Sociodemographic and survival disparities for histologic variants of bladder cancer

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Introduction: *To investigate the impact of perioperative factors on overall survival among patients with histologic variants of bladder cancer treated with radical cystectomy.*

Materials and methods: *The National Cancer Data Base was utilized to identify patients diagnosed with muscle-invasive bladder cancer (cT2-4, N0, M0) from 2004-2013. Variant histology bladder cancers (non-mucinous adenocarcinoma, mucinous/signet ring adenocarcinoma, micropapillary urothelial carcinoma, small cell carcinoma, and squamous cell carcinoma) were compared to urothelial carcinoma with respect to overall survival. Adjusted hazard ratios (aHR) and 95% confidence intervals (95% CI) were calculated from a multivariable Cox regression model to examine factors affecting overall survival, T upstaging, N upstaging, and positive surgical margins. Median survival was calculated using Kaplan-Meier analysis.*

Results: *A total of 5,856 patients were included in this study. Significant predictors of worse overall survival included: African-American ancestry (aHR = 1.24, 95%CI: 1.03-1.48, p = 0.021), age (1.03, 1.02-1.03, p < 0.001), comorbidity (1.30, 1.20-1.40, p < 0.001), cT3 stage (1.41, 1.26-1.57, p < 0.001), and cT4 stage (1.59, 1.38-1.84, p < 0.001). Small cell carcinoma (2.10, 1.44-3.06, p < 0.001) and non-mucinous adenocarcinoma (1.59, 1.15-2.20, p = 0.005) were significant predictors of worse overall survival compared to urothelial carcinoma. Small cell carcinoma had the worst 5 year overall survival (15.5%, 95% CI: 5.2%-30.9%) compared to urothelial carcinoma (48.7%, 95% CI: 47.2%-50.2%). Micropapillary urothelial carcinoma was a significant predictor of increased progression to node positivity and positive margin status after radical cystectomy compared to urothelial carcinoma (6.01, 3.11-11.63, p < 0.001; 4.38, 2.05-9.38; p < 0.001).*

Conclusions: *Among bladder cancer patients with equal treatment and staging, small cell carcinoma and non-mucinous adenocarcinoma variant histologies were predictive of worse overall survival compared to urothelial carcinoma. Patient demographics such as African-American ancestry and age were also predictive of worse overall survival among variant histology bladder cancer and urothelial carcinoma.*

Key Words: bladder cancer, histology, histologic variants, sociodemographic disparities, National Cancer Data Base, NCDB

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Introduction

Bladder cancer is the fifth most common malignancy diagnosed in the United States with almost 80,000 new cases diagnosed last year.[1,2] The vast majority of patients are diagnosed with urothelial carcinoma and present with non-muscle invasive disease.[3] In approximately 5% of cases, bladder cancer is not urothelial cell type in origin.[4] Variant histology bladder cancer often presents as muscle-invasive disease

and has poorer prognosis compared to urothelial carcinoma.[5] Some studies have attributed worse outcomes to biologically more aggressive disease,[6,7] while others have suggested that variant histology bladder cancer presents at a more advanced stage.[8,9]

Although treatment guidelines are well established for urothelial carcinoma, optimal management of variant histology bladder cancer is not as well defined.[5] Treatment modalities such as chemotherapy, radiation therapy, and surgery have been utilized for each histological variant with different agents, dosing, timing, and types of surgery.[10,11] While this has helped elucidate potentially efficacious treatment regimens for specific histological variants, the wide range of treatments has complicated studies comparing survival in variant histology bladder cancer and urothelial carcinoma.[7,12] Also, the majority of these studies have been retrospective in nature, preventing investigators from knowing which patients were treated with palliative or curative intent.[7] Even less is known about sociodemographic predispositions for variant histology bladder cancer.

We investigated the natural history of variant histology bladder cancer by defining clinically relevant groups and comparing overall survival, upstaging, and surgical margin status among patients treated with radical cystectomy alone. We also examined the impact of perioperative and demographic factors on overall survival among patients with variant histology and urothelial carcinoma.

Materials and methods

The National Cancer Data Base (NCDB) is a hospital cancer registry that encompasses 70% of all cancer diagnoses across the United States. The NCDB includes information on patient demographics, insurance status, comorbidity status, disease stage, and disease treatment compiled from patient records and death registries. Each patient's disease course and therapy are recorded according to the American College of Surgeons' Facility Oncology Registry Data Standards.[13] This study was exempt from institutional review board approval since no personal patient information was examined.

We included patients diagnosed with bladder cancer who underwent radical cystectomy using (ICD)-O-3 morphologic codes. For comparison purposes, we created categories of urothelial carcinoma, non-mucinous/signet ring adenocarcinoma, mucinous/signet ring adenocarcinoma, micropapillary urothelial carcinoma, small cell carcinoma, and squamous cell carcinoma. Samples were recorded based on the greatest prevalence within the sample if the tumor had mixed histology. Only bladder cancer with invasive behavior, clinical T2-T4, clinical N0, and clinical M0 stages were included. Patients diagnosed at death or autopsy, follow up < 6 months, and receipt of any chemotherapy or radiation were excluded.

Demographic and clinical characteristics such as age at diagnosis, sex, ancestry, insurance status, treatment at an academic/research program, comorbidity, and clinical T stage were recorded. Ancestry and academic/research program were defined by the NCDB. Charlson-Deyo comorbidity index was derived from six possible comorbidities. Clinical stage was determined using the American Joint Committee on Cancer staging manual edition in use at the time of diagnosis.

Trends in pathologic tumor characteristics were compared among all histologies. The number and percent of patients within each variant who underwent T upstaging, N upstaging, or positive surgical margins were recorded. Those with pathologic stages that were unknown, 0, or X within the NCDB were considered "unknown." Positive margin status included specimens with "residual tumor, NOS involvement is indicated, but not otherwise specified," "microscopic residual tumor cannot be seen by the naked eye," and "macroscopic residual tumor, gross tumor of the primary site which is visible to the naked eye."

Demographic and clinical characteristics were summarized by mean, standard deviation, and median values for continuous variables and by frequencies and percentages for categorical variables. Kaplan-Meier survival analyses were used for overall survival, where median survival and survival rates at 1, 3 and 5 years were calculated for all patients, as well as by histology type. Log-rank test was used to determine differences in survival, upstaging, and surgical margin status among groups. Unadjusted and adjusted hazard ratio (HR), 95% confidence interval (95% CI) along with p value were calculated from fitting several univariable and a multivariable Cox proportional hazard regression models to compare overall survival, upstaging, and surgical margin status between urothelial carcinoma and other histologic types. Overall survival was estimated to be the time between diagnosis and death. Type-I error rate was set to 5%, where p values < 0.05 were considered statistically significant. All statistical analyses were performed using SAS v9.4 statistical software for Windows (SAS Institute Inc., Cary, NC, USA).

Results

A total of 5,856 individuals who underwent radical cystectomy for bladder cancer between 2004 and 2013 met inclusion criteria for this study. The majority of

TABLE 1. **Sociodemographic/clinical characteristics by histology**

			Histology											
	All patients		Small cell carcinoma		Squamous cell carcinoma		Urothelial carcinoma		Micropapillary		Non- mucinous/ signet ring adenocarcinoma		Mucinous/signet ring adenocarcinoma	
	n	col%	n	col%	n	col%	n	col%	n	col%	n	col%	n	col%
All (row%)	**5,856**	**100.0**	**38**	**0.6**	**229**	**3.9**	**5,444**	**93.0**	**41**	**0.7**	**56**	**1.0**	**48**	**0.8**
Age at diagnosis														
N (missing)	5856 (0)		38 (0)		229 (0)		5444 (0)		41 (0)	56 (0)	48 (0)			
Mean (sd)	69.2 (10.3)		72.4 (8.4)		67.6 (11.8)		69.3 (10.2)		70.4 (9.8)		67.9 (11.2)		61.8 (13.9)	
Median (Q1 ; Q3)	70 (62 ; 77)		74 (69 ; 77)		69 (59 ; 77)		70 (62 ; 77)		73 (61 ; 77)		70.5 (59 ; 76)		62.5 (53 ; 71.5)	
Min ; max	24 ; 90		47 ; 87	29 ; 88	28 ; 90		50 ; 88		42 ; 90	24 ; 84				
Sex														
Male	5,243	89.5	34	89.5	177	77.3	4,905	90.1	38	92.7	46	82.1	43	89.6
Female	613	10.5	4	10.5	52	22.7	539	9.9	3	7.3	10	17.9	5	10.4
Race														
Unknown	67	1.2	2	5.3	4	1.7	60	1.1	.	.	1	1.8	.	.
Caucasian	5,419	92.5	34	89.5	211	92.1	5,056	92.9	40	97.6	42	75.0	36	75.0
African-American	253	4.3	2	5.3	10	4.4	220	4.0	1	2.4	8	14.3	12	25.0
Other	117	2.0	.	.	4	1.7	108	2.0	.	.	5	8.9	.	.
Hispanic														
Unknown	406	6.9	6	15.8	23	10.0	369	6.8	3	7.3	4	7.1	1	2.1
No	5,297	90.5	31	81.6	200	87.3	4,936	90.7	37	90.2	50	89.3	43	89.6
Yes	153	2.6	1	2.6	6	2.6	139	2.6	1	2.4	2	3.6	4	8.3
Primary payor														
No Insurance	164	2.8	.	.	7	3.1	154	2.8	2	4.9	.	.	1	2.1
Private Insurance	1,715	29.3	11	28.9	66	28.8	1,591	29.2	12	29.3	15	26.8	20	41.7
Medicaid/ other government	254	4.3	.	.	18	7.9	227	4.2	2	4.9	5	8.9	2	4.2
Medicare	3,652	62.4	27	71.1	137	59.8	3,403	62.5	25	61.0	36	64.3	24	50.0
Unknown status	71	1.2	.	.	1	0.4	69	1.3	.	.	.	.	1	2.1
Academic/research program														
No	3,073	52.5	22	57.9	112	48.9	2,880	52.9	7	17.1	30	53.6	22	45.8
Yes	2,783	47.5	16	42.1	117	51.1	2,564	47.1	34	82.9	26	46.4	26	54.2
Comorbidity[1]														
No	4,055	69.3	20	52.6	161	70.3	3,774	69.3	31	75.6	39	69.6	30	62.5
Yes	1,801	30.7	18	47.4	68	29.7	1,670	30.7	10	24.4	17	30.4	18	37.5
Clinical T stage														
2	4,890	83.5	25	65.8	168	73.4	4,585	84.2	38	92.7	43	76.8	31	64.6
3	620	10.6	11	28.9	47	20.5	545	10.0	3	7.3	6	10.7	8	16.7
4	346	5.9	2	5.3	14	6.1	314	5.8	.	.	7	12.5	9	18.8

[1]comorbidity according to Charlson comorbidity index

patients were male, Caucasian ancestry, non-Hispanic, and insured through Medicare. The most common histological type of bladder cancer was urothelial carcinoma (93.0%), while squamous cell carcinoma was the second most common type (3.9%). Small cell carcinoma and micropapillary urothelial carcinoma were the least common bladder cancer types (0.6% and 0.7%, respectively) as shown in Table 1.

Median overall survival and survival rates by bladder cancer type are shown in Table 2. Median overall survival for all bladder cancer patients was 4.6 years (4.3-4.9). The longest median overall survival was for squamous cell carcinoma 4.8 years (3.4-7.9), which was similar to urothelial cell carcinoma 4.7 years (4.4-5.1). The shortest median overall survival was observed for small cell carcinoma 1.6 years (1.0-2.8), which also had the lowest 5 year survival rate 15.5%. Kaplan-Meier analyses for overall survival by bladder cancer type are shown in Figure 1.

The amount of patients who underwent T-upstaging, N-upstaging, and had positive surgical margins on radical cystectomy specimen are characterized in Table 3. The majority of the patients among all histologies did not undergo T-upstaging, but T-upstaging was most common in patients with small cell carcinoma (42.1%) and micropapillary urothelial carcinoma (41.5%). Patients had low incidences of progressing to node positive disease at time of radical cystectomy (9.6%-16.1%), except for patients with micropapillary urothelial carcinoma (43.9%) and small cell carcinoma (23.7%). Patients also had low incidences of a positive surgical margin status on cystectomy specimen, with micropapillary urothelial carcinoma having the highest incidence of margin positivity (22.0%).

Multivariable Cox proportional hazards regression models predicting overall survival by bladder cancer type and sociodemographic characteristics were performed. Patients with small cell carcinoma and non-mucinous adenocarcinoma had significantly worse survival than urothelial carcinoma (HR 2.10, 95% CI 1.44-3.06, $p < 0.001$; 1.59, 1.15-2.20, $p = 0.005$). Patients with squamous cell carcinoma had worse overall survival compared to urothelial carcinoma (1.07, 0.88-1.32, $p = 0.496$) despite a longer median survival time, but this was not statistically significant. There were no significant differences in survival across genders, insurance status, or practice settings, however; age at diagnosis, African-American ancestry, comorbidity, clinical T3 stage, and clinical T4 stage were significant predictors of worse survival (1.03, 1.02-1.03, $p < 0.001$; 1.24, 1.03-1.48, $p = 0.021$; 1.30, 1.20-1.40, $p < 0.001$; 1.41, 1.26-1.57, $p < 0.001$; 1.59, 1.38-1.84, $p < 0.001$).

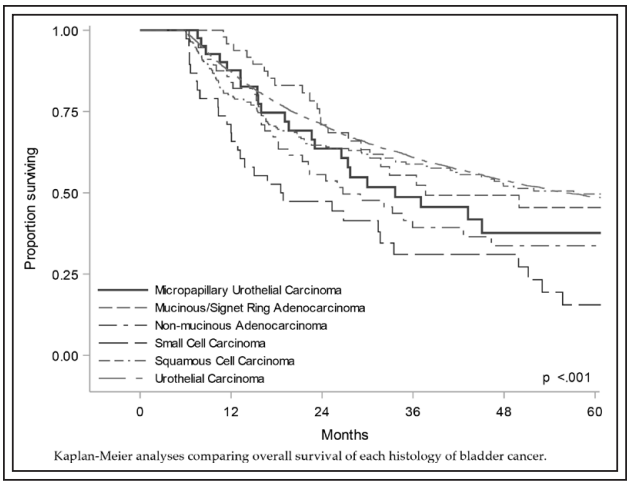

Figure 1. Bladder cancer overall survival.

TABLE 2. **Median overall survival and survival rates**

Histology	Median survival Mean (95% CI)	1 year Mean (95% CI)	3 years Mean (95% CI)	5 years Mean (95% CI)
All	4.6 (4.3-4.9)	86.8% (85.9-87.7)	60.3% (59.0-61.6)	48.3% (46.8-49.7)
Non-mucinous/ signet ring adenocarcinoma	2.2 (1.5-3.6)	83.9% (71.4-91.3)	39.3% (26.1-52.3)	33.7% (20.7-47.2)
Micropapillary	2.8 (1.9-6.3)	87.7% (72.9-94.7)	48.7% (31.7-63.7)	37.7% (21.3-54.0)
Mucinous/signet ring adenocarcinoma	3.1 (2.3-.)	95.8% (84.4-98.9)	55.4% (39.1-69.0)	45.5% (29.0-60.5)
Small cell carcinoma	1.6 (1.0-2.8)	68.4% (51.1-80.7)	31.1% (16.6-46.8)	15.5% (5.2-30.9)
Squamous cell carcinoma	4.8 (3.4-7.9)	79.7% (73.9-84.4)	58.8% (51.8-65.2)	49.7% (42.1-56.7)
Urothelial carcinoma	4.7 (4.4-5.1)	87.2% (86.3-88.1)	60.9% (59.5-62.2)	48.7% (47.2-50.2)

TABLE 3. **Trends in pathologic tumor characteristics**

			Histology											
	All patients		Small cell carcinoma		Squamous cell carcinoma		Urothelial carcinoma		Micropapillary urothelial carcinoma		Non- mucinous adenocarcinoma		Mucinous/signet ring adenocarcinoma	
	n	col%	n	col%	n	col%	n	col%	n	col%	n	col%	n	col%
All	38	0.6	229	3.9	5,444	93.0	41	0.7	56	1.0	48	0.8	38	0.6
T-upstaged														
Unknown	536	9.2	2	5.3	22	9.6	497	9.1	1	2.4	6	10.7	8	16.7
No	3,503	59.8	20	52.6	126	55.0	3,280	60.2	23	56.1	32	57.1	22	45.8
Yes	1,817	31.0	16	42.1	81	35.4	1,667	30.6	17	41.5	18	32.1	18	37.5
N-upstaged														
Unknown	721	12.3	4	10.5	36	15.7	657	12.1	4	9.8	10	17.9	10	20.8
No	4,454	76.1	25	65.8	171	74.7	4,169	76.6	19	46.3	37	66.1	33	68.8
Yes	681	11.6	9	23.7	22	9.6	618	11.4	18	43.9	9	16.1	5	10.4
Surgical margins status														
Unknown	228	3.9	1	2.6	9	3.9	213	3.9	3	7.3	1	1.8	1	2.1
Negative	5,219	89.1	31	81.6	207	90.4	4,862	89.3	29	70.7	49	87.5	41	85.4
Positive	409	7.0	6	15.8	13	5.7	369	6.8	9	22.0	6	10.7	6	12.5

Multivariable Cox proportional hazards regression models predicting other clinical outcomes were also performed. After including all patient demographic and clinical characteristics listed in Table 1, no histological variants were significant predictors of T upstaging. However, each year of increasing age predicted an increased odds of T upstaging (1.02, 1.01-1.03, $p < 0.001$). Micropapillary urothelial carcinoma and small cell carcinoma were more likely to have node positivity than other histologies (6.01, 3.11-11.63, $p < 0.001$; 2.32, 1.08-5.00, $p = 0.032$), while African-American ancestry, comorbidity, clinical T3 stage, and clinical T4 stage were not. The odds of a positive margin status at radical cystectomy were predicted by micropapillary urothelial carcinoma and clinical T4 stage (4.38, 2.05-9.38, $p < 0.001$; 3.38, 2.49-4.58, $p < 0.001$). Sociodemographic factors including ancestry, gender, insurance, and practice setting were not predictive of positive surgical margin status.

Discussion

We present the largest study investigating overall survival for histologic variants and urothelial carcinoma among patients with equal treatment and staging. Identification of factors such as age, comorbidity, and clinical stage as predictors of worse overall survival validates the credibility and robustness of our statistical analyses. We also identified histologic variants with adverse tumor behavior that may contribute to their poor survival. An understanding of which histologic variants portend significantly worse survival compared to urothelial carcinoma may provide insight into which variants need to be treated more aggressively.

Small cell carcinoma emerged as a predictor of significantly worse overall survival compared to urothelial carcinoma and had the worst overall survival compared to any other bladder cancer variant. This finding is consistent with previous studies that have observed worse prognosis for patients with small cell carcinoma localized to the bladder who did not receive treatment with curative intent.[14] In contrast, some studies have reported that small cell carcinoma of the bladder had worse cancer-specific and overall survival compared to urothelial carcinoma until patients were matched by stage, suggesting that the worse prognosis associated with small cell carcinoma may be due to late presentation, rather than biologically more aggressive disease.[15] Similarly, it has been reported that T-stage upgrading and lymph node status at time of radical cystectomy were not significantly greater ($p < 0.05$) for small cell carcinoma than urothelial carcinoma when

patients were matched by age, race, stage, chemotherapy, and radiation.[7] However, these findings were likely a result of an unequal matching of chemotherapy between small cell carcinoma and urothelial carcinoma, which did not take into account agent, dosing, duration, or timing.

Non-mucinous adenocarcinoma was found to be a significant predictor of worse overall survival compared to urothelial carcinoma. Our results are consistent with previous findings that suggest adenocarcinoma presents at a later stage and has a poor prognosis.[16] Mucinous/signet ring adenocarcinoma actually yielded the third best 5 year overall survival among histologic variants, likely because it was not a predictor of T-upstaging, N-upstaging, or positive surgical margin status. In contrast with the molecular understanding of this disease, these findings are in line with clinical observations that survival for mucinous adenocarcinoma approaches 75%-100% for localized tumors.[17]

We found that micropapillary variant histology behaves aggressively and has similar survival statistics compared to non-mucinous adenocarcinoma, even though none reached statistical significance. One retrospective review found that micropapillary histology was associated with twice the risk of all-cause mortality compared to urothelial carcinoma after adjusting for demographics, clinical and pathological stage, and chemotherapy.[18] However, other studies have found similar recurrence and survival rates between micropapillary and urothelial carcinoma after controlling for stage and grade.[9,19] These mixed findings suggest that micropapillary disease may behave only slightly more aggressively than urothelial carcinoma, but not to the same extent as the variants previously discussed. Although the difference in overall survival between micropapillary and urothelial carcinoma was not statistically significant ($p = 0.063$) on multivariate analysis, its aggressive behavior is substantiated by significant risk of progression to node positive disease and presence of positive surgical margins at the time of radical cystectomy. While micropapillary histology may not be as poor a prognostic factor as other variant histologies, the treatment of micropapillary disease warrants additional caution compared to urothelial carcinoma.

We also found that African-American ancestry was a significant predictor of worse overall survival among T2-4 bladder cancer across the entire cohort of urothelial and non-urothelial histologies. This survival disparity has been previously observed and has been attributed to more advanced disease at presentation,[20] yet the survival disparity remains after controlling for stage and grade.[21] Non-biologic factors associated with socioeconomic class such as differences in treatment, quality of care, access to care, education, and adherence to surveillance may also contribute to this phenomenon.[22] However, even when socioeconomic class is controlled, African-Americans still have worse bladder cancer survival.[23] African-Americans were found to have a trend for greater recurrence on multivariate analysis when no differences in the use of perioperative chemotherapy or radiation therapy were detected, suggesting that there may be a biologic component to this ancestry disparity.[24] Our results imply a similar biologic etiology, since this disparity was observed on multivariate analysis with no significant difference in overall survival when private insurance was compared to no insurance and Medicaid.

Although the National Cancer Data Base contains a large number of localized muscle-invasive bladder cancer patients of bladder cancer variant histologies, a retrospective study using this dataset has certain limitations. Perhaps the most important confounder is potential selection bias for patients who only received surgery instead of multimodal therapy. This is particularly important for variants such as small cell carcinoma, because the use of neoadjuvant chemotherapy has become a standard of care. A limitation of other studies comparing survival for variant histology bladder cancer and urothelial carcinoma relates to differences in chemotherapy and radiation treatments, which are frequently assumed to be equal.[7] Our study is the first to avoid this potential confounding factor by selecting patients who only received radical cystectomy, thus more accurately reflecting the biological nature of each histologic subtype. We also limited our patient selection to muscle-invasive bladder cancer, since the accuracy of detecting variant histology is extremely low in non-muscle invasive bladder cancer.[25,26] Other limitations of using the NCDB for this study are the lack of central pathology review for diagnosis of pure histological variants and the inability to standardize surgical technique. Although the sample size for some of the variants is small, these numbers are still substantially larger than those from single institution studies that attempt to extrapolate survival among patients with differing treatments and stages of disease.

In conclusion, small cell carcinoma had the worst overall survival among variant histology bladder cancer, but non-small cell carcinoma neuroendocrine tumors and non-mucinous adenocarcinoma also had significantly worse survival compared to urothelial carcinoma. Squamous cell carcinoma and mucinous/signet ring adenocarcinoma of the bladder have a similar survival prognosis compared to urothelial carcinoma. African-Americans are at risk for significantly worse overall survival compared to Caucasians after radical cystectomy for muscle-invasive bladder cancer. □

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