experience. Urol Oncol 34:59.e1-59.e8, 2016

27. Kaplan RN, Psaila B, Lyden D: Bone marrow cells in the 'pre-metastatic niche': Within bone and beyond. Cancer Metastasis Rev 25:521-529, 2006

28. Hiratsuka S, Watanabe A, Aburatani H, et al: Tumour-mediated upregulation of chemoattractants and recruitment of myeloid cells predetermines lung metastasis. Nat Cell Biol 8:1369-1375, 2006

29. Heng DYC, Wells JC, Rini BI, et al: Cytoreductive nephrectomy in patients with synchronous metastases from renal cell carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium. Eur Urol 66:704-710, 2014

30. Sooriakumaran P, Karnes J, Stief C, et al: A multi-institutional analysis of perioperative outcomes in 106 men who underwent radical prostatectomy for distant metastatic prostate cancer at presentation. Eur Urol10.1016/j.eururo.2015.05.023 [epub ahead of print on May 30, 2015]

31. Verwaal VJ, van Ruth S, de Bree E, et al: Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol 21:3737-3743, 2003

32. Slotman BJ, van Tinteren H, Praag JO, et al: Use of thoracic radiotherapy for extensive stage small-cell lung cancer: A phase 3 randomised controlled trial. Lancet 385:36-42, 2015

33. James ND, Hussain SA, Hall E, et al: Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. N Engl J Med 366: 1477-1488, 2012

34. Lodde M, Palermo S, Comploj E, et al: Four years experience in bladder preserving management for muscle invasive bladder cancer. Eur Urol 47: 773-778, 2005; discussion 778-779

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Efficacy of High-Intensity Local Treatment for Metastatic Urothelial Carcinoma of the Bladder: A Propensity Score–Weighted Analysis From the National Cancer Data Base

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

Thomas Seisen
No relationship to disclose

Maxine Sun
No relationship to disclose

Jeffrey J. Leow
No relationship to disclose

Mark A. Preston
No relationship to disclose

Alexander P. Cole
No relationship to disclose

Francisco Gelpi-Hammerschmidt
No relationship to disclose

Nawar Hanna
No relationship to disclose

Christian P. Meyer
Travel, Accommodations, Expenses: Olympus

Adam S. Kibel
Consulting or Advisory Role: Dendreon, Sanofi, Tokai Pharmaceuticals, MTG Biotherapeutics, Profound Medical

Stuart R. Lipsitz
No relationship to disclose

Paul L. Nguyen
Consulting or Advisory Role: Medivation, Abbott Laboratories (I), GenomeDx, Ferring Pharmaceuticals, Nanobiotix
Patents, Royalties, Other Intellectual Property: Patent on volatile diagnostics of infections (I)

Joaquim Bellmunt
Consulting or Advisory Role: Pierre Fabre, Astellas Pharma, Pfizer, Merck, Genentech
Research Funding: Millennium Pharmaceuticals (Inst), Sanofi (Inst)
Travel, Accommodations, Expenses: Pfizer, MSD Oncology

Toni K. Choueiri
Honoraria: National Comprehensive Cancer Network, UpToDate
Consulting or Advisory Role: Pfizer, Bayer AG, Novartis, GlaxoSmithKline, Merck, Bristol-Myers Squibb, Genentech, Eisai, Prometheus Labs, Foundation Medicine
Research Funding: Pfizer (Inst), Novartis (Inst), Merck (Inst), Exelixis (Inst), TRACON Pharmaceuticals (Inst), GlaxoSmithKline (Inst), Bristol-Myers Squibb (Inst), AstraZeneca (Inst), Peloton Therapeutics (Inst), Genentech (Inst)

Quoc-Dien Trinh
Honoraria: Intuitive Surgical

Appendix

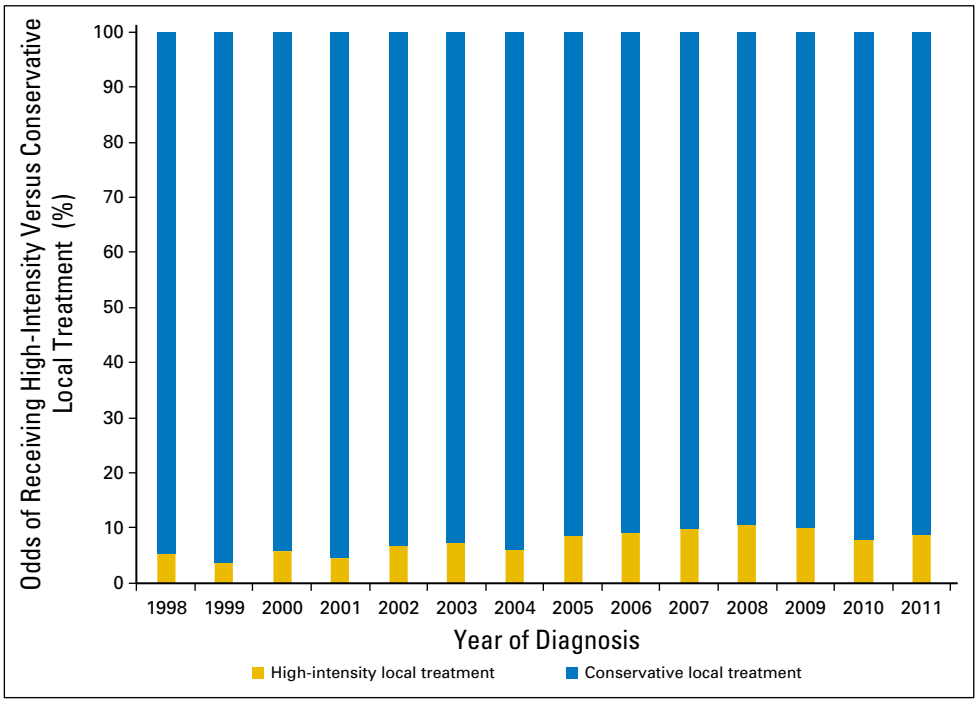

Fig A1. Odds of receiving high-intensity local treatment combined with multiagent systemic chemotherapy for metastatic urothelial carcinoma of the bladder over time in the unweighted study population.

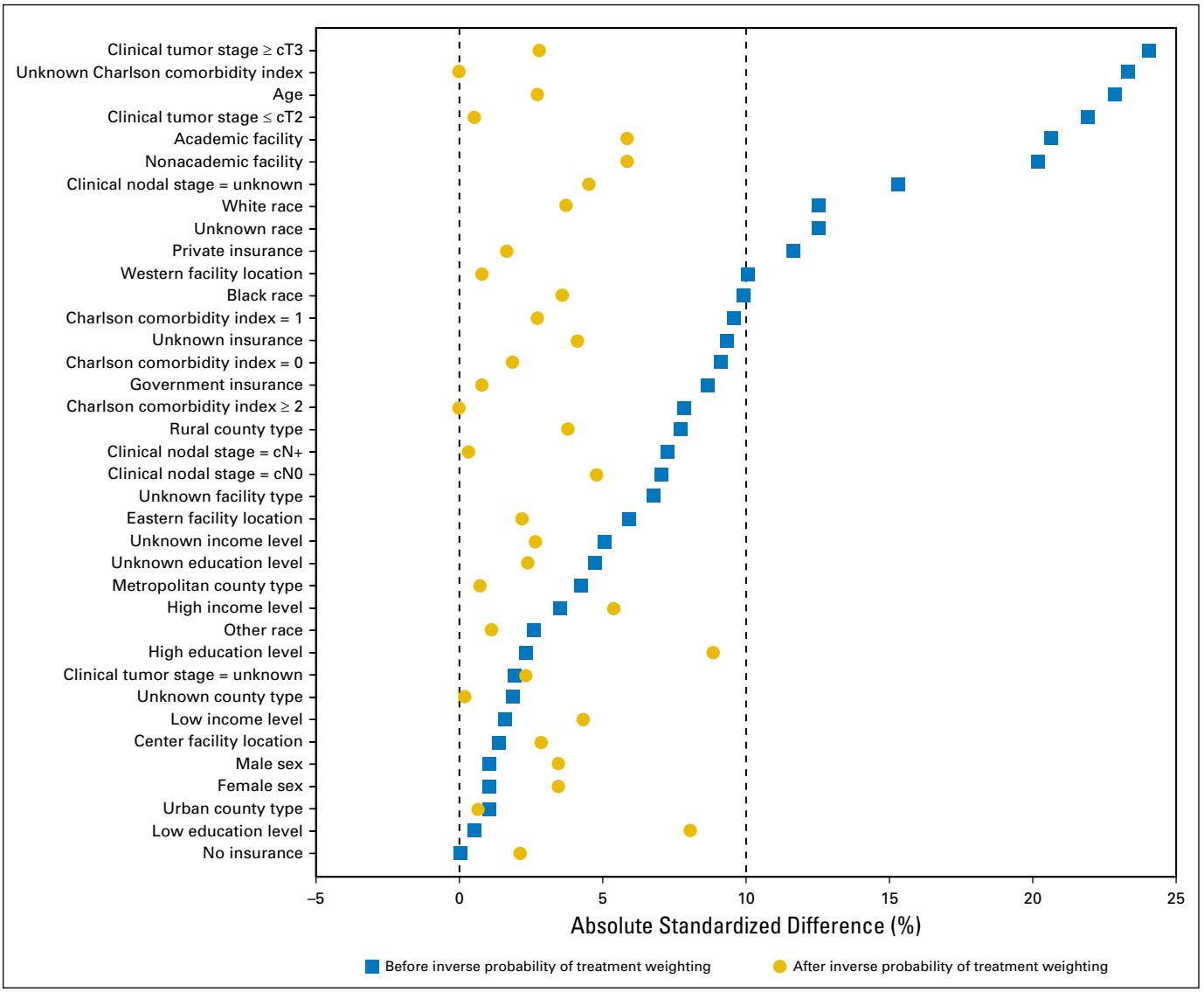

Fig A2. Effect of inverse probability of treatment weighting adjustment on the baseline characteristics distribution of patients who received multiagent systemic chemotherapy combined with high-intensity versus conservative local treatment for metastatic urothelial carcinoma of the bladder.

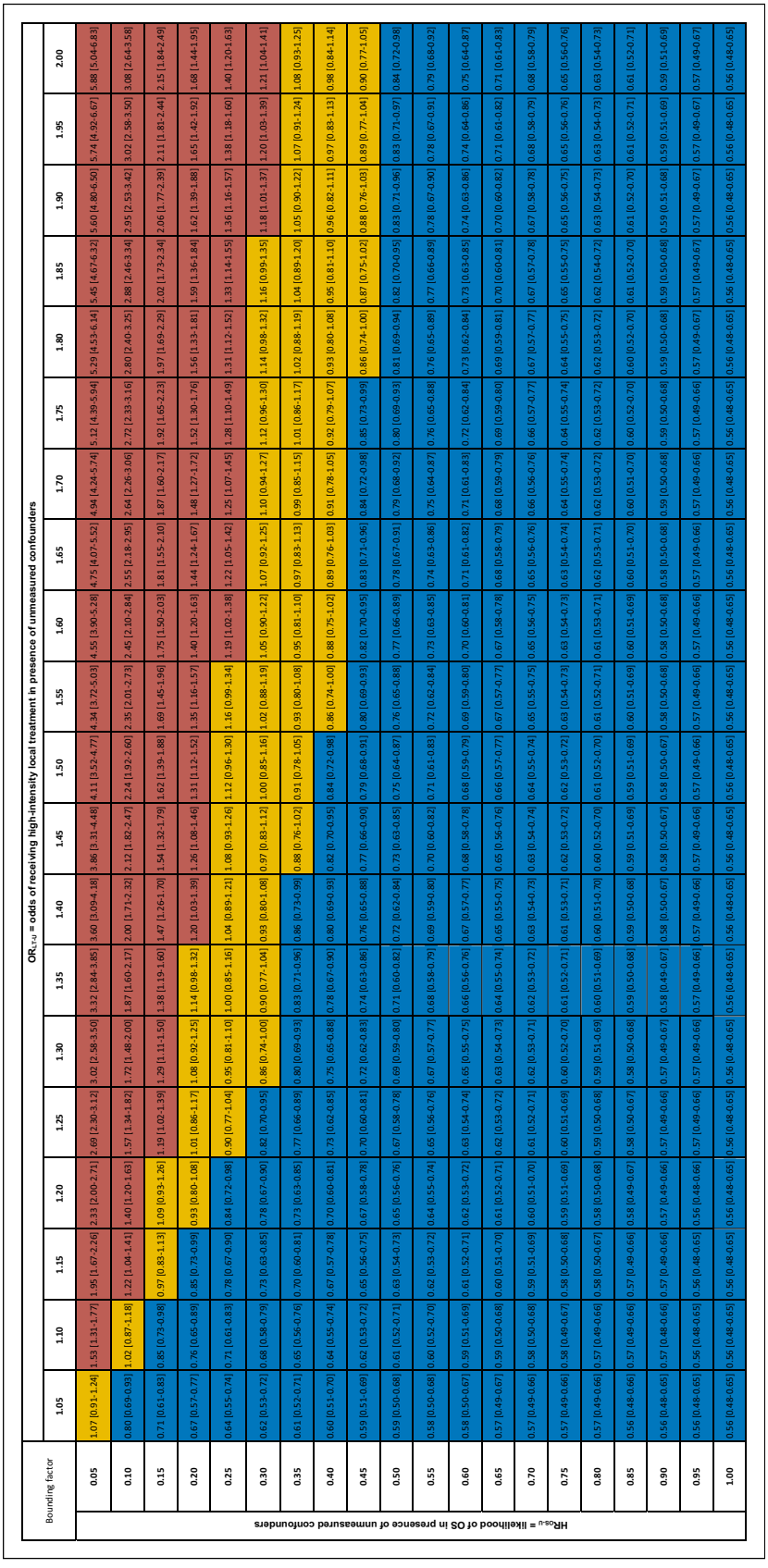

Fig A3. Magnitudes of the joint bounding factor for various combinations of the odds of receiving high-intensity local treatment (OR_{LT-U}) and likelihood of overall survival (HR_{OS-U}), in the presence of unmeasured confounders. Blue, gold, and red areas correspond to a joint bounding factor suggestive of significant, nonsignificant, and opposite treatment effect, respectively.