The effect of chemotherapy in sarcomatoid bladder cancer patients treated with radical cystectomy

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ABSTRACT

Introduction: Data about the role of chemotherapy in sarcomatoid bladder cancer (SBC) are limited. We addressed the effect of chemotherapy in non-metastatic SBC patients treated with radical cystectomy.

Methods: Using the Surveillance, Epidemiology, and End Results database (2001–2018), we identified 331 patients with non-metastatic muscle-invasive or higher SBC ($T_{2\text{-}4}N_{0\text{-}3}M_0$). Kaplan-Meier plots and Cox regression models tested cancer-specific mortality (CSM). Sample size and power analyses tested for power limitations.

KEY MESSAGES

- Sarcomatoid bladder cancer is a rare and aggressive malignancy about which our knowledge is still limited, especially in terms of treatment.
- Based on the current study, chemotherapy might play a crucial role in the treatment of non-metastatic sarcomatoid bladder cancer patients, both in organ-confined and non-organ-confined stages.

Results: Of 331 SBC patients, 129 (38.9%) were exposed to chemotherapy. The rate of organ-confined stage ($T_2N_0M_0$) was 33% in both chemotherapy-exposed and chemotherapy-naive patients. In the overall cohort, median CSM-free survival was 84 months (interquartile range [IQR] 21–NA) vs. 26 months (IQR 17–84) in chemotherapy exposed vs. chemotherapy-naive patients, respectively. In multivariable Cox regression models, chemotherapy was associated with lower CSM, without reaching statistical significance (hazard ratio [HR] 0.72, confidence interval [CI] 0.51–1.01, p=0.054). In subgroup analyses, chemotherapy exposure in organ-confined (n=110) vs. non-organ-confined (n=221) patients, resulted in a HR of 0.51 (p=0.12) vs. 0.77 (p=0.17), respectively. Power analyses, based on two-sided α=0.05, revealed values of 52%, 14%, and 43% in the entire population, organ-confined, and non-organ-confined subgroups, respectively.
Conclusions: In non-metastatic SBC treated with RC, the association between chemotherapy and lower CSM is particularly strong in organ-confined stage. A substantially larger cohort would be required to confirm the statistical significance of the recorded protective effect of chemotherapy.

INTRODUCTION

Sarcomatoid bladder cancer (SBC) is a rare and highly aggressive histological variant of urothelial carcinoma, accounting for 0.3-0.6% of all bladder cancers [1–5]. Prospective studies addressing management of SBC are not available and data from retrospective reports are scarce. Specifically, a knowledge gap exists regarding efficacy of chemotherapy, in non-metastatic SBC patients treated with radical cystectomy (RC). Most studies addressing this topic are limited by small sample size (from 15 to 40 patients) [6–10]. Conversely, three existing large scale population-based studies originating from the National Cancer Database (NCDB) (155, 304, and 501 patients), are all invariably limited by lack of information on cancer-specific mortality (CSM) [11–13]. This methodological shortfall critically undermines their observations, since an important proportion of non-metastatic SBC patients treated with RC, die of non-cancer-related causes. Therefore, overall mortality (OM) clearly lacks specificity, when it is used as an endpoint in non-metastatic SBC patients treated with RC. In consequence, it is unknown whether chemotherapy may improve CSM in such patient population.

We addressed this knowledge gap and tested the effect of chemotherapy on CSM in non-metastatic SBC patients treated with RC. We hypothesized that chemotherapy might be associated with lower CSM. We relied on the Surveillance, Epidemiology and End Results (SEER 2001-2018) database.

METHODS

Study population

The SEER database samples 34.6% of the United States (US) population in terms of demographic composition and cancer incidence [14]. Within the SEER database (2001-2018), we identified patients aged ≥ than 18 years, with histologically confirmed non-metastatic muscle-invasive or higher ($T_{2\text{-}4}N_{0\text{-}3}M_0$) bladder cancer (BCa) (International Classification of Disease for

Oncology [ICD-O] site code C67.0-67.9), who harbored SBC histology (ICD-O code: 8122-sarcomatoid). Only patients treated with RC were included. American Joint Committee on Cancer (AJCC) stage was used, according to the eight edition [15]. Autopsy or death certificate only cases were excluded.

Statistical analyses

Descriptive statistics included frequencies and proportions for categorical variables. Medians and interquartile ranges (IQR) were reported for continuously coded variables. Wilcoxon rank sum test, Pearson's Chi-squared test, and Fisher's exact test examined the statistical significance of differences in medians and proportions, respectively. Rates and estimated annual percentage changes (EAPCs) were displayed graphically.

The endpoint of interest consisted of CSM. Kaplan–Meier plots and Cox regression models tested CSM in two different sets of analyses. First, we tested the effect of chemotherapy on CSM in all non-metastatic SBC patients treated with RC. Covariates consisted of age at surgery (continuous), and stage (organ-confined [$T_2N_0M_0$] vs non-organ-confined [$T_{3-4}N_0M_0$ or $T_{2-4}N_{1-3}M_0$]). Second, we relied on two subgroups. Here, we first tested the effect of chemotherapy in organ-confined and thereafter in non-organ-confined SBC patients. Sample size and power analyses relied on two-sided $\alpha = 0.05$, to estimate sample size for 80% power or power at the observed patients' distributions.

In all statistical analyses, R software environment for statistical computing and graphics (R version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria) was used [16]. All tests were two sided, with a level of significance set at $p<0.05$. Owing to the anonymously coded design of the SEER database, study-specific ethics approval was waived by the institutional review board.

RESULTS

Descriptive characteristics of the entire SBC population

Within the SEER database (2001-2018), 331 non-metastatic muscle-invasive or higher ($T_{2-4}N_{0-3}M_0$) SBC patients treated with RC were identified (Table 1). Of those, 129 (38.9%) received chemotherapy. Chemotherapy exposed patients were younger (median age 66 years vs 70, p= 0.01) and had higher rates of N_{1-3} disease (p= 0.03). The rate of organ-confined stage ($T_2N_0M_0$) was 33% in both chemotherapy exposed and chemotherapy naïve patients.

After stratification between organ-confined vs non-organ-confined stage, the rates of chemotherapy exposure were, respectively, 39.1 vs 38.9%. Over time, the rates of chemotherapy exposure increased from 13.6 to 56.5% in the entire population (EAPC +6.7 %, p= 0.001; Figure 2A), from 37.5 to 53.6% in organ-confined patients (EAPC +4.8 %, p= 0.029; Figure 2B), and from 6.3 to 58.3% in non-organ-confined patients (EAPC +6.7 %, p= 0.003; Figure 2B).

Effect of chemotherapy on CSM in the entire SBC population

Median CSM-free survival was 84 months (Interquartile range [IQR]: 21-NA) vs 26 months (IQR: 17-84) in respectively, chemotherapy exposed vs chemotherapy naïve patients (Figure 1a). This resulted in a univariable hazard ratio (HR) of 0.72 (p= 0.052). In multivariable Cox regression analyses (Table 2), chemotherapy exposure was associated with a HR of 0.72 (p= 0.054). At 60 months of follow-up, other-cause mortality (OCM) rate was 18.4% in the overall

cohort, regardless of chemotherapy exposure status. Specifically, in chemotherapy exposed vs chemotherapy naïve patients, 60-months OCM rates were 20.8 vs 17.1%, respectively.

Effect of chemotherapy on CSM in organ-confined SBC patients
Median CSM-free survival was not reached in chemotherapy exposed patients vs 118 months in chemotherapy naïve patients, respectively (Figure 1b). This resulted in a univariable HR of 0.49 (p= 0.10). In multivariable Cox regression models (Table 2), chemotherapy exposure was associated with a HR of 0.51 (p= 0.12). At 60 months of follow-up, OCM rates were 16.1% in the entire cohort, and 13.9 vs 17.4% in chemotherapy exposed vs chemotherapy naïve patients, respectively.

Effect of chemotherapy on CSM in non-organ-confined SBC patients
Median CSM-free survival was 21 months vs 14 months in, respectively, chemotherapy exposed vs chemotherapy naïve patients (Figure 1c). This resulted in a univariable HR of 0.80 (p= 0.23). In multivariable Cox regression models (Table 2), chemotherapy was associated with a HR of 0.77 (p= 0.17). At 60 months of follow-up, OCM rates were 20.2% in the entire cohort, and 25.8 vs 17.1% in chemotherapy exposed vs chemotherapy naïve patients, respectively.

Sample size and power analyses
In the entire population of non-metastatic SBC patients treated with RC, with 129 chemotherapy exposed and 202 chemotherapy naïve patients (ratio= 0.64), for two-sided α= 0.05, power of 52% was detected. Based on the same assumptions, in organ-confined vs non-organ-confined stage subgroups power of 14 vs 43% was detected.

The required sample size calculations to achieve 80% power with two-sided α= 0.05 were made. In the entire population, at least 253 chemotherapy exposed patients and 396 chemotherapy naïve patients would have been required to demonstrate the statistical significance of the recorded HR of 0.72. In organ-confined stage, 125 chemotherapy exposed and 194 chemotherapy naïve patients would have been required to demonstrate the statistical significance of the recorded HR of 0.51. In non-organ-confined patients, 333 chemotherapy exposed and 523 chemotherapy naïve patients would have been required to demonstrate the statistical significance of the recorded HR of 0.77.

DISCUSSION
Efficacy of chemotherapy in non-metastatic SBC patients treated with RC is unknown [17,18]. We addressed this knowledge gap within the SEER database (2001-2018). We tested the effect of chemotherapy on CSM in non-metastatic SBC patients treated with RC. We hypothesized that chemotherapy might be associated with lower CSM, and we arrived at several noteworthy observations.

First, SBC is a rare histological variant of urothelial carcinoma of the bladder. It presents with higher rates of advanced stage at initial diagnosis and worse prognosis over time than urothelial carcinoma [2–5]. We identified 331 non-metastatic SBC patients treated with RC. Of those, 67% harbored non-organ-confined disease. To the best of our knowledge, this is the second largest study examining such patient population [13]. The majority of studies addressing SBC relied on small populations: from 15 to 40 patients [6–10]. Conversely, three NCDB based studies, by Sui et al. (n= 155), Vetterlein et al. (n = 304), and Chakiryan et al. (n= 501) reported

on series of comparable or even larger size than the current series. However, their analyses only addressed overall mortality (OM). This metric is suboptimal, when efficacy of chemotherapy, in the setting of non-metastatic SBC patients treated with RC represents the outcome of interest, since an important proportion of such patients succumb to OCM [11–13]. In consequence, analyses addressing OM are not of sufficient specificity in non-metastatic SBC patients treated with RC. Interestingly, the overall 60-months OCM rate in the current study was as high as 18.4%. OCM rate was higher in chemotherapy exposed than chemotherapy naïve patients (20.8 vs 17.1%).

Second, the rates of chemotherapy exposure in the current study were virtually the same in the entire population, as well as in subgroups of organ-confined vs non-organ-confined patients: 38.9; 39.1 vs 38.9%, respectively. Despite similarity in chemotherapy rates according to disease stage, more detailed analyses of chemotherapy rates over time revealed important differences. Specifically, over time chemotherapy rate in organ-confined patients increased from 37.5 to 53.6%. Conversely, chemotherapy rate in non-organ-confined patients also increased from 6.3% to 58.3%. In consequence, a much larger proportion of organ-confined patients benefited of chemotherapy, especially in the initial years of the study. Such difference in chemotherapy rates may have an implication on the recorded differences in chemotherapy efficacy.

Third, regarding efficacy of chemotherapy a HR of 0.72 was recorded in the entire cohort. Such HR compares very favorably with several retrospective studies and prospective trials of chemotherapy or immunotherapy in the context of locally-advanced BCa [19–21]. For example, in a meta-analysis of nine randomized trials including 945 muscle-invasive BCa patients, cisplatin-based chemotherapy was associated with a HR 0.77 (95% CI 0.59–0.99, p= 0.049) [19]. Moreover, in a NCDB based study by Galsky et al., the association between RC and multiagent chemotherapy resulted in a HR of 0.70 (95% CI 0.64-0.76) in 1,293 locally-advanced BCa patients [20]. Furthermore, the CheckMate 274 phase III trial reported a HR of 0.70 for disease recurrence or death (98.22% CI, 0.55 to 0.90, p< 0.001), for adjuvant immunotherapy, namely nivolumab, vs. placebo, in 709 patients with muscle-invasive BCa treated with RC [21].

Fourth, we also made noteworthy observations in subgroup analyses. It is of utmost interest that a chemotherapy protective HR of 0.51 was recorded in organ-confined stage patients (p= 012). Conversely, a weaker albeit protective association was recorded in non-organ-confined stage patients (HR: 0.77, p= 0.17). This discrepancy may be related to higher rate of chemotherapy exposure in organ-confined stage patients, as described above. Despite highly encouraging protective effect of chemotherapy in the entire cohort, as well as in the stratified stage-specific analyses, all three highly protective HRs (0.51, 0.72, and 0.77) failed to achieve statistical significance in multivariable regression models adjusted for chemotherapy exposure and age.

Fifth, to address lack of statistical significance in HRs with highly protective effect on CSM, we relied on sample size and power analyses. The current sample sizes and ratios between chemotherapy exposed and naïve patients (ratio= 0.64 in all three cohorts), using two-sided α= 0.05, revealed power values of 52% for the entire population vs 14% in organ-confined patients vs 43% in non-organ-confined patients. In consequence, clearly and evidently, lack of power contributed to lack of statistical significance. Indeed, in sample size analyses, that required 80% power, 253 chemotherapy exposed patients and 396 chemotherapy naïve patients would have

been required in the entire cohort, to demonstrate the statistical significance of the recorded HR of 0.72.

In organ-confined stage analyses, at 80% power, 125 chemotherapy exposed and 194 chemotherapy naïve patients would have been required. In non-organ-confined stage analyses, at 80% power, 333 chemotherapy exposed and 523 chemotherapy naïve patients would have been required. Based on incidence data [22], such sample sizes are not achievable in the context of either retrospective studies, and even less so, in the context of prospective studies. Therefore, it is highly likely that underpowered analyses will represent the highest evidence level, when chemotherapy is compared to non-chemotherapy in non-metastatic SBC treated with RC. In consequence, it is clear that observations made in the current study do represent an important addition to the existing body of evidence about non-metastatic SBC patients treated with RC.

Despite its value, our study is not devoid of limitations. First and foremost, our database did not have the benefit of central pathology review to validate histological diagnosis of SBC. Second, although our study represents the second largest existing cohort of non-metastatic SBC patients, its sample size is still not sufficient. Insufficiently large sample size contributed to important methodological limitations within the analyses, due to insufficient numbers of observations. Third, our database does not allow us to distinguish between neoadjuvant vs adjuvant chemotherapy. Moreover, our database does not contain information regarding the type and dose of administered chemotherapy. Finally, the SEER database only includes patients from the United States. Therefore, the current findings may not be generalized to patients with SBC from other parts of the world. Moreover, even within the United States, these findings are mainly applicable to Caucasians patients, since they account for the vast majority (80.0%) of the study population. These, as well as all other limitations related to the retrospective, population-based nature of the SEER database, also apply to the current study, as well as to other similar analyses that were based on other, albeit similar large-scale data repositories.

CONCLUSIONS

In non-metastatic SBC treated with RC, the association between chemotherapy and lower CSM is particularly strong in organ-confined stage. A substantially larger cohort would be required to confirm the statistical significance of the recorded protective effect of chemotherapy.

References

1. Humphrey PA, Moch H, Cubilla AL, Ulbright TM, Reuter VE. The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs-Part B: Prostate and Bladder Tumours. *Eur Urol*. 2016;70(1):106-119. doi:10.1016/J.EURURO.2016.02.028
2. Moschini M, D'Andrea D, Korn S, et al. Characteristics and clinical significance of histological variants of bladder cancer. *Nature Reviews Urology*. 2017;14(11):651-668. doi:10.1038/nrurol.2017.125
3. Stamatiou K, Galariotis N, Michailidis I, Petrakopoulou N, Moustou H, Zizi-Sermpetzoglou A. Sarcomatoid carcinoma of the urinary bladder: A clinicopathological study of 4 cases and a review of the literature. *Korean Journal of Urology*. 2010;51(10):724-728. doi:10.4111/kju.2010.51.10.724
4. Malla M, Wang JF, Trepeta R, Feng A, Wang J. Sarcomatoid Carcinoma of the Urinary Bladder. *Clinical Genitourinary Cancer*. 2016;14(5):366-372. doi:10.1016/j.clgc.2016.03.004
5. Wang J, Wang FW, Lagrange CA, Hemstreet GP, Kessinger A. Clinical features of sarcomatoid carcinoma (carcinosarcoma) of the urinary bladder: Analysis of 221 cases. *Sarcoma*. 2010;2010. doi:10.1155/2010/454792
6. Moschini M, Dell'Oglio P, Luciano R, et al. Incidence and effect of variant histology on oncological outcomes in patients with bladder cancer treated with radical cystectomy. *Urologic Oncology: Seminars and Original Investigations*. 2017;35(6):335-341. doi:10.1016/j.urolonc.2016.12.006
7. Monn MF, Kaimakliotis HZ, Pedrosa JA, et al. Contemporary bladder cancer: Variant histology may be a significant driver of disease. *Urologic Oncology: Seminars and Original Investigations*. 2015;33(1):18.e15-18.e20. doi:10.1016/j.urolonc.2014.10.001
8. Xylinas E, Rink M, Robinson BD, et al. Impact of histological variants on oncological outcomes of patients with urothelial carcinoma of the bladder treated with radical cystectomy. *European Journal of Cancer*. 2013;49(8):1889-1897. doi:10.1016/j.ejca.2013.02.001
9. Lopez-Beltran A, Pacelli A, Rothenberg HJ, et al. *CARCINOSARCOMA AND SARCOMATOID CARCINOMA OF THE BLADDER: CLINICOPATHOLOGICAL STUDY OF 41 CASES*. Vol 159.; 1998.
10. Hajiran A, Azizi M, Aydin AM, et al. Pathological and Survival Outcomes Associated with Variant Histology Bladder Cancers Managed by Cystectomy with or without Neoadjuvant Chemotherapy. *J Urol*. 2021;205(1):100-108. doi:10.1097/JU.0000000000001325
11. Vetterlein MW, Wankowicz SAM, Seisen T, et al. Neoadjuvant chemotherapy prior to radical cystectomy for muscle-invasive bladder cancer with variant histology. *Cancer*. 2017;123(22):4346-4355. doi:10.1002/cncr.30907
12. Sui W, Matulay JT, Onyeji IC, et al. Contemporary treatment patterns and outcomes of sarcomatoid bladder cancer. *World Journal of Urology*. 2017;35(7):1055-1061. doi:10.1007/s00345-016-1962-8
13. Chakiryan NH, Jiang DD, Gillis KA, et al. Pathological Downstaging and Survival Outcomes Associated with Neoadjuvant Chemotherapy for Variant Histology Muscle Invasive Bladder Cancer. *J Urol*. 2021;206(4):924-932. doi:10.1097/JU.0000000000001855

14. Howlader N, Noone A, Krapcho M, Miller D, Brest A, Cronin K. Cancer Statistics Review, 1975-2018 - SEER Statistics. Accessed April 13, 2022. https://seer.cancer.gov/csr/1975_2018/
15. Amin MB, Edge SB, Greene FL, et al. *American Joint Committee on Cancer (AJCC). AJCC Cancer Staging Manual*.; 2017. Accessed April 13, 2022. https://link.springer.com/book/9783319406176
16. R: The R Project for Statistical Computing. Accessed April 13, 2022. https://www.r-project.org/
17. Witjes JA, Babjuk M, Bellmunt J, et al. EAU-ESMO Consensus Statements on the Management of Advanced and Variant Bladder Cancer—An International Collaborative Multistakeholder Effort†[Formula presented]: Under the Auspices of the EAU-ESMO Guidelines Committees. *European Urology*. 2020;77(2):223-250. doi:10.1016/j.eururo.2019.09.035
18. Chang SS, Bochner BH, Chou R, et al. Treatment of Non-Metastatic Muscle-Invasive Bladder Cancer: AUA/ASCO/ASTRO/SUO Guideline. *Journal of Urology*. 2017;198(3):552-559. doi:10.1016/j.juro.2017.04.086
19. Leow JJ, Martin-Doyle W, Rajagopal PS, et al. Adjuvant chemotherapy for invasive bladder cancer: a 2013 updated systematic review and meta-analysis of randomized trials. *Eur Urol*. 2014;66(1):42-54. doi:10.1016/J.EURURO.2013.08.033
20. Galsky MD, Stensland KD, Moshier E, et al. Effectiveness of Adjuvant Chemotherapy for Locally Advanced Bladder Cancer. *J Clin Oncol*. 2016;34(8):825-832. doi:10.1200/JCO.2015.64.1076
21. Bajorin DF, Witjes JA, Gschwend JE, et al. Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma. *New England Journal of Medicine*. 2021;384(22):2102-2114. doi:10.1056/nejmoa2034442
22. Deuker M, Martin T, Stolzenbach F, et al. Bladder Cancer: A Comparison Between Non-urothelial Variant Histology and Urothelial Carcinoma Across All Stages and Treatment Modalities. *Clinical Genitourinary Cancer*. 2021;19(1):60-68.e1. doi:10.1016/J.CLGC.2020.07.011

Figures and Tables

Figure 1. Kaplan-Meier curves of cancer-specific mortality according to chemotherapy exposyre status in **(A)** overall sarcomatoid bladder cancer (SBC) patients treated with radical cystectomy; **(B)** organ-confined SBC patients; and **(C)** non-organ-confinred SBC patients.

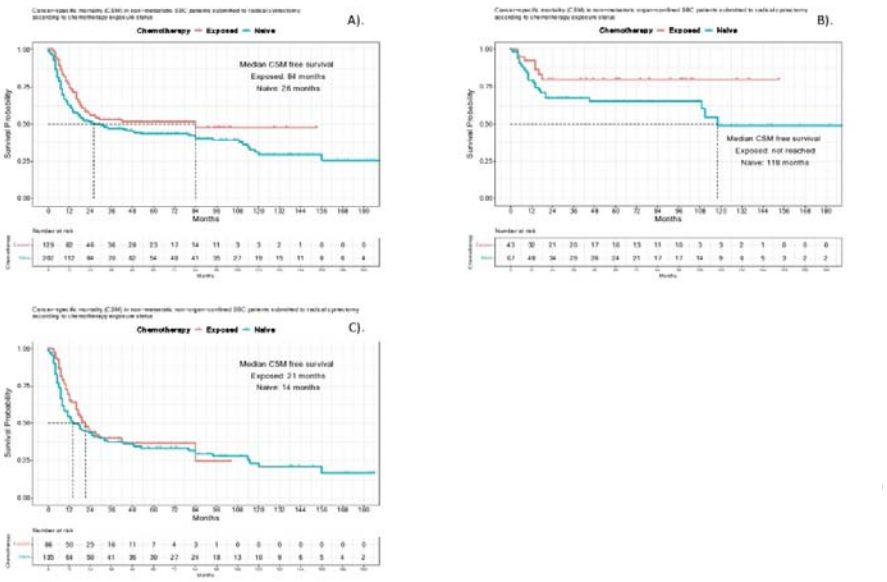

Figure 2. Estimated annual percentage change (EAPCs) of chemotherapy exposure in (A) overall sarcomatoid bladder cancer (SBC) patients treated with radical cystectomy; and **(B)** organ-confined vs. non-organ-confined SBC patients.

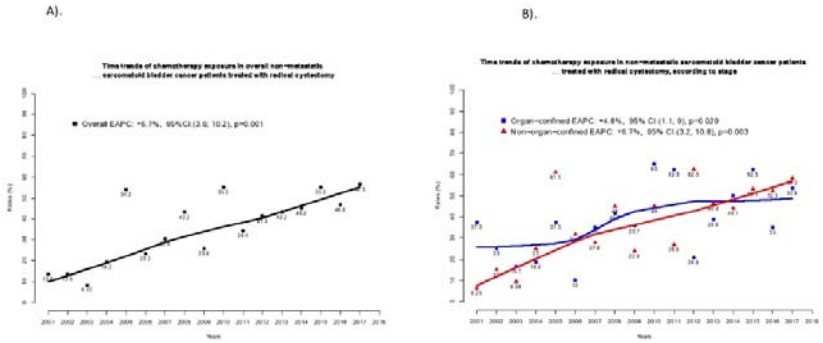

Table 1. Descriptive characteristics of 331 non-metastatic sarcomatoid bladder cancer (SBC) patients treated with radical cystectomy, according to chemotherapy exposure status				
Characteristic	**Overall N=331[1]**	**Chemotherapy -naive, n= 202[1] (61.1%)**	**Chemotherapy-exposed, n=129[1] (38.9%)**	**p[2]**
Age	69 (62, 75)	70 (63, 76)	66 (59, 74)	0.005
Sex				0.8
Female	111 (33.5%)	69 (34.2%)	42 (32.6%)	
Male	220 (66.5%)	133 (65.8%)	87 (67.4%)	
Race				0.2
African American	24 (7.3%)	16 (7.9%)	8 (6.2%)	
Asian	18 (5.4%)	7 (3.5%)	11 (8.5%)	
Caucasian	264 (80%)	163 (81%)	101 (78%)	
Hispanic	25 (7.6%)	16 (7.9%)	9 (7.0%)	
T stage				0.3
T2	125 (37.8%)	72 (35.6%)	53 (41.1%)	
T3	149 (45.0%)	98 (48.5%)	51 (39.5%)	
T4	57 (17.2%)	32 (15.9%)	25 (19.3%)	
N stage				0.028
N0	255 (77.0%)	166 (82.3%)	89 (69.0%)	
N1	36 (10.9%)	15 (7.4%)	21 (16.3%)	
N2	31 (9.4%)	17 (8.5%)	14 (10.8%)	
N3	9 (2.7%)	4 (2.2%)	5 (3.9%)	
Stage				>0.9
Organ-confined $T_2N_0M_0$	110 (33.2%)	67 (33.2%)	43 (33.3%)	
Non-organ-confined $T_{3-4}N_0M_0$ or $T_{any}N_{1-3}M_0$	221 (66.8%)	135 (66.8%)	86 (66.7%)	

[1]Median (interquartile range), n (%). [2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test.

Table 2. Univariable and multivariable Cox regression analyses predicting cancer-specific mortality in 331 non-metastatic sarcomatoid bladder cancer (SBC) patients						
Cancer-specific mortality	**Entire population, N=331**					
	Univariable			**Multivariable**		
Characteristic	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
Age	1.00	0.99, 1.02	0.75	1.00	0.98, 1.01	0.73
Chemotherapy (exposure vs. no-exposure)	0.72	0.52, 1.00	0.052	0.72	0.51, 1.01	0.054
Stage (non-organ-confined[1] vs. organ-confined[2])	2.89	1.95, 4.28	<0.001	2.90	1.95, 4.28	<0.001
Cancer-specific mortality	**Organ-confined SBC, n=110**					
	Univariable			**Multivariable**		
Characteristic	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
Age	1.02	0.99, 1.06	0.20	1.02	0.99, 1.06	0.26
Chemotherapy (exposure vs. no-exposure)	0.49	0.21, 1.14	0.10	0.51	0.22, 1.19	0.12
Cancer-specific mortality	**Non-organ-confined SBC, n=221**					
	Univariable			**Multivariable**		
Characteristic	HR	95% CI	p	HR	95% CI	p
Age	0.99	0.98, 1.01	0.51	0.99	0.97, 1.01	0.34
Chemotherapy (exposure vs. no-exposure)	0.80	0.55, 1.15	0.23	0.77	0.53, 1.12	0.17

[1]Non-organ-confined stage = $T_{3\text{-}4}N_0M_0$ or $T_{any}N_{1\text{-}3}M_0$. [2]Organ-confined stage = $T_2N_0M_0$. CI: confidence interval; HR: hazard ratio.