ELSEVIER

Urologic Oncology: Seminars and Original Investigations 37 (2019) 353.e17–353.e24

UROLOGIC ONCOLOGY

Clinical-Bladder cancer

The impact of squamous histology on survival in patients with muscle-invasive bladder cancer

Justin T. Matulay, M.D.[a,*], Solomon L. Woldu, M.D.[b], Amy Lim, M.D., Ph.D.[a], Vikram M. Narayan, M.D.[a], Gen Li, Ph.D.[c], Ashish M. Kamat, M.D., M.B.B.S.[a], Christopher B. Anderson, M.D.[d]

[a] *Department of Urology, Division of Surgery, University of Texas MD Anderson Cancer Center, Houston, TX*
[b] *Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX*
[c] *Department of Biostatistics, Columbia University Medical Center, New York, NY*
[d] *Department of Urology, Columbia University Medical Center, New York, NY*

Received 21 November 2018; received in revised form 10 January 2019; accepted 16 January 2019

Abstract

Background: Bladder cancer is the ninth most common noncutaneous malignancy worldwide, though a fraction (2%–5%) are diagnosed as squamous cell carcinoma (SCC) in the Western world. Current understanding is based on small, single-institution studies and SEER-database reviews with conflicting results. We used the National Cancer Database to explore clinical characteristics and outcomes from a large cohort of invasive bladder SCC.

Methods: We queried the National Cancer Database for diagnoses of urothelial carcinoma (UC) or SCC using International Classification of Disease-O-3 morphologic codes from cases reported between 2004 and 2015. Primary outcome was overall survival in cT2-4N0M0 bladder cancer. Statistical analysis performed using chi-squared test, Kaplan-Meier survival, binomial logistic regression, and Cox proportional hazards.

Results: The final cohort included 394,979 bladder cancer patients, of which 4,783 (1.2%) were classified as SCC histology. In comparison to UC, patients with SCC were more likely female (49% vs. 24%; $P < 0.01$) and African American (11% vs. 5%; $P < 0.01$). Patients with SCC presented at a higher stage than UC with muscle-invasive bladder cancer (MIBC) present at diagnosis in 70% vs. 19%. On multivariate analysis, SCC independently predicted poorer prognosis (hazard-ratio [HR] 1.79, $P < 0.01$) when controlling for patient characteristics and treatment modality. Unlike UC, there was no benefit with the use of NAC over radical cystectomy alone (HR 0.93, $P = 0.69$) for patients with SCC.

Conclusions: Invasive SCC of the bladder carries a worse prognosis as compared to UC histology, both overall and on a stage-for-stage basis. As opposed to UC, we did not observe a survival benefit for NAC among SCC patients treated with cystectomy.

Keywords: Invasive bladder cancer; Squamous cell carcinoma; Neoadjuvant chemotherapy

Introduction

Bladder cancer is the ninth most common noncutaneous malignancy in world with approximately 430,000 new diagnoses annually. In the United States (US) alone there will be an estimated 81,000 new cases in 2018 [1]. Outside of Africa and the Middle East, approximately 90% of all bladder cancers are urothelial carcinoma (UC). Squamous cell carcinoma (SCC) of the bladder comprises only 2% to 5% of cases in the US, making it difficult to collect sufficient numbers for robust, institution-level research [2–5].

The Bilharzial form of SCC is very common in regions with endemic *schistosomiasis haematobium*, previously responsible for 80% of all bladder cancers in Egypt [6].

Funding sources: None.
*Corresponding author. Tel.: +1-347-903-4454; fax: +1-844-596-0408.
E-mail address: jtmatulay@mdanderson.org (J.T. Matulay).

https://doi.org/10.1016/j.urolonc.2019.01.020
1078-1439/

Much of our knowledge regarding the prognosis and treatment of SCC comes from cohorts heavily enriched with Bilharzial disease. Based on these studies, Bilharzial-associated SCC is associated with younger age, lower stage, and a more indolent disease course with better survival outcomes [7–9].

In European and US cohorts controversies still exist regarding the optimal management of SCC [4,10,11]. While some series have suggested that SCC carries a worse prognosis, others have found that survival is similar to UC when controlling for pathologic characteristics such as stage [5,10,12–15]. The confusion likely stems from rarity of pure SCC cases within single institution cohorts where most of the publications originate.

Our objective was to use a large, population-based dataset to describe differences in disease characteristics at the time of presentation between patients with UC and SCC. We additionally sought to determine if, among patients with invasive bladder cancer, there are survival differences between patients with SCC and UC and whether receipt of NAC provided a survival benefit among patients with SCC.

2. Materials and methods

2.1. Dataset

The National Cancer Database (NCDB) captures over 70% of all new invasive cancer diagnoses annually from over 1,500 programs participating in the American College of Surgeons Commission on Cancer approvals program. Available data include patient-level demographics, facility characteristics, cancer-specific information, and treatment modality.

2.2. Cohort

We identified 496,988 patients who were at least 18 years of age with bladder cancer diagnosed between 2004 and 2015. We used International Classification of Disease-O-3 (ICD-O-3) morphologic codes for pure SCC (8052, 8070–8076, 8078) and pure UC (8120–8124, 8130, 8131). We excluded codes for the divergent differentiation subtypes of UC (i.e., micropapillary, nested, squamous differentiation, etc.). For the survival analyses we wished to focus on a cohort of muscle-invasive bladder cancer (cT2-T4N0M0) and, as such, excluded patients with clinically positive lymph nodes or metastatic disease at the time of diagnosis. Patients were also excluded if they were not assigned a clinical T stage (cTx) or had a concomitant diagnosis of a nonbladder malignancy.

2.3. Outcomes

Our primary outcome was overall survival (OS) after diagnosis of bladder cancer, defined as the time from diagnosis to last follow-up (last known alive date or date of last contact). The NCDB registry does not include cause of death so cancer-specific survival (CSS) information was not available.

2.4. Independent variables

Patient level demographic information included age, race, county characteristics, year of diagnosis, location, insurance status, Deyo-Charlson comorbidity index (CCI). County characteristics included income and high school graduation rates which were derived from U.S. Census data from the year 2000 or 2012. Cancer facility characteristics included type, geographic location, and distance from home to facility. Facility types are defined based on the volume of patients per year as comprehensive (>500), community (100–500) and academic (>500). Additionally, academic programs were defined as providing graduate medical programs in at least 4 areas. Facility location was collapsed into Northeast, South/Southeast, Midwest, and West. Cancer-specific information includes American Joint Committee on Cancer clinical and pathological tumor (T), lymph node (N), and metastatic (M) stages. Pathologic complete response was defined as stage T0N0M0 on radical cystectomy (RC) pathology. Definitive local therapy was defined as RC or external beam radiation therapy. Patients who had partial cystectomy or transurethral resection of bladder tumor as the most aggressive form of surgical therapy were classified as having nondefinitive therapy for the purposes of our analysis. We were able to determine the timing of when, if ever, chemotherapy was administered and defined NAC as a chemotherapy start date within 120 days prior to RC.

2.5. Statistical analysis

We first described the demographic characteristics of patients diagnosed with SCC and then used chi-square (categorical) and Student's t test (continuous) for univariate comparison. We used Kaplan-Meier curves stratified by clinical T stage with log-rank tests to visually demonstrate differences in survival by histology. We use multivariate proportional hazards regression to estimate the association between histologic subtype and OS. Model covariates included age, sex, race, type of facility, Charlson comorbidity index, clinical T stage, clinical grade, histology, and type of definitive local therapy. We use a separate proportional hazards regression model stratified by histologic type to determine if NAC was independently associated with survival. For all statistical measures, P value <0.05 was considered statistically significant. All analyses were performed using SPSS v23.0. Given the retrospective nature of this project, it was deemed exempt by our institutional review board.

Results

From a total cohort of 394,956 patients with a diagnosis of bladder cancer and complete clinical staging information

Table 1
Demographic and clinical characteristics of squamous cell carcinoma of the bladder.

Variable	UC *n* = 390,196 (98.8%)	SCC *n* = 4,783 (1.2%)	*P* value
Age (mean)	71.2	70.6	**<0.01**
<50	16,081 (4)	333 (7)	
50–59	48,151 (12)	668 (14)	
60–69	97,443 (25)	922 (19)	
70–79	122,859 (32)	1,316 (28)	
>=80	105,662 (27)	1,544 (32.3)	**<0.01**
Gender			
Male	294,642 (76)	2,418 (51)	
Female	95,554 (24)	2,365 (49)	**<0.01**
Race			
White	359,126 (92)	4108 (86)	
Black	19,091 (5)	540 (11)	
Other	7,989 (2)	99 (2)	
Unknown	3990 (1)	36 (1)	**<0.01**
Charlson comorbidity index			
0	281,792 (72)	3,261 (68)	
1	80,598 (21)	1,031 (22)	
>1	27,806 (7)	491 (10)	**<0.01**
Type of facility			
Academic/research program	109,492 (28)	1,733 (37)	
Community cancer program	50,126 (13)	504 (11)	
Comprehensive Community Cancer Program	186,776 (48)	1,984 (42)	
Other	40,421 (11)	490 (10)	**<0.01**
Geographic location			
Northeast	100,461 (26)	1,187 (25)	
South/Southeast	124,030 (32)	1,646 (34)	
Midwest	108,923 (28)	1,280 (27)	
West	56,782 (14)	670 (14)	**<0.01**
Insurance status			
Uninsured	7,207 (2)	152 (3)	
Private	110,656 (28)	1,061 (22)	
Medicaid	10,587 (3)	288 (6)	
Medicare	252,864 (65)	3,167 (66)	
Other government	3,399 (1)	41 (1)	
Other/unknown	5,483 (1)	74 (2)	**<0.01**
Income			
<$38,000	54033 (14)	916 (19)	
$38,000–$47,999	87,521 (23)	1,124 (24)	
$48,000–$63,000	107,048 (28)	1,209 (26)	
>$63,000	137,366 (36)	1,455 (31)	**<0.01**
Year of diagnosis			
2004–2009	164,886 (42)	2,216 (46)	
2010–2015	225,310 (58)	2,567 (54)	**<0.01**
Clinical grade			
G1	67,888 (17)	461 (10)	
G2	82,112 (21)	1,729 (36)	
G3	90,486 (23)	1,434 (30)	
G4	83,062 (21)	398 (8)	
Unknown	66,648 (17)	761 (16)	**<0.01**
AJCC T Stage (clinical)			
≤cT1	317,964 (81)	1,437 (30)	
cT2	54,617 (14)	1,889 (40)	
cT3	7,802 (2)	553 (11)	
cT4	9811 (3)	904 (19)	**<0.01**
AJCC N Stage (clinical)			
cN0	358,203 (92)	3,786 (79)	
cN(+)	8,310 (2)	532 (11)	
cNX	23,681 (6)	465 (10)	**<0.01**

(*continued*)

Table 1 (*Continued*)

Variable	UC $n = 390,196$ (98.8%)	SCC $n = 4,783$ (1.2%)	*P* value
AJCC M Stage (clinical)			
cM0	372,568 (96)	4,235 (88)	
cM1	8,402 (2)	423 (9)	
cMX	9,223 (2)	125 (3)	**<0.01**

AJCC = American Joint Committee on Cancer; M = metastasis; N = nodal; SCC = squamous cell carcinoma; T = tumor; UC = urothelial carcinoma.,
Note: Bold indicates statistically significant P value.

there were 63,482 patients with clinically localized MIBC of whom 4,783 (1.2%) had SCC. As shown in **Table 1**, SCC patients were younger and included a higher proportion of women (51% vs. 24%; P < 0.01) and nonwhites (14% vs. 8%; $P < 0.01$) when compared to UC. SCC was associated with significantly higher T stage at diagnosis, with muscle-invasion present in 70% compared to only 19% for UC. Furthermore, nodal involvement and metastatic disease were also significantly more common in SCC.

Among patients with cT2-4N0M0 bladder cancer, the use of external beam radiation therapy for definitive therapy was similar between SCC and UC (17% for each, $P = 0.10$) but RC was performed in a higher proportion of the former (39% vs. 35%, $P = 0.03$). Within the RC subset, utilization of NAC was significantly higher for UC (19.3% vs. 7.4%, $P < 0.01$, **Table 2**).

There was a large difference in median OS among patients with cT2-4N0M0 between SCC and UC (9.6 months and 24.6 months [$P < 0.01$], respectively). Patients with invasive SCC had inferior survival compared to UC when stratified by stage (**Fig. 1**). On multivariable analysis (**Table 3**), SCC was independently associated with an increased risk of death (HR 1.79, 95% confidence interval [CI] 1.70−1.88, $P < 0.01$).

The median OS for SCC patients who received RC alone was 25.4 months compared to 34.0 months with NAC ($P = 0.34$, **Fig. 2**), whereas NAC was associated with a survival benefit among patients with UC (39.2 months vs. 63.4 months, $P < 0.01$). In a multivariate analysis, NAC was independently associated with better OS in UC compared to RC alone (HR 0.83, 95% CI 0.79−0.88, $P < 0.01$) but this was not seen in patients with SCC (HR 0.93, 95% CI 0.66−1.30, $P = 0.65$).

Table 2
Treatment patterns of localized MIBC (cT2-4N0M0).

Definitive treatment	UC *n* (%)	SCC *n* (%)	*P* value
Total	58,144 (96)	2,604 (4)	
No definitive therapy*	28,204 (48)	1,137 (44)	**<0.01**
XRT	9,720 (17)	454 (17)	0.10
Alone	5,933 (61)	309 (68)	
Chemoradiation	3,787 (39)	145 (32)	**<0.01**
RC	20,220 (35)	1,013 (39)	**0.03**
Alone	16,324 (81)	938 (93)	
+NAC	3,896 (19)	75 (7)	**<0.01**

RC = radical cystectomy; SCC = squamous cell carcinoma; UC = urothelial carcinoma; XRT = external beam radiation therapy.

Discussion

The present study includes the largest cohort of SCC patients of any publication to date, at 4,783 individuals comprising 1.2% of the total bladder cancer population of the NCDB between 2004 and 2015. We found that SCC presents at a more advanced stage than UC, with nearly 70% of the former having muscle-invasion at diagnosis. In a stage-for-stage comparison of patients with muscle-invasive localized bladder cancer, SCC consistently fared worse than UC for all T stages. Furthermore, on multivariate analysis SCC histology independently predicted worse survival when adjusting for all relevant confounders, such as grade, stage, and treatment type. Finally, we did not observe a survival benefit with NAC for SCC patients whereas it was associated with significantly improved survival among UC as has been demonstrated in randomized controlled trials [16−18].

The largest body of literature on SCC comes from Egypt and the Middle East where series have demonstrated better disease specific and OS in Bilharzial SCC in comparison to UC [7,9]. Non-Bilharzial series from the US and Europe are much smaller and their conclusions about survival differences by histology are mixed. For example, one retrospective cohort study of 955 RC patients, of whom 26 had SCC, found no difference in CSS between UC and SCC (5-year CSS 57% vs. 68%; $P = 0.5$) [19]. In another retrospective cohort study of 424 RC patients, the median CSS for SCC ($n = 60$) was significantly shorter than UC ($n = 364$; 64.6 months vs. 82.5 months, respectively; $P = 0.01$) but on multivariate analysis histologic subtype was not predictive of OS (HR 1.42; $P = 0.2$) [13]. A report from MD Anderson Cancer Center found that the 2-year CSS (48%) and median CSS (12.4 months) for SCC were lower than what would be expected for UC, but a formal statistical comparison was not performed [20].

Analysis of other population-based registries has been similarly inconclusive regarding the impact of SCC on survival outcomes. In one study, the SEER dataset was used to examine records of all patients with nonmetastatic bladder cancer from 1988 to 2003 and found 1,422 SCCs and

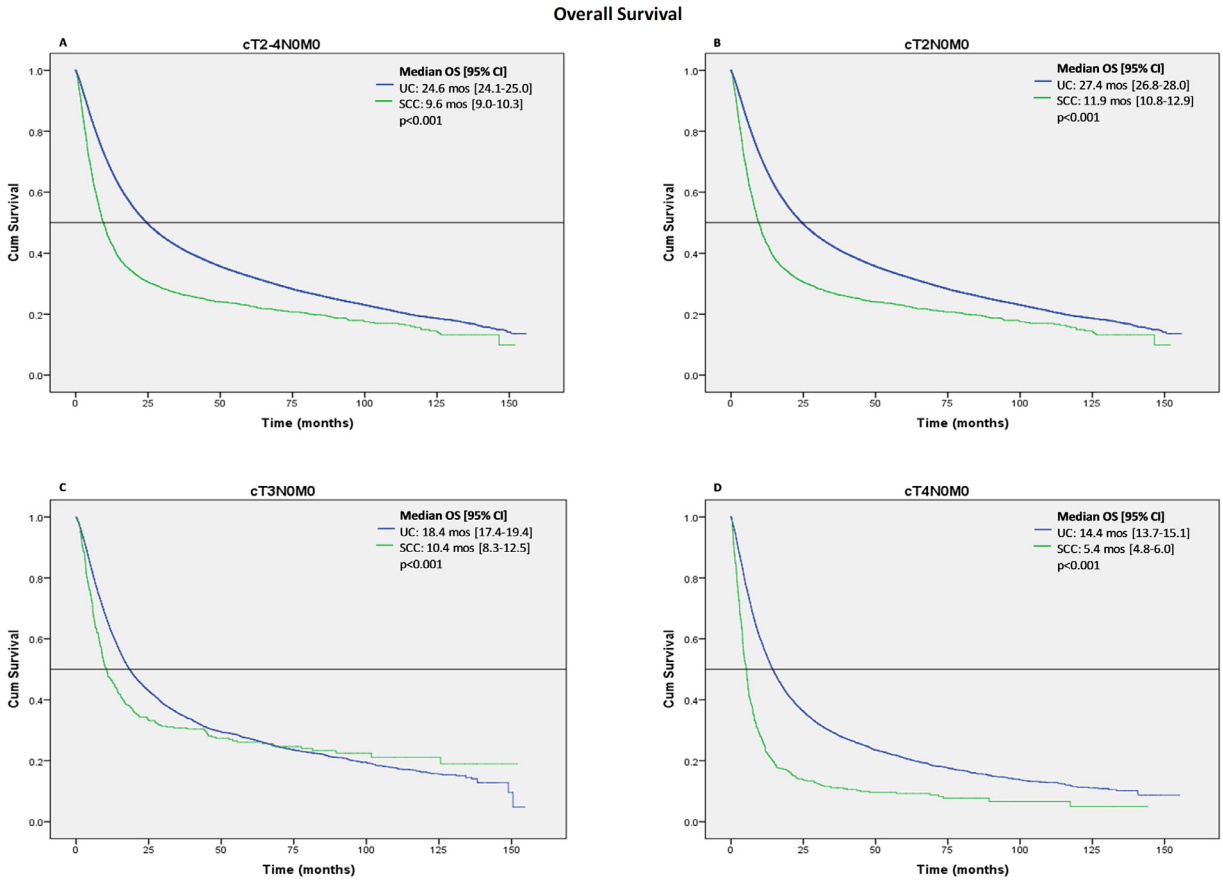

Fig. 1. Kaplan-Meier analysis for overall survival by histology among (A) clinically localized muscle-invasive bladder cancer patients (cT2-4N0M0) and substratified into (B) cT2N0M0, (C) cT3N0M0, and (D) cT4N0M0. OS = overall survival; SCC = squamous cell carcinoma; UC = urothelial carcinoma.

106,613 UCs [5]. They observed higher percentages of non-whites and women among SCC patients, a similarly high rate of muscle-invasion (≥cT2) among SCC patients as our NCDB cohort (85%), and found that SCC was associated with worse survival only among nonorgan confined disease (stage III or IV). Their total proportion of SCC diagnoses among all bladder cancer patients was similar to what we observed (1.3% vs. 1.4%), however our study had a lower proportion of SCC patients presenting with invasive disease and worse survival for SCC among all stages of invasive bladder cancer.

A second study using SEER data from 1988 to 2006 compared pathologic outcomes and survival among patients with SCC ($N = 614$) and UC ($N = 11,697$) who underwent RC for invasive bladder cancer [3]. The rate of pathologic nonorgan confined disease (≥pT3) was 68% in the SCC patients compared to 47.3% in UC, but there was no statistical difference in survival between histologic types on a stage-for-stage basis.

Unlike these prior population-based studies, our analysis of the NCDB registry shows that SCC is associated with worse OS compared to UC, within in each stage and independently on multivariate analysis. Perhaps our more contemporary cohort lends itself to improved classification of SCC, which has helped to highlight the discrepancy between histologies. There is also the possibility that pathologic reporting in SEER differs from NCDB since hospitals reporting to the NCDB must be accredited by the Commission on Cancer and represent only a small proportion of all hospitals (~1,500), which potentially makes them a more reliable resource for pathologic outcomes.

Another explanation for the discrepancy between the prior SEER studies and our findings could be the increased adoption of NAC for UC that occurred in the early- to mid-2000s [17]. The use of NAC would have been in its early stages at the latest time points from the prior SEER studies, perhaps translating to inferior UC survival relative to more contemporary cohorts that have greater utilization of chemotherapy [21]. In the present study, NAC was used in 19.3% and 7.4% of patients with cT2-4N0M0 UC and SCC, respectively, resulting in a significant OS advantage for UC (HR 0.81, $P < 0.01$) with a similar effect size to what was found on a recent meta-analysis of NAC (HR 0.87) [22].

Although relatively few SCC patients in our cohort were treated with NAC and RC, we did not observe a survival benefit with use of NAC. There are few other examples of the potential lack of efficacy of NAC for SCC. In a retrospective analysis of 33 consecutive patients with SCC of

Table 3
Cox proportional hazards analysis of overall survival in patients with clinically localized MIBC (cT2-4N0M0).

	HR (95% CI)	*P* value
Age (continuous)	1.034 (1.033–1.035)	**<0.01**
Sex		
Male	ref	
Female	1.09 (1.06–1.11)	**<0.01**
Race		
White	ref	
Black	1.16 (1.11–1.21)	**<0.01**
Other	0.81 (0.75–0.88)	**<0.01**
Unknown	0.88 (0.79–0.98)	**0.04**
Type of facility		
Academic/research program	ref	
Community cancer program	1.10 (1.06–1.14)	**<0.01**
Comprehensive community cancer program	1.06 (1.04–1.09)	**<0.01**
Other	1.06 (1.02–1.10)	**<0.01**
Charlson comorbidity score		
0	ref	
1	1.24 (1.21–1.27)	**<0.01**
2	1.56 (1.51–1.62)	**<0.01**
3	1.82 (1.70–1.93)	**<0.01**
Grade		
1	ref	
2	1.19 (1.08–1.30)	**<0.01**
3	1.52 (1.40–1.65)	**<0.01**
4	1.50 (1.38–1.63)	**<0.01**
AJCC stage (clinical)		
cT2	ref	
cT3	1.32 (1.28–1.36)	**<0.01**
cT4	1.58 (1.54–1.63)	**<0.01**
Histology		
UC	ref	
SCC	1.81 (1.72–1.90)	**<0.01**
Definitive local therapy		
RC alone	ref	
RC+ NAC	0.85 (0.81–0.90)	**<0.01**
XRT alone	1.38 (1.33–1.44)	**<0.01**
Chemoradiation	1.08 (1.04–1.13)	**<0.01**
No definitive therapy	1.47 (1.44–1.51)	**<0.01**

AJCC = American Joint Committee on Cancer; CI = confidence interval; HR = hazard ratio; RC = radical cystectomy; SCC = squamous cell carcinoma; UC = urothelial carcinoma; XRT = external beam radiation therapy.

the urinary tract ($n = 21$ located in the bladder), Japanese researchers found no difference in OS between patients who underwent radical surgery with or without NAC (2-year OS 75% vs. 83% [$P = 0.7$]), respectively [23]. Another series of SCC ($n = 32$) or squamous predominant UC-variant ($n = 10$) from the Cleveland Clinic found no pathologic response for the 4 patients with squamous histology who received cisplatin-based NAC [24]. A prospective, randomized trial of 114 Egyptian bladder cancer patients compared immediate RC for T3-T4N0M0 to 3 cycles of gemcitabine/cisplatin followed by cystoscopic re-evaluation before proceeding to either radiotherapy (cT0-T1) or RC (≥cT2) [25]. In this population, approximately half of the cohort consisted of SCC patients, many of which likely had Bilharzial disease. The authors described a clinical complete response rate in the chemo group of 28.6% (14/49), of which 5 patients had SCC. These findings support our own observations that standard NAC had no significant impact on OS for SCC treated with RC (HR 0.93, $P < 0.69$). A different approach to NAC may be required for SCC with an alternative to the cisplatin-based regimens that are efficacious for UC or forgoing neoadjuvant therapy altogether in favor of immediate RC.

There is no clear explanation for why SCC exhibits a more aggressive phenotype than UC, but we may soon be able to look toward genetic information to help shed light. By clinically demonstrating a more aggressive course for SCC, studies such as ours suggest that there is likely an underlying genetic difference of this rare subtype worth exploring at the molecular level. The Cancer Genome Atlas describes a "basal-squamous" molecular subtype due to its enrichment in both basal markers (*CD44*, *KRT6A*, etc.) and squamous markers (*DSC3*, *GSDMC*, etc.) [26]. This subgroup also contains the highest proportion of SCCs and UC with squamous differentiation, and has one of the worst OS among all subtypes. However, the actual number of histologically classified pure SCC cases is low ($n = 3$) and may explain why, unlike our findings of no benefit to NAC, basal-squamous subtype is actually associated with the best response neoadjuvant cisplatin-based chemotherapy of all molecular subtypes [27]. Though there are no studies using immunotherapies specifically for SCC of the bladder, up-regulation of immune markers (*CXCL11*, *L1CAM*, *IDO1*, *CD274*) within this group makes this an encouraging area of future research [26].

Our study does have some limitations, largely related to the use of a nationwide registry to extract patient data. Pathologic data in the NCDB is based on the reporting institution's diagnosis and submitted in the form of an ICD-O-3 code without centralized pathologic review or confirmation. While there are specific codes for each major histologic subtype, it is possible UC with squamous features could be misidentified as SCC and included in our cohort. Squamous differentiation within a background of typical UC is likely a different disease entity than pure SCC and recent evidence suggests that only the pure form impacts outcomes [11]. A further limitation is the definition of NAC since the NCDB data only reports timing of treatments (i.e., chemotherapy and surgery) but does not include a specific NAC variable. We have defined NAC as patients who received their first cycle within 120 days of RC in order to minimize the inclusion of patients who received induction chemotherapy for advanced disease but subsequently went on to RC as a salvage measure for symptom control. OS is a suboptimal endpoint when studying bladder cancer due to the advanced age of the patient population and divergence with CSS [28], which may lead to an underestimation of the effect of treatment. This again is a limitation of using the NCDB as only OS is reported.

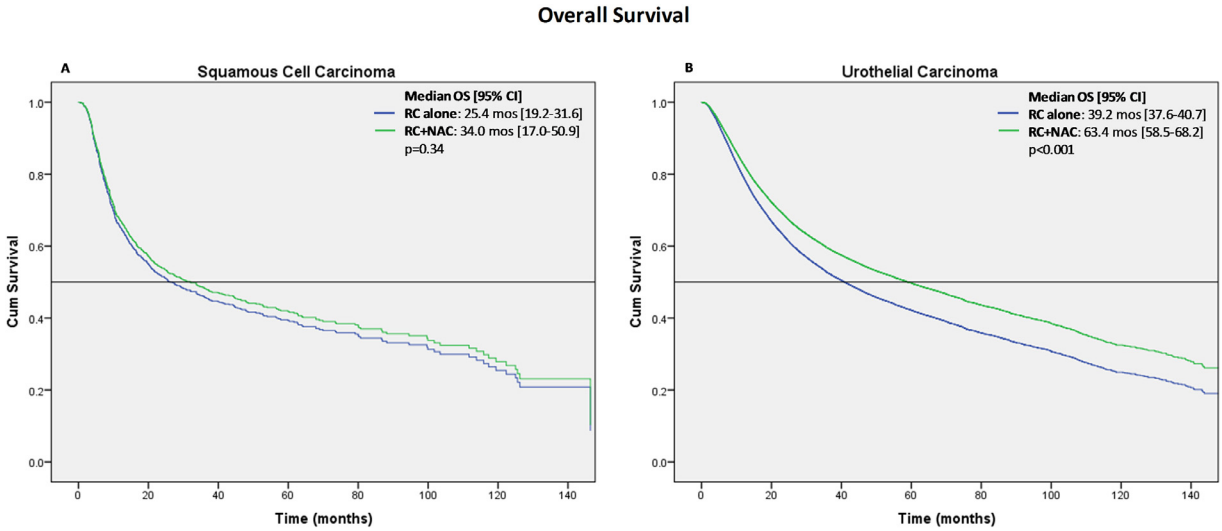

Fig. 2. Kaplan-Meier analysis for overall survival in clinically localized muscle-invasive bladder cancer patients (cT2-4N0M0) with (A) squamous cell carcinoma and (B) urothelial carcinoma treated with radical cystectomy either alone or with neoadjuvant chemotherapy. NAC = neoadjuvant chemotherapy; OS = overall survival; RC = radical cystectomy; SCC = squamous cell carcinoma; UC = urothelial carcinoma.

Conclusions

We observed inferior survival among patients with muscle-invasive SCC as compared to muscle-invasive UC. The use of NAC is less common in SCC but when used, we did not observe a significant impact on survival. This information is only hypothesis generating, though can be used to aid in designing multi-institutional trials for more effective therapies for bladder SCC.

Conflicts of interest

AMK is a consultant to TMC Innovation, Merck, BMS, Arquer, MDxHealth, Photocure, Theralase, Cepheid, Medac, Asieris, Pfizer, and Astra Zeneca and has received research funding from FKD, Merck, Telesta, and Adolo. The other authors have no competing interests to declare.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68(1):7–30.
[2] Rausch S, Lotan Y, Youssef RF. Squamous cell carcinogenesis and squamous cell carcinoma of the urinary bladder: a contemporary review with focus on nonbilharzial squamous cell carcinoma. Urol Oncol 2014;32(1):32 e11–36.
[3] Abdollah F, Sun M, Jeldres C, et al. Survival after radical cystectomy of non-bilharzial squamous cell carcinoma vs urothelial carcinoma: a competing-risks analysis. BJU Int 2012;109(4):564–9.
[4] Martin JW, Carballido EM, Ahmed A, et al. Squamous cell carcinoma of the urinary bladder: systematic review of clinical characteristics and therapeutic approaches. Arab J Urol 2016;14(3):183–91.
[5] Scosyrev E, Yao J, Messing E. Urothelial carcinoma versus squamous cell carcinoma of bladder: is survival different with stage adjustment. Urology 2009;73(4):822–7.
[6] Gouda I, Mokhtar N, Bilal D, El-Bolkainy T, El-Bolkainy NM. Bilharziasis and bladder cancer: a time trend analysis of 9843 patients. J Egypt Natl Cancer Inst 2007;19(2):158–62.
[7] Ghoneim MA, Abdel-Latif M, el-Mekresh M, et al. Radical cystectomy for carcinoma of the bladder: 2,720 consecutive cases 5 years later. J Urol 2008;180(1):121–7.
[8] El-Sebaie M, Zaghloul MS, Howard G, Mokhtar A. Squamous cell carcinoma of the bilharzial and non-bilharzial urinary bladder: a review of etiological features, natural history, and management. Int J Clin Oncol 2005;10(1):20–5.
[9] Ghoneim MA, el-Mekresh MM, el-Baz MA, el-Attar IA, Ashamallah A. Radical cystectomy for carcinoma of the bladder: critical evaluation of the results in 1,026 cases. J Urol 1997;158(2):393–9.
[10] Chen C, Hu L, Chen Y, Hou J. The prognostic value of histological subtype in patients with metastatic bladder cancer. Oncotarget 2017;8(17):28408–17.
[11] Moschini M, Shariat SF, Luciano R, et al. Pure but Not Mixed histologic variants are associated with poor survival at radical cystectomy in bladder cancer patients. Clin Genitourin Cancer. 2016;15(4):e603–7.
[12] Liu Y, Bui MM, Xu B. Urothelial carcinoma with squamous differentiation is associated with high tumor stage and pelvic lymph-node metastasis. Cancer Control 2017;24(1):78–82.
[13] Balci U, Ozer K, Gorgel SN, Sefik E, Girgin C, Dincel C. Do pure squamous cell carcinomas and urothelial carcinomas have similar prognosis after radical cystectomy. World J Urol 2013;31(5):1177–82.
[14] Izard JP, Siemens DR, Mackillop WJ, et al. Outcomes of squamous histology in bladder cancer: a population-based study. Urol Oncol 2015;33(10):425 e427–413.
[15] Arslan B, Bozkurt IH, Yonguc T, et al. Clinical features and outcomes of nontransitional cell carcinomas of the urinary bladder: analysis of 125 cases. Urol Ann 2015;7(2):177–82.
[16] Advanced Bladder Cancer Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. Eur Urol 2005;48(2):202–5:discussion 205–206.
[17] Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 2003;349:859–66.

[18] International Collaboration of Trialists. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the ba06 30894 trial. J Clin Oncol 2011;29(16):2171–7.

[19] Rogers CG, Palapattu GS, Shariat SF, et al. Clinical outcomes following radical cystectomy for primary nontransitional cell carcinoma of the bladder compared to transitional cell carcinoma of the bladder. J Urol 2006;175(6):2048–53; discussion 2053.

[20] Kassouf W, Spiess PE, Siefker-Radtke A, et al. Outcome and patterns of recurrence of nonbilharzial pure squamous cell carcinoma of the bladder: a contemporary review of The University of Texas M D Anderson Cancer Center experience. Cancer 2007;110(4):764–9.

[21] Zaid HB, Patel SG, Stimson CJ, et al. Trends in the utilization of neoadjuvant chemotherapy in muscle-invasive bladder cancer: results from the National Cancer Database. Urology 2014;83(1):75–80.

[22] Yin M, Joshi M, Meijer RP, et al. Neoadjuvant chemotherapy for muscle-invasive bladder cancer: a systematic review and two-step meta-analysis. Oncologist 2016;21(6):708–15.

[23] Makino T, Izumi K, Natsagdorj A, et al. Significance of perioperative chemotherapy in squamous cell carcinoma of the upper and lower urinary tract. Anticancer Res 2018;38(4):2241–5.

[24] Zahoor H, Elson P, Stephenson A, et al. Patient Characteristics, treatment patterns and prognostic factors in squamous cell bladder cancer. Clin Genitourin Cancer 2018;16(2):e437–42.

[25] Khaled HM, Shafik HE, Zabhloul MS, et al. Gemcitabine and cisplatin as neoadjuvant chemotherapy for invasive transitional and squamous cell carcinoma of the bladder: effect on survival and bladder preservation. Clin Genitourin Cancer 2014;12(5):e233–40.

[26] Robertson AG, Kim J, Al-Ahmadie H, et al. Comprehensive molecular characterization of muscle-invasive bladder cancer. Cell 2017;171(3):540–56:e525.

[27] Seiler R, Ashab HAD, Erho N, et al. Impact of molecular subtypes in muscle-invasive bladder cancer on predicting response and survival after neoadjuvant chemotherapy. Eur Urol 2017;72(4):544–54.

[28] Gschwend JE, Dahm P, Fair WR. Disease specific survival as endpoint of outcome for bladder cancer patients following radical cystectomy. Eur Urol 2002;41(4):440–8.