

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 (RC).

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

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-naïve 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-naïve 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 $\alpha=0.05$, 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 15–40 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 a 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.

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.

METHODS

Study population

The SEER database samples 34.6% of the U.S. population in terms of demographic composition and cancer incidence.¹⁴ Within the SEER database (2001–2018), we identified patients aged ≥ 18 years with histologically confirmed non-metastatic muscle-invasive or higher ($T_{2-4}N_{0-3}M_0$) 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 eighth 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 vs. 70 years, $p=0.01$) 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-naive patients.

After stratification between organ-confined vs. non-organ-confined stage, the rates of chemotherapy exposure were 39.1% vs 38.9%, respectively. 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 1A), from 37.5% to 53.6% in organ-confined patients (EAPC +4.8%, $p=0.029$) (Figure 1B), and from 6.3% to 58.3% in non-organ-confined patients (EAPC +6.7%, $p=0.003$) (Figure 1B).

Effect of chemotherapy on CSM in the entire SBC population

Median CSM-free survival was 84 months (IQR 21–NA) vs. 26 months (IQR 17–84) in chemotherapy-exposed vs. chemotherapy-naive patients, respectively (Figure 2A). 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 followup, other-cause mortality (OCM) rate was 18.4% in the overall cohort, regardless of chemotherapy exposure status. Specifically, in chemotherapy-exposed vs. chemotherapy-naive patients, 60-month OCM rates were 20.8% vs. 17.1%, respectively.

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= 2021 (61.1%)	Chemotherapy-exposed, n=1291 (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 T2N0M0	110 (33.2%)	67 (33.2%)	43 (33.3%)	
Non-organ-confined T3-4N0M0 or TanyN1-3M0	221 (66.8%)	135 (66.8%)	86 (66.7%)	

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

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-naive patients, respectively (Figure 2B). 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 followup, OCM rates were 16.1% in the entire cohort, and 13.9% vs. 17.4% in chemotherapy-exposed vs. chemotherapy-naive patients, respectively.

Effect of chemotherapy on CSM in non-organ-confined SBC patients

Median CSM-free survival was 21 months vs. 14 months in chemotherapy-exposed vs. chemotherapy-naive patients, respectively (Figure 2C). 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 followup, OCM rates were 20.2% in the entire cohort, and 25.8 vs. 17.1% in chemotherapy-exposed vs. chemotherapy-naive 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-naive patients (ratio=0.64) — for two-sided $\alpha=0.05$, 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 $\alpha=0.05$ were made. In the entire population, at least 253 chemotherapy-exposed patients and 396 chemotherapy-naive 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-naive 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-naive 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

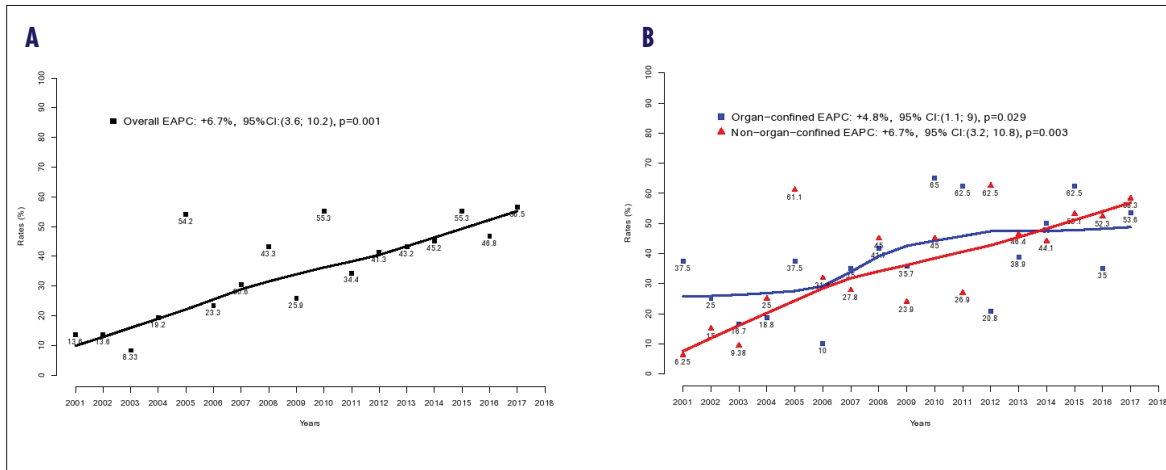


Figure 1. Estimated annual percentage change (EAPCs) of chemotherapy exposure in (A) overall sarcomatoid bladder cancer (SBC) patients treated with radical cystectomy; and (B) organ-confined vs. non-organ-confined SBC patients.

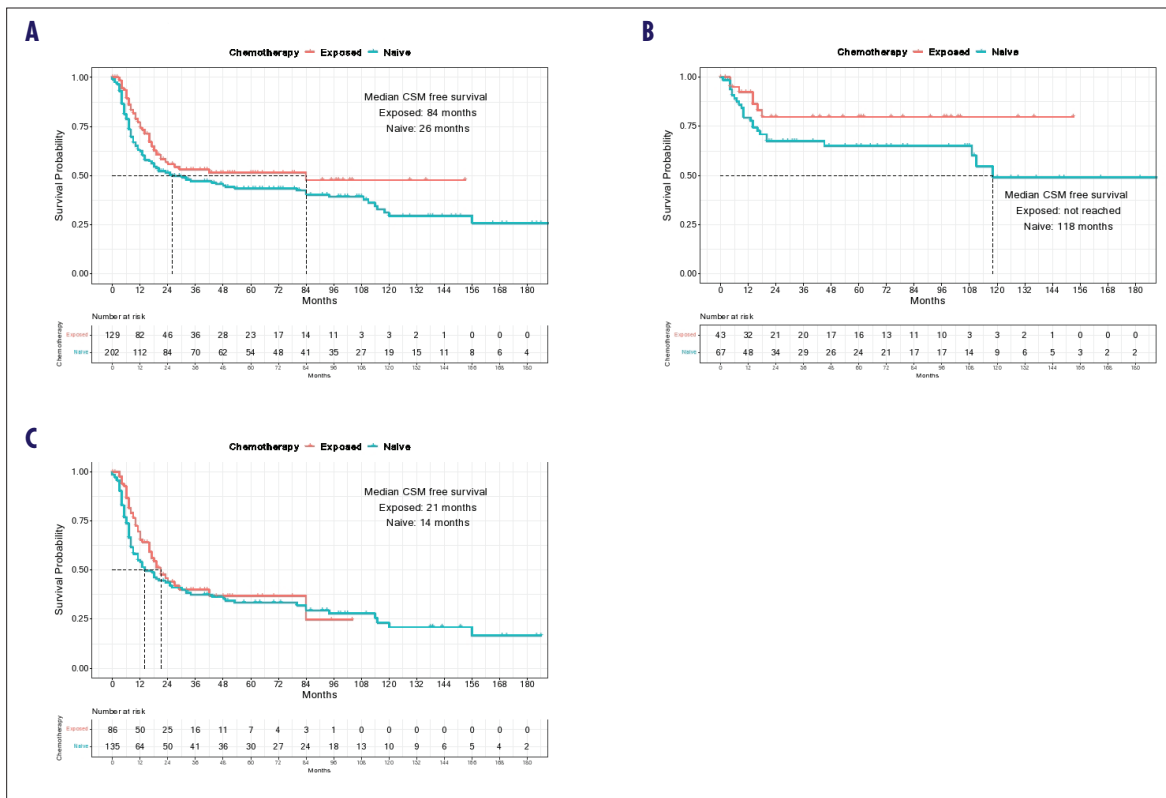


Figure 2. Kaplan-Meier curves of cancers-specific mortality according to chemotherapy exposure status in (A) overall sarcomatoid bladder cancer (SBC) patients treated with radical cystectomy; (B) organ-confined SBC patients; and (C) non-organ-confined SBC patients.

The majority of studies addressing SBC relied on small populations: from 15–40 patients.^{6–10} Conversely, three NCDDB-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

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

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

¹Non-organ-confined stage=T3-4N0M0 or TanyN1-3M0. ²Organ-confined stage=T2N0M0. CI: confidence interval; HR: hazard ratio.

SBC patients treated with RC. Interestingly, the overall 60-month OCM rate in the current study was as high as 18.4%. OCM rate was higher in chemotherapy-exposed than chemotherapy-naive 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 from 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% confidence interval [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 1293 locally advanced BCa patients.²⁰ Furthermore, the CheckMate 274 phase 3 trial reported a HR of 0.70 for disease recurrence or death (98.22% CI 0.55–0.90, 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=0.12). 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 naive patients (ratio=0.64 in all three cohorts), using two-sided $\alpha=0.05$, 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-naive 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-naive patients would have been required. In non-organ-confined stage analyses, at 80% power, 333 chemotherapy-exposed and 523 chemotherapy-naive patients would have been required. Based on incidence data,²² such sample sizes are not achievable in the context of either retrospective study 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.

Limitations

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 U.S. Therefore, the current findings may not

be generalized to patients with SBC from other parts of the world. Moreover, even within the U.S., 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.

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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