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ORIGINAL ARTICLE

Squamous cell carcinoma of the bladder: poor response to neoadjuvant chemotherapy

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Abstract

Background Squamous cell carcinoma (SCC) of the bladder is a rare, aggressive malignancy. Unlike urothelial cell carcinoma, SCC is resistant to chemotherapy and guidelines recommend radical cystectomy (RC) without neoadjuvant chemotherapy (NAC). We aimed to evaluate the current management and survival of patients with invasive SCC treated with or without NAC.

Methods 671 patients with invasive SCC bladder cancer from 2004 to 2015 in the National Cancer Data Base were identified. Patients were stratified by treatment with RC alone or NAC prior to RC (NAC + RC). Survival analysis was performed with Kaplan–Meier and Cox regression. Secondary outcomes included length of stay and readmission.

Results Of 671 patients, 92.8% were treated with RC alone and 7.2% with NAC + RC. Cox regression for mortality was performed including age, Charlson score, clinical stage, and NAC. Increased risk of mortality was noted with increasing age (OR 1.01, $p = 0.023$) and Charlson score of 1–3 (HR 1.58–1.68, $p < 0.05$). NAC did not confer survival advantage (HR 1.17, $p = 0.46$). On Kaplan–Meier analysis, the overall survival was equivalent (log-rank $p = 0.804$). Hospital stay and readmission were similar between RC and NAC + RC groups.

Conclusions Analysis of a national tumor registry suggests a lack of overall survival benefit for NAC with localized, muscle invasive SCC of the bladder. Further research directed at chemotherapy regimens for SCC is needed to optimize treatment and improve survival outcomes.

Keywords Bladder cancer · Squamous cell cancer · Cystectomy · Neoplasm invasion

Introduction

Bladder cancer is an aggressive malignancy of the genitourinary system and the 7th most commonly diagnosed cancer in America, with more than 81,000 new cases and 17,000 deaths estimated for 2018 [1, 2]. Urothelial cell carcinoma (UCC) is the most common histologic type of bladder cancer comprising more than 90% of cases in the United States [3]. UCC is often responsive to cisplatin-based combined chemotherapy; thus, neoadjuvant or adjuvant cisplatin-based chemotherapy is considered standard of care for invasive UCC of the bladder [4]. Studies reveal a 5% increase in overall survival at 5 years for patients undergoing neoadjuvant chemotherapy (NAC) for muscle invasive UCC prior to radical cystectomy (RC) [5].

Primary squamous cell carcinoma (SCC), a variant histology of bladder cancer, is a rare subtype that accounts for 2–5% of all bladder cancers and approximately 500 new cases annually in the United States [1, 6]. Variant histology is correlated with higher staging upon diagnosis compared to pure UCC, and this may result in worsened survival outcomes [7]. SCC is typically more aggressive than UCC, often presents at a later stage upon diagnosis, and commonly causes aggressive local invasion rather than systemic spread [8, 9]. Pure SCC, unlike UCC, is typically unresponsive to cisplatin-based chemotherapy, and therefore guidelines recommend upfront RC without NAC for muscle invasive disease [10]. Unfortunately due to the rarity of variant histology, such as SCC, there are no large scale randomized studies to guide specific treatment. In this study, we aim to evaluate the current management and survival trends in patients with muscle invasive SCC and treated with or without NAC.

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Materials and methods

Data source

The National Cancer Database (NCDB) is a joint project by the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The NCDB includes data from all cancer patients treated at participating Commission on Cancer-accredited institutions and is estimated to capture over 70% of new cancer cases in the United States [11]. Standardized coding definitions specific to the NCDB are utilized and collected by specialized coders at each referring institution. The data is freely available to participating institutions after application for projects are submitted and approved. The data used in the study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed or the conclusions drawn from these data by the investigator.

Study population

The NCDB bladder cancer dataset was queried for patients with SCC histology, including clinical stage T2–T3 disease between 2004 and 2015. Patients with clinical stage T4, evidence of nodal enlargement (cN positive), or with distant metastasis were excluded from analysis. Patients were included only if they had undergone RC. The study population was additionally categorized by receipt of NAC. Of note, the NCDB does not include the specific regimen or cycles of chemotherapy agent utilized. Treatment categories included RC alone or NAC + RC.

Patient demographic variables included age, race, gender, Charlson comorbidity index, clinical TNM stage, income status, treatment facility type and insurance status [12]. Treatment facility type was categorized as low volume or high volume. Treatment facilities that accrued 500 or more newly diagnosed cancer cases per year were considered high-volume (including academic centers), whereas facilities with less than 500 were labeled low volume. Post-treatment outcomes included pathologic T stage and nodal status, all-cause mortality (within 30 days of treatment, 90 days of treatment, and at last follow-up), and length of follow-up. Length of follow-up and overall survival was calculated with the date of diagnosis as the start date.

Statistical analysis and outcome measure

One-way ANOVA or Student's *t* test was performed for continuous variables, and Fisher's exact or Pearson Chi-square tests for categorical variables to compare differences in patient demographics, clinical characteristics, and survival outcomes. Multivariable analysis was performed using Cox regression to identify risk factors for mortality. Kaplan–Meier analysis was performed for survival outcome by treatment type. We utilized SPSS v25 (New York, United States) for all analyses, with p value of < 0.05 denoting statistical significance. Our primary outcome was overall survival, stratified by treatment type. Secondary outcomes included length of stay and readmission with 30 days of surgery.

Results

In total, 671 patients were identified from the NCDB from 2004 to 2015 with muscle invasive SCC of the bladder (Table 1). 623 patients were treated with upfront RC and 48 were treated with NAC + RC. The average patient age was 67 years. Patients treated with NAC were younger compared to those treated with immediate RC (61.0 years vs 67.5 years, $p < 0.001$). Race was not a significant factor in treatment type. The majority of patients (69%) had Charlson comorbidity score of 0, and Charlson score was not associated with type of treatment. Tumor stage, income status and treatment facility volume were not significantly related to treatment type. Patients with private insurance were more likely to be treated with NAC and those with medicare were more likely to be treated with immediate RC ($p = 0.026$).

Outcome data (Table 2) demonstrated a significant difference between the treatment groups in pathological tumor stage despite no significant difference in clinical tumor stage. There were more patients downstaged to non-invasive disease (pT < 2) in the NAC group (10.4% vs 1.6%, $p < 0.001$). Pathological nodal stage was not different between the groups with 18.7% pN + in the NAC group and 17.5% in the immediate RC group ($p = 0.884$). The average hospital stay was similar between the two treatment group (10.4 days RC vs 12.8 days NAC + RC, $p = 0.223$). 30-day unplanned readmission was not different between the two groups. Average length of follow-up was 36.3 months and was not significantly different between the two groups ($p = 0399$). Overall mortality was 53.1%, and mortality within 30 and 90 days were 4.1% and 9.4%, respectively. Mortality was not significantly different between the groups.

Cox regression was done to examine correlations with overall mortality. The multivariable model included preoperative factors of age, Charlson score, clinical T stage, and NAC use. Older patients had a higher mortality (OR 1.01, $p = 0.023$). Increasing Charlson score also was associated with mortality risk (OR 1.581–1.677, $p < 0.05$). Clinical stage was not associated with mortality risk and receipt of

Table 1 Demographics and clinical tumor characteristics

Variable	All ($n=671$)	RC alone ($n=623$)	NAC + RC ($n=48$)	Sig
Mean age	67.0 ± 12.5	67.5 ± 12.4	61.0 ± 13.0	0.001
Race				0.268
White	607 (90.5%)	564 (90.5%)	43 (89.6%)	
Black	45 (6.7%)	43 (6.9%)	2 (4.2%)	
Other	19 (2.8%)	16 (2.6%)	3 (6.3%)	
Charlson				0.792
0	463 (69.0%)	427 (68.5%)	36 (75.0%)	
1	129 (19.2%)	122 (19.6%)	7 (14.6%)	
2	53 (7.9%)	50 (8.0%)	3 (6.3%)	
3 +	26 (3.9%)	24 (3.9%)	2 (4.2%)	
cT stage				0.723
2	517 (77.0%)	481 (77.2%)	36 (75.0%)	
3	154 (23.0%)	142 (22.8%)	12 (25.0%)	
Income				0.891
< $38,000	110 (16.6%)	101 (16.5%)	9 (18.8%)	
$38–47,999	166 (25.1%)	153 (25.0%)	13 (27.1%)	
$48–62,999	167 (25.3%)	157 (25.6%)	10 (20.8%)	
$63,000 +	218 (33.0%)	202 (33.0%)	16 (33.3%)	
Facility type				0.224
Low volume	537 (82.4%)	503 (82.9%)	34 (75.6%)	
High volume	115 (17.6%)	104 (17.1%)	11 (24.4%)	
Insurance				0.026
Uninsured	19 (2.8%)	17 (2.7%)	2 (4.2%)	
Private	201 (30.0%)	180 (28.9%)	21 (43.8%)	
Medicaid	42 (6.3%)	40 (6.4%)	2 (4.2%)	
Medicare	396 (59.0%)	375 (60.2%)	21 (43.8%)	
Other govt	6 (0.9%)	4 (0.6%)	2 (4.2%)	
Unknown	7 (1.0%)	7 (1.1%)	0 (0%)	

RC radical cystectomy, *NAC* neoadjuvant chemotherapy, *Govt* government

Table 2 Perioperative and survival outcomes

Variable	All ($n=671$)	RC alone ($n=623$)	NAC + RC ($n=48$)	Sig
30-day Readmit	54 (8.0%)	52 (8.4%)	2 (4.2%)	0.416
Hospital stay	10.6 ± 12.2	10.4 ± 10.3	12.8 ± 26.8	0.223
pT stage				0.001
< 2	15 (2.2%)	10 (1.6%)	5 (10.4%)	
2	156 (23.2%)	148 (23.8%)	8 (16.7%)	
3	343 (51.1%)	319 (51.2%)	24 (50.0%)	
4	88 (13.1%)	80 (12.8%)	8 (16.7%)	
Unknown	69 (10.3%)	66 (10.6%)	3 (6.3%)	
pN +	118 (17.6%)	109 (17.5%)	9 (18.7%)	0.844
Follow-up (months)	36.3 ± 34.6	36.6 ± 35.1	31.9 ± 26.8	0.399
Mortality	356 (53.1%)	331 (53.1%)	25 (52.1%)	1.000
30 days	25 (4.1%)	25 (4.4%)	0 (0%)	0.247
90 days	57 (9.4%)	54 (9.6%)	3 (7.3%)	0.789

RC radical cystectomy, *NAC* neoadjuvant chemotherapy, *Readmit* readmission

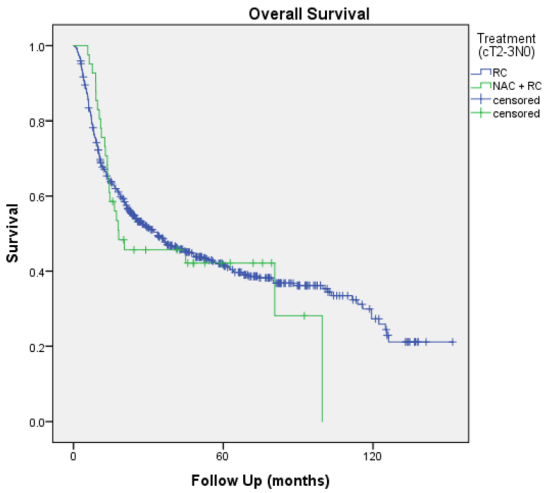
Table 3 Cox regression for mortality (all patients)

Variable	HR	95% CI low	95% CI high	Sig
Age	1.010	1.001	1.019	0.023
Charlson score (0 ref)				
1	1.628	1.253	2.114	< 0.001
2	1.581	1.106	2.259	0.012
3 +	1.677	1.008	2.792	0.047
cT3 stage	0.985	0.771	1.259	0.905
NAC	1.169	0.773	1.767	0.460

HR hazard ratio, *CI* confidence interval, *NAC* neoadjuvant chemotherapy

Variable	2 year OS	SD
RC	54.8%	2.1
NAC + RC	45.7%	7.9

Log rank p=0.804



Variable	# at risk			
RC	563	277	130	21
NAC + RC	41	17	7	0
Time	0 months	24 months	60 months	120 months

Abbreviations: RC, radical cystectomy; NAC, neoadjuvant chemotherapy; OS, overall survival; SD, standard deviation

Fig. 1 Kaplan–Meier analysis of overall survival

NAC was not a significant factor associated with mortality ($p = 0.46$) (Table 3).

Kaplan–Meier analysis (Fig. 1) revealed no significant difference in survival between the two groups. The 2-year overall survival was 54.8% for RC alone and 45.7% for NAC + RC (log-rank $p = 0.804$).

Discussion

We present a large comprehensive national review of survival in patients receiving RC with or without NAC for SCC of the bladder, noting the rarity of the variant histology and poor survival outcomes overall. Additionally, we found that NAC did not confer any overall survival benefit for those with cT2–3N0 disease. This is in contrast to classic UCC, where there is level one evidence to support the use of NAC prior to RC; however, the efficacy of NAC in SCC of the bladder is poorly understood [13–15]. Due to the rarity of SCC, there are no large prospective studies to provide guideline statements. Given this paucity of data, we aimed to define the outcomes regarding NAC for SCC of the bladder.

For traditional UCC of the bladder, the SWOG (Southwest Oncology Group) trial demonstrated a 5-year overall survival of 57% in patients with muscle invasive disease undergoing NAC and RC, compared to 43% for those undergoing RC alone [13]. Although this was not statistically significant ($p = 0.06$), the results have been used to support the use of NAC. A later meta-analysis, which included the SWOG trial and other randomized trials involving NAC for bladder cancer, demonstrated a statistically significant improvement of overall survival of 5% and a disease free survival of 9% from the use of NAC [14]. Due to the rarity of SCC in the bladder, there are no prospective studies showing a benefit to chemotherapy for SCC, and multiple small retrospective reviews have failed to show improvement on survival with NAC for SCC [16, 17]. However, given the lack of large scale analysis, the use of NAC for SCC has been debatable. For example, Kassouf et al. performed a retrospective review of 27 patients with pure SCC, three of whom underwent NAC [18]. Two of the three patients with NAC were downstaged at the time of RC and remained disease free at latest follow-up. The study, however, did not find any difference in disease-free survival or overall survival between patients treated with NAC and RC vs upfront RC. The rarity of SCC of the bladder, combined with a lack of a prospective analysis, has led to confusion regarding the optimum sequence of definitive therapy.

In our review of the NCDB, we did not find any survival benefit in the use of NAC for SCC. The 2-year overall survival for those treated with NAC + RC was 45.7%, compared to 54.8% for those treated with upfront RC. Additionally, on a multivariable Cox regression for survival, we found associations with age and underlying comorbidity (Charlson score) but no association with the receipt of NAC. Based on our results, further revisions in guideline statements for bladder malignancy should continue to emphasize this finding and encourage providers to pursue upfront RC with SCC variant. Of note, it is interesting that a small but significant number of patients were downstaged to non-invasive disease (< pT2) after receiving NAC. The reasons for this are unclear from our analysis, but future study may need to focus on this subgroup of patients. The limited number of patients in this category did not allow for sub-analysis but should be considered for further research.

Despite the current recommendations regarding RC in pure SCC, 7.2% of the patients in our study were treated

with NAC prior to RC. This may be due to the confusion and unclear consensus in the literature regarding the efficacy of NAC in SCC. In addition, it may be that many of those treated with NAC were patients with mixed histology, including both UCC and SCC. Studies regarding the use of NAC in mixed histology are rare, and guidelines typically recommend treating such cases of mixed histology in the same manner as pure UCC (i.e., NAC + RC). However, based on our data, this assumption should be re-evaluated. Patients with a significant amount of SCC of the bladder may not receive benefit from NAC and should be counseled regarding early RC. The NCDB does not specify the amount of SCC histology present, and this is a limitation of our study. However, it is likely that patients coded as SCC of the bladder in the NCDB have a high volume of SCC, if not pure SCC, and these findings should encourage providers to pursue upfront RC in this setting.

The reason for the difference in survival response with NAC between UCC and SCC is unclear. UCC has significant understaging and a high rate of recurrence with distant metastasis [19]. On the contrary, SCC is more likely to present with local invasion with less than 10% of new cases presenting with distant metastasis [5]. Thus, it may be more important to excise local disease in SCC rather than prevent or treat micro-metastatic disease in UCC with chemotherapy. In a review of the SEER database, Scosyrev et al. found that among patients with muscle invasive disease who did not undergo RC, SCC was significantly associated with increased bladder cancer-specific mortality within 2 years [20]. Although their results did not specify which patients had or had not undergone NAC, they do highlight the significant impact of RC on survival in SCC, particularly among less advanced stages.

Our study is subject to the limitations inherent in any retrospective review. Due to the retrospective design, only statistical correlations could be established without the ability to control for confounders. We cannot account for selection bias which may have impacted treatment choice as well as outcomes. For example, many patients may have received NAC if there was concern the tumor was unresectable on initial diagnosis, although we attempted to limit this by only evaluating patients with cT2–3N0 disease. Another limitation was the inability to establish concrete histological classification with centralized pathologic review. We instead had to rely on coding for categorization as pure SCC or majority SCC. It was not possible to differentiate the percentage of SCC present on any specimen and we cannot account for coding errors. There may have been underreporting of mixed histology SCC with UCC, as such specimens may have been coded as UCC. The diagnosis of histologic variants itself is subject to inter-observer variability which further complicates the categorization. Finally, the NCDB does not specify survival outcomes by cancer-related outcomes (recurrence free survival or cancer specific survival) or specific chemotherapy regimens.

Conclusion

Analysis of a national tumor registry suggests a lack of overall survival benefit for NAC with localized, muscle invasive SCC of the bladder. Further research directed at chemotherapy regimens for SCC is needed to optimize treatment and improve survival outcomes.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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