

Regional differences in metastatic urothelial carcinoma of the urinary bladder patients across the United States SEER registries

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ABSTRACT

INTRODUCTION: Despite advances in treatment, metastatic urothelial carcinoma of the urinary bladder (mUCUB) is associated with high mortality and treatment risk. We tested for regional differences in mUCUB within a large-scale, population-based database.

METHODS: Using the Surveillance, Epidemiology and End Results (SEER) database (2010–2018), patient (age, sex, race/ethnicity), tumor (T-stage, N-stage, number of metastatic sites), and treatment (systemic therapy, radical cystectomy) characteristics were tabulated for mUCUB patients according to 11 SEER registries. Multinomial regression models and multivariable Cox regression models tested overall mortality (OM), adjusting for patient, tumor, and treatment characteristics.

RESULTS: In 4817 mUCUB patients, registry-specific patient counts ranged from 1855 (38.5%) to 105 (2.2%). Important inter-regional differences existed for race/ethnicity (3–36% for others than non-Hispanic Whites), N-stage (28–39% for N1–3, 44–58% for N0, 8–22% for unknown N-stage), systemic therapy (38–54%), and radical cystectomy (3–11%). In multivariable analyses adjusting for these patient, tumor, and treatment characteristics, one registry exhibited significantly lower OM (SEER registry 10: hazard ratio [HR] 0.83) and two other registries exhibited significantly higher OM (SEER registry 9: HR 1.13; SEER registry 8: HR 1.24) relative to the largest reference registry (n=1855).

CONCLUSIONS: We identified important regional differences that included patient, tumor, and treatment characteristics. Even after adjustment for these characteristics, important OM differences persisted, which may warrant more detailed investigation.

INTRODUCTION

Despite advances in treatment, metastatic urothelial carcinoma of the urinary bladder (mUCUB) is associated with high mortality and treatment risk.^{1–3} Large-scale studies examining practice patterns and patient case mix have not been addressed in mUCUB.^{4–6} Specifically, it is unknown whether, in mUCUB patients, regional differences in patient, tumor, and treatment characteristics may result in regional overall mortality (OM) differences. We addressed these knowledge gaps and tested for inter-regional differences of mUCUB patients, according to the Surveillance, Epidemiology, and End Results (SEER) geographic registries. We hypothesized that higher than expected OM rates may be identified in select SEER registries, even after adjustment for patient, tumor, and treatment characteristics.

METHODS

Study population

The SEER database approximates U.S. demographic composition and cancer incidence by collecting incidence and survival data from population-based cancer registries. Specifically, U.S. death data are provided from the National Center of Health Statistics (NCHS) to the SEER database, including cause of death. Within the SEER database (2010–2018), we identified patients aged ≥ 18 years, with histologically confirmed mUCUB (International Classification of Disease for Oncology [ICD-O] site codes C67.0–C67.9). Autopsy-only and death certificate-only cases were

excluded as reporting sources. The currently used SEER database is divided into 13 geographic registries. SEER registries with less than 100 cases (n=2) were excluded from the analyses. These selection criteria resulted in an overall cohort of 4817 assessable patients within 11 SEER registries, namely from SEER Registry 1 to SEER Registry 11 in ascending order of patient count. Death was defined according to the SEER mortality codes.⁷

Statistical analyses

Descriptive statistics included frequencies and proportions for categorical variables. Medians and interquartile ranges (IQR) were reported for continuously coded variables. Kruskal-Wallis rank sum and Pearson Chi-squared tested for statistical significant differences in medians and proportions, respectively.

Statistical analyses relied on three steps. First, baseline patient (age at initial diagnosis, sex, race/ethnicity) and tumor (tumor stage [T-stage], nodal stage [N-stage], and number of metastatic sites) characteristics were tabulated and graphically displayed, according to SEER registries. Second, we tabulated rates of systematic therapy and radical cystectomy before and after multivariable adjustment for year of diagnosis, age, sex, race/ethnicity, T-stage, N-stage, and number of metastatic sites using multinomial regression models. Here, a predicted treatment probability was calculated for each patient. Additionally, treatment rates were displayed focusing on the two largest registries (SEER Registries 10 and 11) that accounted for more than 50% of the study population, as well as on the nine smaller registries (SEER Registries 1–9) separately. Finally, unadjusted and adjusted OM hazard ratios (HR) were computed for each SEER registry. Adjustment variables consisted of year of diagnosis, baseline patient (age at initial diagnosis, sex, race/ethnicity), tumor (T-stage, N-stage, and number of metastatic sites) and treatment (systemic therapy, radical cystectomy) characteristics. All tests were two-sided, with a level of significance set at $p < 0.05$; R software environment for statistical computing and graphics (version 4.1.2) was used for all analyses.⁸ Owing to the anonymously coded design of the SEER database, study-specific ethics approval was waived by the institutional review board.

RESULTS

Descriptive characteristics

Overall, 4817 mUCUB patients were identified. Median age at initial diagnosis was 72 years (IQR 63–80), 28% were female, and 21% were of race/ethnicity other than

non-Hispanic Whites. According to T-stage, mUCUB patients were distributed as follows: 54% organ-confined (n=2621) vs. 24% non-organ-confined (n=1159) vs. 22% unknown (n=1037). N-stage distribution was as follows: 52% N0 (n=2487) vs. 34% N1–3 (n=1659) vs. 14% unknown N-stage (n=671). According to number of metastatic sites, mUCUB patients were distributed as follows: 51% one site (n=2456) vs. 15% two sites (n=720) vs. 4% ≥ 3 sites (n=188) vs. 30% unknown (n=1453). The rate of systemic therapy was 47% (n=2276), and 8% underwent radical cystectomy (n=386) (Table 1).

Table 1. Descriptive characteristics of 4817 metastatic urothelial carcinoma of the urinary bladder (mUCUB) patients within the Surveillance, Epidemiology, and End Results (SEER) database, 2010–2018

Characteristics	mUCUB, N=4817
Age at diagnosis	72 (63, 80)
Female sex	1357 (28%)
Race/ethnicity	
Non-Hispanic Whites	3782 (79%)
Others	1035 (21%)
T-stage	
Organ-confined	2621 (54%)
Non-organ-confined	1159 (24%)
TX	1037 (22%)
N-stage	
N0	2487 (52%)
N1–3	1659 (34%)
NX	671 (14%)
Number of metastatic sites	
1	2456 (51%)
2	720 (15%)
≥ 3	188 (4%)
Unknown	1453 (30%)
Type of treatment	
Systematic therapy	2276 (47%)
Radical cystectomy	386 (8%)

Data shown as median (interquartile range) or n (%), as appropriate.

Differences in patient and tumor characteristics across SEER registries

Registry-specific patient counts ranged from 105 (2.2%) in SEER Registry 1 to 1855 (38.4%) in SEER Registry 11 (Figure 1). Median age at initial diagnosis ranged from 70 years (SEER Registry 4) to 74 years (SEER Registry 2; $p=0.4$) (Figure 2A). The proportion of females ranged from 25% (SEER Registry 5) to 35% (SEER Registry 2; $p=0.3$) (Figure 2B). The proportion of race/ethnicity other than non-Hispanic White ranged from 3% (SEER Registry 3) to 36% (SEER Registry 2; $p<0.001$) (Figure 2C).

In 4817 mUCUB patients, the proportion of non-organ-confined stage ranged from 19% (SEER Registry 5) to 28% (SEER Registry 4) vs. 51% (SEER Registry 8) to 58% (SEER Registries 7 and 8) for organ-confined stage vs. 16% (SEER Registry 3) to 25% (SEER Registries 2 and 5) for unknown T-stage ($p=0.2$) (Figure 3A). Regarding N-stage, the proportions of N1–3 ranged from 28% (SEER Registry 2) to 39% (SEER Registry 1) vs. 44% (SEER Registry 5) to 58% (SEER Registries 8) for N0 vs. 8% (SEER Registry 8) to 22% (SEER Registry 5) for unknown N-stage ($p<0.001$) (Figure 3B).

Within 4817 mUCUB patients, the rate of individuals with one metastatic site ranged from 47% (SEER Registry 7) to 61% (SEER Registries 6) vs. 10% (SEER Registry 6) to 18% (SEER Registries 1 and 8) for two metastatic sites vs. 3% (SEER Registries 1, 2, 4, and 6) to 5% (SEER Registry 7) for ≥ 3 metastatic sites vs. 25% (SEER Registry 2) to 34% (SEER Registries 3 and

4) for unknown numbers of metastatic sites ($p=0.4$) (Figure 3C).

Unadjusted and adjusted differences in systemic therapy and radical cystectomy rates across SEER registries

The rates of systemic therapy ranged from 38% (SEER Registry 2) to 54% (SEER Registry 3, $p=0.002$). After multivariable adjustment, inter-regional differences in systemic therapy persisted (37–54%). When focusing on the two largest registries (SEER Registries 10 and 11), systematic therapy rates ranged from 45–48% ($\Delta=3\%$). In the nine remaining smaller registries (SEER Registries 1–9), systematic therapy rates ranged from 37–54% ($D=17\%$) (Figure 4A).

The rates of radical cystectomy ranged from 3% (SEER Registry 2) to 11% (SEER Registry 4, $p<0.001$). After multivariable adjustment, inter-regional differences in radical cystectomy persisted (3–11%). When focusing on the two largest registries (SEER Registries 10 and 11), radical cystectomy rates ranged from 7–10% ($\Delta=3\%$). In the nine remaining smaller registries (SEER Registries 1–9), radical cystectomy rates ranged from 3–11% ($\Delta=8\%$) (Figure 4B).

Overall mortality, unadjusted and adjusted differences in overall mortality rates across SEER registries

Two-year OM rate was 87% for all 4817 mUCUB patients (Figure 5). Two-year registry-specific OM rates ranged from 82–91%. Focusing on the two largest registries, two-year OM rates ranged from 85–87% ($\Delta=2\%$). In the nine remaining smaller registries, two-year OM rates ranged from 82–91% ($D=9\%$). Unadjusted HR predicting OM ranged from 0.98–1.26, relative to SEER Registry 11. Two registries exhibited statistically higher unadjusted HR: SEER Registry 9 (HR 1.11) and SEER Registry 8 (HR 1.26). Finally, multivariable adjusted HR predicting OM ranged from 0.83–1.24. Three registries were statistically significantly different from SEER registry of reference (SEER Registry 11, HR 1.0) regarding HR predicting OM. Specifically, multivariable adjusted HR in SEER Registry 10 was 0.83 ($p<0.001$), in SEER Registry 9 was 1.13 ($p=0.02$), and in SEER Registry 8 was 1.24 ($p=0.002$) (Table 2).

DISCUSSION

It is unknown whether, in mUCUB patients, regional differences regarding patient, tumor, and treatment characteristics exist and potentially even contribute to inter-regional OM differences. We hypothesized that

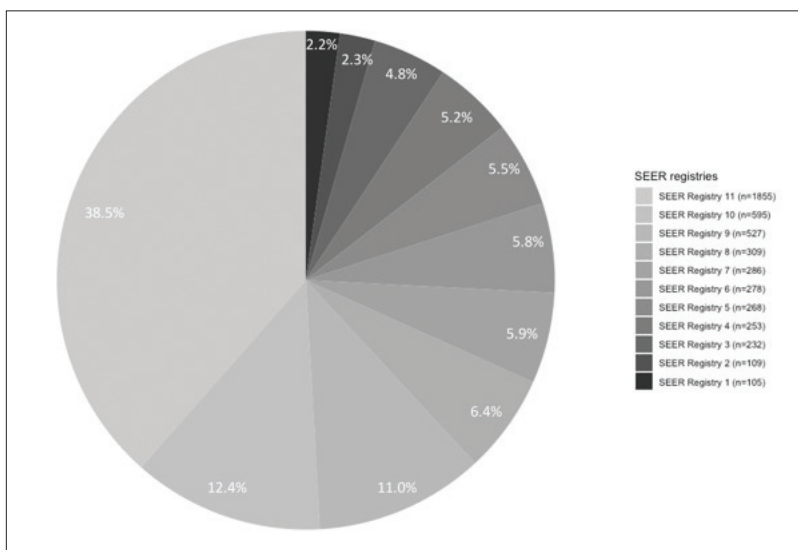


Figure 1. Pie chart depicting the distribution of metastatic urothelial carcinoma of the urinary bladder patients, according to Surveillance, Epidemiology, and End Results (SEER) 2010–2018 geographic registries across the U.S.

higher than expected OM rates may be identified in select SEER registries, even after adjustment for patient, tumor, and treatment characteristics. We tested this hypothesis within the SEER 2010–2018 database and made several important observations.

First, we recorded important inter-regional differences in patient characteristics between the SEER registries. Specifically, the proportion of race/ethnicity other than non-Hispanic White was 21% overall and ranged from 3–36% ($p < 0.001$). This wide distribution of race/ethnicity other than non-Hispanic White is difficult to interpret. It may be predominantly related to race/ethnicity composition of different SEER registries. Despite important inter-regional differences in race/ethnicity, no meaningful differences in median age (overall 72 years, range 70–74 years, $p = 0.4$) and female sex (overall 28%, ranged 25–35%, $p = 0.3$) were recorded. Female sex, older age, and race/ethnicity other than non-Hispanic White were previously described as risk factors for unfavorable outcomes in mUCUB patients.^{9–12} Consequently, multivariable adjustment for these baseline patient characteristics is needed when OM rates are examined.

Second, we recorded important inter-regional differences in tumor characteristics between the SEER registries. Specifically, rates of N1–3 stage was 34% overall and ranged from 28–39%, and those of unknown N-stage ranged from 8–22% ($p < 0.001$). Conversely, no meaningful inter-regional differences were recorded in T-stage ($p = 0.2$) and number of metastatic sites ($p = 0.4$). Previous studies reported that presence of N1–3 stage, as well as non-organ-confined tumor and multiple numbers of metastatic sites are associated with higher OM.^{13,14} Therefore, for patient characteristics, adjustment for tumor characteristics is clearly required when OM is interpreted.

Third, overall rate of systemic therapy was 47%. Moreover, we recorded important inter-regional differences in rates of systemic therapy. Specifically, rate of systemic therapy ranged from 38–54% ($\Delta = 16$, $p = 0.002$). This wide rate of systemic therapy across SEER registries persisted even after multivariable adjustment for patient and tumor characteristics (37–54%, $\Delta = 17$). It is of note that inter-regional differences in systemic therapy rates were marginal, at best (45–48%, $\Delta = 3\%$), when the two largest registries were compared (SEER Registries 10 and 11). Conversely, pronounced inter-regional variability was recorded between the nine smaller-sized registries (37–54%, $\Delta = 17\%$). These observations indicate that more random variability regarding the rate of systemic therapy may be operational

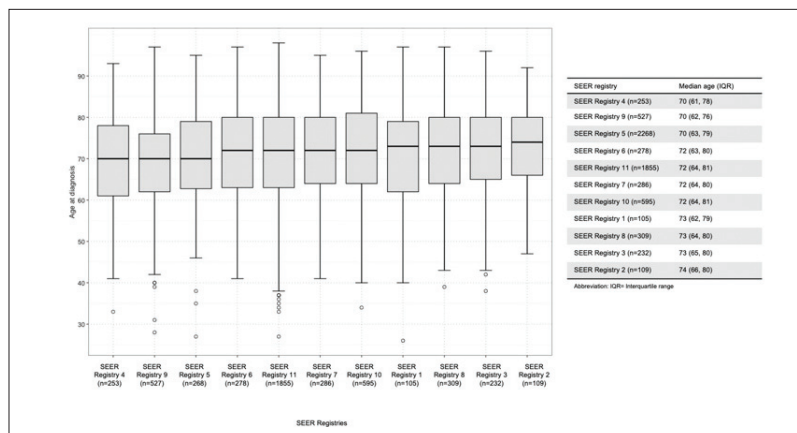


Figure 2A. Box and whisker plots depicting patient age at diagnosis distribution in 4817 metastatic urothelial carcinoma of the urinary bladder patients according to Surveillance, Epidemiology, and End Results (SEER) 2010–2018 geographic registries.

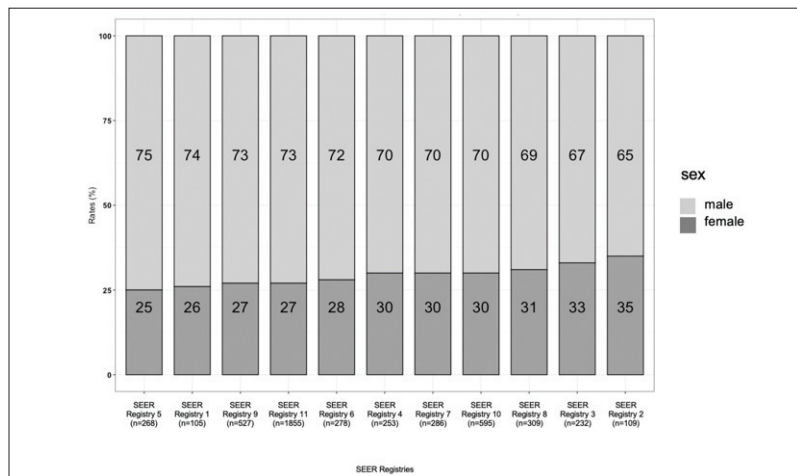


Figure 2B. Stacked bar plots depicting sex distribution in 4817 metastatic urothelial carcinoma of the urinary bladder patients according to Surveillance, Epidemiology, and End Results (SEER) 2010–2018 geographic registries.

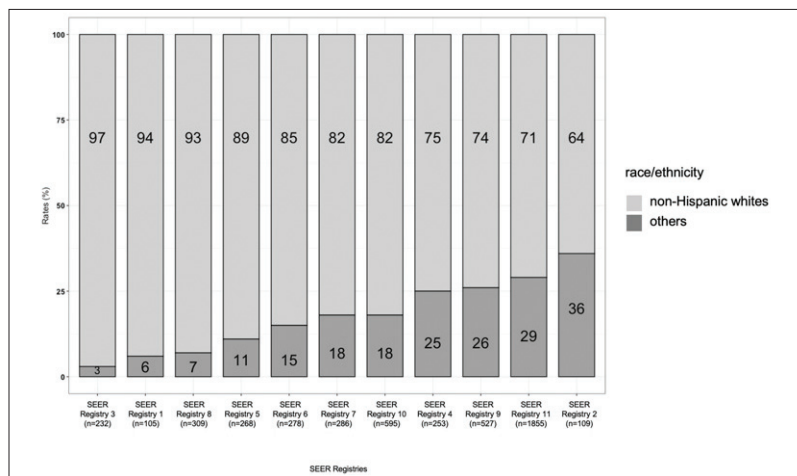


Figure 2C. Stacked bar plots depicting race/ethnicity distribution in 4817 metastatic urothelial carcinoma of the urinary bladder cancer patients according to Surveillance, Epidemiology, and End Results (SEER) 2010–2018 geographic registries.

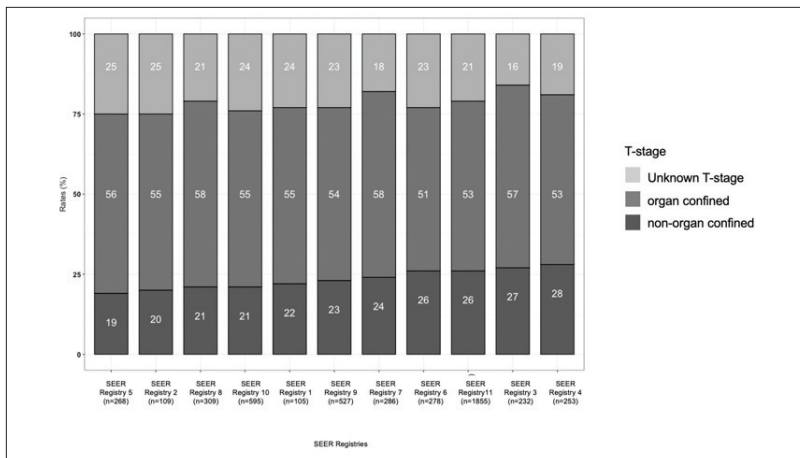


Figure 3A. Stacked bar plots depicting tumor stage (T-stage) distribution in 4817 metastatic urothelial carcinoma of the urinary bladder patients according to Surveillance, Epidemiology, and End Results (SEER) 2010–2018 geographic registries.

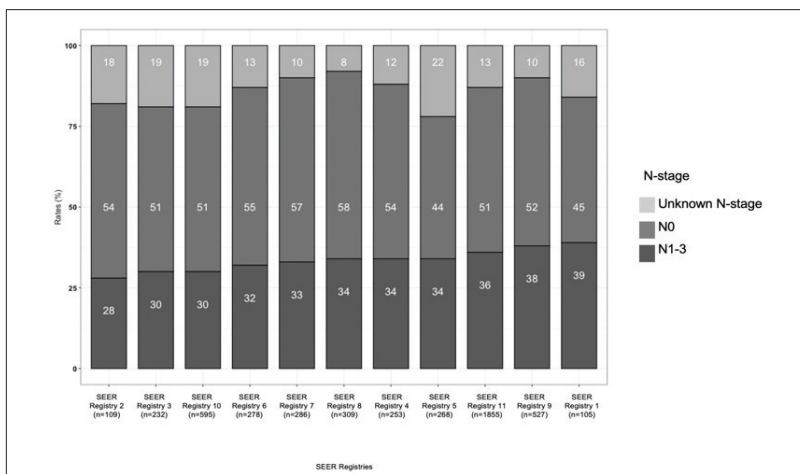


Figure 3B. Stacked bar plots depicting node stage (N-stage) distribution in 4817 metastatic urothelial carcinoma of the urinary bladder patients according to Surveillance, Epidemiology, and End Results (SEER) 2010–2018 geographic registries.

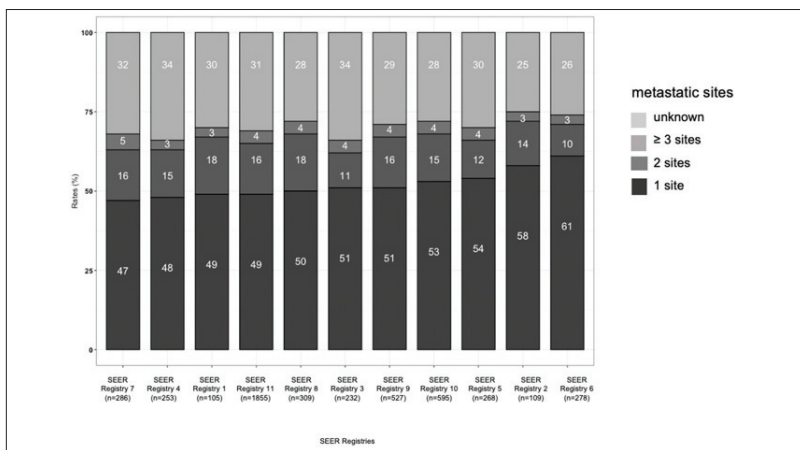


Figure 3C. Stacked bar plots depicting distribution of number of metastatic sites in 4817 metastatic urothelial carcinoma of the urinary bladder patients according to Surveillance, Epidemiology, and End Results (SEER) 2010–2018 geographic registries.

in smaller registries. Such inter-regional variability may warrant more detailed analyses aimed at standardizing rates of systemic therapy between registries.

Fourth, the overall rate of radical cystectomy was 8% and important inter-regional differences in rates of radical cystectomy were recorded (3–11%, $\Delta=8\%$, $p<0.001$). These inter-regional differences persisted even after multivariable adjustment for patient and tumor characteristics (3–11%, $\Delta=8$). It is of note that only highly selected mUCUB patients may benefit from radical cystectomy.^{14,15} Use of radical cystectomy in mUCUB patients may be an indicator of low-volume tumor burden.

Fifth, two-year OM in all 4817 mUCUB patients was 87%. Moreover, we observed important inter-regional differences in two-year OM that ranged from 80–91% ($\Delta=11\%$). Specifically, differences in two-year OM were marginal, at best, when the two largest registries (SEER Registries 10 and 11) were compared (85–87%, $\Delta=2\%$). Conversely, more pronounced inter-regional variability was recorded between the nine smaller registries (80–91%, $\Delta=11\%$). When OM rates were compared relative to the largest registry (SEER Registry 11, $n=1855$), the resulting HR ranged from 0.98–1.26. Of those 10 registries, two registries exhibited statistically significantly higher unadjusted HR relative to SEER Registry 11: SEER Registry 9 (HR 1.11) and SEER Registry 8 (HR 1.26). Conversely, no statistically significant difference in predicting OM was recorded for the seven smaller registries (SEER Registries 1–7).

It is possible that the observed variability may originate from underlying inter-regional differences in race/ethnicity, N-stage, and/or differences in systemic therapy and radical cystectomy rates. After most detailed adjustment for the presence of significant inter-regional differences in those characteristics, as well as after adjustment for all other available variables, statically significant differences in multivariable HR predicting OM persisted. Specifically, SEER Registry 9 (HR 1.13, $p=0.02$) and SEER Registry 8 (HR 1.24, $p=0.002$) still exhibited statistically significant and clinically meaningful higher risk of OM relative to SEER Registry 11. It may be postulated that cancer control outcomes can be improved in these two registries. Last but not least, the second-largest registry (SEER Registry 10) exhibited statically significant and clinically meaningful lower OM (HR 0.83; $p<0.001$) after multivariable adjustment. This may be indicative of ideal patient management within SEER Registry 10, relative to the remaining registries.

Taken together, important combined heterogeneity regarding patient, tumor, and treatment charac-

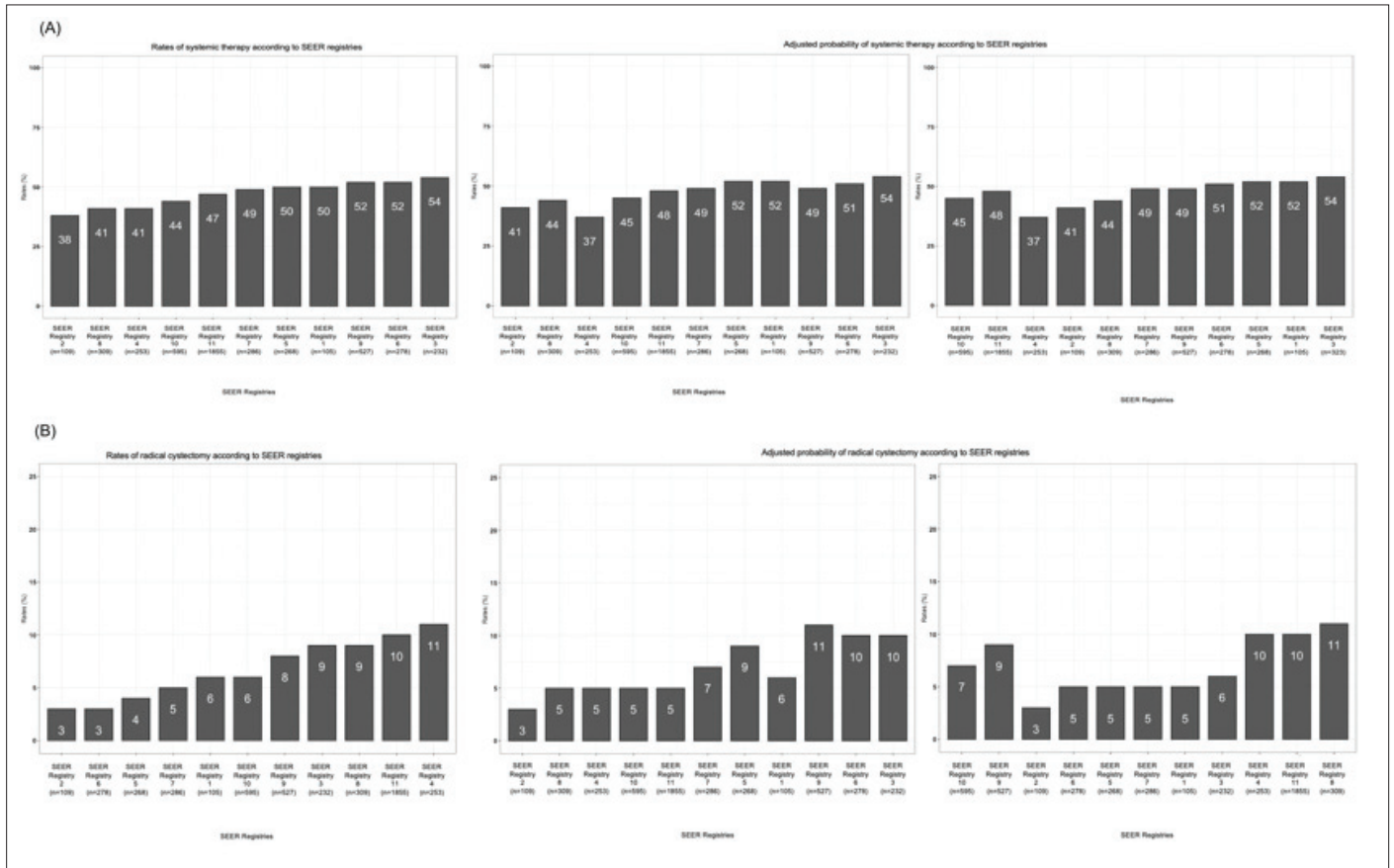


Figure 4. Bar plots depicting rates of (A) systemic therapy, as well as (B) radical cystectomy before and after multinomial adjustment in 4817 metastatic urothelial carcinoma of the urinary bladder patients according to Surveillance, Epidemiology, and End Results (SEER) geographic registries (the first plot shows SEER registries in ascending order according to rates of treatment before adjustment, the second plot shows SEER registries in the same order after adjustment and the third plot the largest SEER registries (9, 10, 11) and then the smallest in ascending order after adjustment).

teristics was observed between the SEER registries. Moreover, these patient, tumor, and treatment characteristics were previously identified as independent predictors of mortality.^{9,11-17} Based on these important registry-specific differences, it is of utmost importance to adjust cancer control analyses for those characteristics. After most detailed adjustment, one registry was associated with lower risk of OM (SEER Registry 10 HR 0.83). Conversely, two registries were associated with higher risk of OM (SEER Registry 9 HR 1.13 and SEER Registry 8 HR 1.24) relative to the largest registry (SEER Registry 11, n=1855). These persistent inter-regional differences clearly require more detailed assessment and, ideally, validation in independent large-scale databases. Moreover, the presence of such differences may attest to the variability in patients' care and expertise in mUCUB management. In consequence, there is still space for improvement in clinical care and more detailed assessment to standardize the care of mUCUB patients.

Limitations

Despite the novelty of the current study, our work has limitations and should be interpreted in the context of its retrospective and population-based design.

The current SEER version provides a sampling of patients from only 13 specific registries. This sample may not perfectly reflect the entire U.S. population. Additionally, since the SEER database is designed with the intent of providing a representation of the U.S. population, our findings cannot be applicable to patients from other countries and should be ideally validated after adjustment for mUCUB characteristics using large-scale databases in multicollaborative studies in other countries or macro-areas.

Moreover, no information about the exact number of academic institutions, dedicated repositories, and the caseload in different areas is available in the current SEER database.

There is also limited detail regarding treatment type. Specifically, the SEER database does provide informa-

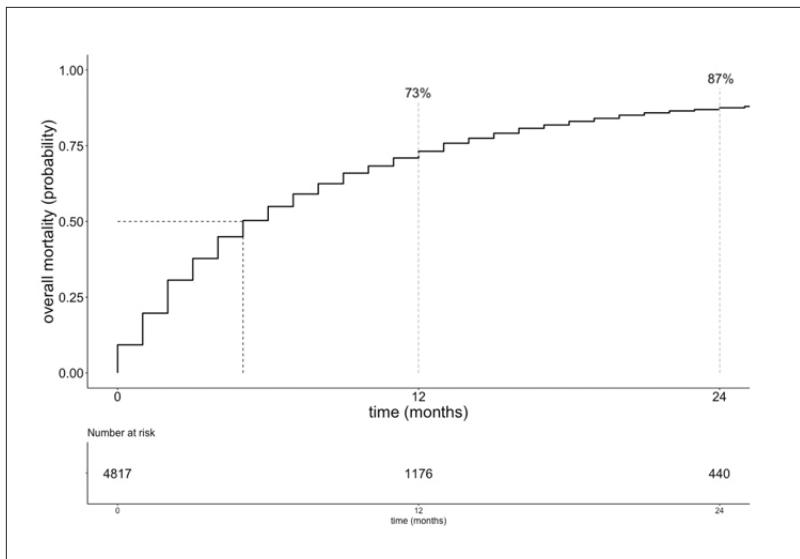


Figure 5. Incidence plot depicting two-year overall mortality of 4817 metastatic urothelial carcinoma of the urinary bladder patients within the Surveillance, Epidemiology, and End Results (SEER) 2010–2018.

tion on systemic therapy; however, it does not have the granularity to allow the identification of specific systemic therapy regimens and does not provide information on number of cycles or duration of its administration. In addition, no information about the surgical techniques (open vs. laparoscopic vs. robotic-assisted) was available in patients undergoing radical cystectomy.

Furthermore, multivariable adjustment relied on tumor, patient, and treatment characteristics available in the SEER database. It is possible that other available characteristics — performance status,^{18,19} palliative care,² comorbidities, information about the exact multimodal treatment strategy, or even patient will or denial — also affected the observed rates without being amenable to inclusion in either stratification or multivariable adjustment.

And finally, SEER lacks of information about the reason for not receiving chemotherapy.

CONCLUSIONS

We identified important regional differences that included patient, tumor, and treatment characteristics. Even after adjustment for these characteristics, important OM differences persisted, which may warrant further investigation and even more detailed assessment to standardize the care of mUCUB patients.

COMPETING INTERESTS: The authors do not report any competing personal or financial interests related to this work.

This paper has been peer-reviewed.

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Table 2. OM in mUCUB patients according to Surveillance, Epidemiology, and End Results (SEER) 2010–2018 geographic registries across the U.S.

SEER registries	11 (n=1855)	10 (n=595)	9 (n=527)	8 (n=309)	7 (n=286)	6 (n=278)	5 (n=268)	4 (n=253)	3 (n=232)	2 (n=109)	1 (n=105)
Two-year OM (%)	87	85	90	91	89	90	86	85	80	87	82
Unadjusted OM HR	Ref.	0.98	1.11**	1.26**	1.10	1.04	1.00	1.04	0.90	1.10	1.12
Adjusted OM HR*	Ref.	0.83**	1.13**	1.24**	1.11	1.04	1.05	0.94	0.93	1.09	1.13

*Adjusted for age at diagnosis, sex, year of diagnosis, T-stage, N-stage, race/ethnicity, number of metastatic site, systemic therapy, radical cystectomy. **p<0.05. HR: hazard ratio; mUCUB: metastatic urothelial carcinoma of the urinary bladder; OM: overall mortality.

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