Original Article

Trends in the use of neoadjuvant chemotherapy for bladder cancer with nonurothelial variant histology: An analysis of the National Cancer Database

Campbell M Grant*, Richard Amdur[1], Michael J Whalen

Departments of Urology and [1]Surgery, George Washington University Hospital, Washington, DC, USA
*E-mail: camgrant@gwu.edu

ABSTRACT

Introduction: The aim of this study is to evaluate the trends in the use of neoadjuvant chemotherapy (NAC) over time (2006–2014) for patients diagnosed with muscle-invasive bladder cancer (MIBC) with nonurothelial variant histology (NUVH) in the National Cancer Database.

Materials and Methods: We queried the NCDB for patients with muscle-invasive (i.e. cT2-4N0-3M0/X) urothelial carcinoma (UC) of the bladder. We examined demographic, clinical, and pathologic features associated with NAC, also substratifying into pure UC and NUVH. Tests of association were performed using Chi-square/Fisher's exact test for categorical variables and *t*-tests, ANOVA, or Kruskal–Wallis test for continuous variables. Outcomes were examined with Cox proportional hazards and 90-day mortality with the Kaplan–Meier method.

Results: Totally 22,320 patients met our inclusion criteria, of whom 22.6% received NAC. The proportion of NAC increased significantly over time in the neuroendocrine and urothelial cell categories with 57.1% and 34.1% of patients in 2014 receiving NAC vs. 44% and 10.6% in 2006. No other variant histology showed a significant increase across the time sampled. Patients receiving NAC were more likely to have downstaging to pT0 (13.4% vs. 2.7%), negative surgical margin (89.1% vs. 86%), and pN0 (63.2% vs. 60.5%) and were less likely to have 30-day (1.4% vs. 3%) or 90-day (5% vs. 8.3%) mortality. Rates of downstaging to pT0 after NAC were similar among histologies.

Conclusion: Neoadjuvant chemotherapy utilization continues to slowly increase in patients with MIBC. Patients with variant histology lag behind in terms of receiving NAC but appear to derive as much benefit as patients with pure urothelial cell bladder cancer.

INTRODUCTION

Neoadjuvant platinum-based chemotherapy has been shown in multiple randomized trials and meta-analyses to provide a 5% absolute overall survival benefit at 5 years compared to radical cystectomy alone for patients with muscle-invasive bladder cancer (MIBC).[1,2] There has been a trend towards increased use of neoadjuvant chemotherapy (NAC) over time, from 7.6% in 2006 to 21% in 2010, as demonstrated in an earlier publication that queried the NCDB.[3]

Although it is considered the new standard of care, the use of NAC in eligible patients is not universal. A recent study by Krabbe *et al.* determined that ~ 41% of the eligible patients actually received NAC from 2008 to 2012, and this was associated with a higher rate of pathologic downstaging after RC (21% vs. 7%).[4] Given the greater potential for locally advanced disease, micrometastasis,[5-7] and even local tumor recurrence in the settings of nonurothelial variant histology (NUVH),[8,9] the use of NAC for MIBC with variant histology is especially important. This study will update the previously observed trends in NAC recorded in the NCDB,[3] expanding the time interval by 4 years.

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MATERIALS AND METHODS

The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. It is a hospital-based cancer registry capturing over 70% of the new cancer diagnoses in the United States, with data submitted by >1400 facilities that are accredited by the Commission on Cancer. Data on clinical course and treatments are coded and disclosed based on the Facility Oncology Registry Data Standards manual (http://www.facs.org/cancer/coc/fordsmanual.html).

We queried the NCDB for patients with muscle-invasive (i.e. cT2-4N0-3M0/X) urothelial carcinoma (UC) of the bladder. We examined demographic, clinical, and pathologic features associated with the receipt of NAC overall and within two subgroups: pure UC and NUVH. Using the ICD-O-3 classification, the histology included pure UC, encoded as 8120/3; pure squamous and squamous differentiation (8070/3, 8051/3, and 8052/0); adenocarcinoma and glandular differentiation (8140/3 and 8261/0); micropapillary (8131/3); sarcomatoid (8122/3); and neuroendocrine/small cell (8041/3 and 8240/3). Demographic features included patient age, sex, race, urban/rural treatment location, income, treatment facility type, insurance type, and Charlson Comorbidity Index. Clinical variables included receipt of NAC and year of surgery (YOS). Pathologic features included clinical T stage, grade, clinical node status, pathologic stage, pathologic node status, and pathologic surgical margin status.

Categorical variables were compared using Chi-square or Fisher's exact test. Associations between categorical and continuous variables were analyzed using *t*-tests/analysis of variance for normally distributed variables or the Kruskal–Wallis test if skewed. To assess the independent effect of NAC on outcomes, we used logistic regression, adjusting for potential confounders. We defined confounders as presurgery variables that differed between those who did versus did not receive NAC and which also might be associated with outcomes. These were chosen based on having $P < 0.20$ for the association with NAC.

This analysis was performed for all UC patients and then specifically for patients with NUVH. The proportion of patients receiving NAC over time was also examined using the Pearson coefficient and linear regression analysis with YOS as a continuous variable. In addition to receipt of NAC, additional clinical outcome measures included pathologic downstaging (pT0), surgical margin status, pN0, radiation treatment after surgery, 30-day readmission rate, and 30-day and 90-day mortality. Predictors of these endpoints were examined via univariable and multivariable logistic regression analysis, with NUVH included as a separate covariate. Subgroups within variant histology were also examined against pure urothelial histology.

Results are reported with odds ratios and 95% confidence intervals. SAS (version 9.3, Cary, NC, USA) was used for all data analyses. All statistical tests were two-sided with statistical significance defined as $P < 0.05$.

RESULTS

Out of the 484,367 cases in the database, there were 54,235 that had data missing regarding NAC and an additional 407,812 that did not have AJCC T stage 2–4, leaving 22,320 with NAC information and an AJCC T stage 2, 3, or 4 who subsequently underwent radical cystectomy for further analysis. Of these, 5053 (22.6%) received NAC [Figure 1]. Median follow-up for patients was 25.4 months (0–117). The proportion of patients who received NAC increased significantly over time [Figure 2] ($P < 0.0001$). The increase in NAC in other variant histologies was more irregular. There are fewer variant histology cases receiving NAC each year that leads to a lower *n* value and more variability. The one variant histology that had a significantly higher percentage of patients receiving NAC was neuroendocrine [Figure 3 and Supplementary Table 1]. Each year after 2006 (the reference group) had a significantly higher level of NAC use than 2006. Compared with urothelial histology, none of the other histologies had a significantly different pattern of NAC use over time (histology × year interaction, $P = 0.56$, 0.16, 0.40, 0.47, and 0.64 for glandular, micropapillary, neuroendocrine, sarcomatoid, and squamous versus urothelial histology, respectively). Despite their overall low numbers, the incidence of variant histology increased from 34% to 37% between 2006 and 2014 ($P = 0.048$).

Patients who received NAC were significantly younger than those who did not, were more likely to have private insurance, and were less likely to have Medicare [Table 1]. In addition, NAC was more commonly given at Integrated Network Cancer Programs and Academic/Research Programs (26%) versus Comprehensive Community and Community Cancer Programs (17%–19%) ($P < 0.001$). Grade and AJCC stage were significantly higher in the NAC group. Among NUVH cases, 20.4% received NAC versus 23% of urothelial cases ($P < 0.0001$). Comparing urothelial histology to the NUVH, neuroendocrine histology was much more likely to receive NAC (44% vs. 23%) ($P < 0.0001$). Glandular and squamous histologies were much less likely to receive NAC (11% each), while the use for micropapillary and sarcomatoid was similar to UC (24% and 21%, respectively).

Regarding clinical outcomes, patients with NAC were more likely than those without NAC to have downstaging to pT0 (13.4% versus 2.7%, $P < 0.0001$) [Supplementary Table 2], negative surgical margin (89.1% vs. 86%, $P < 0.0001$), and

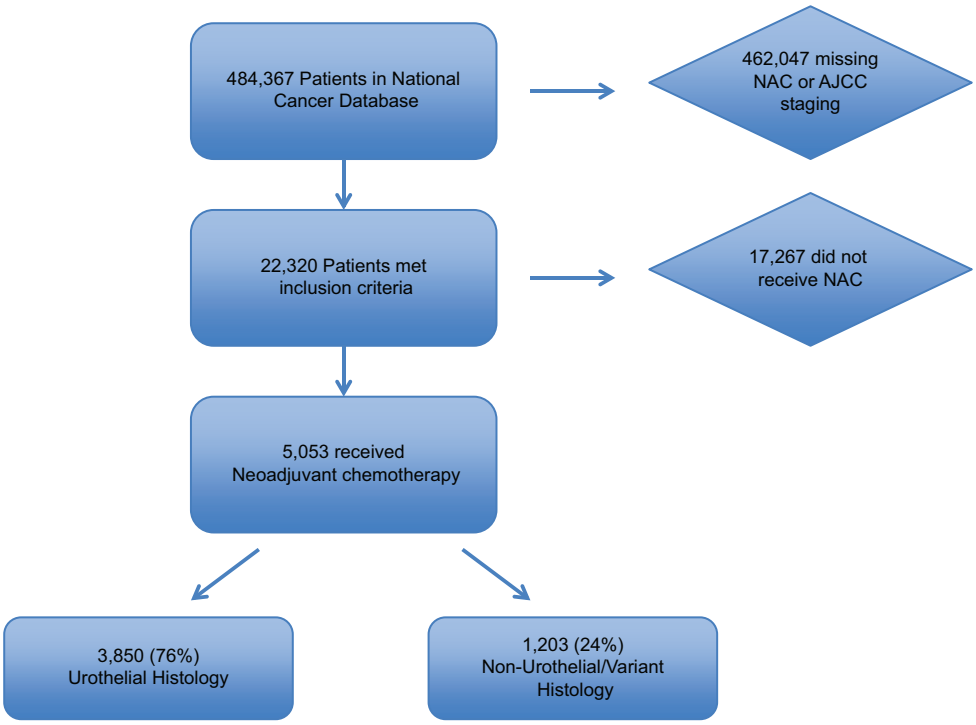

Figure 1: Patient selection for retrospective review

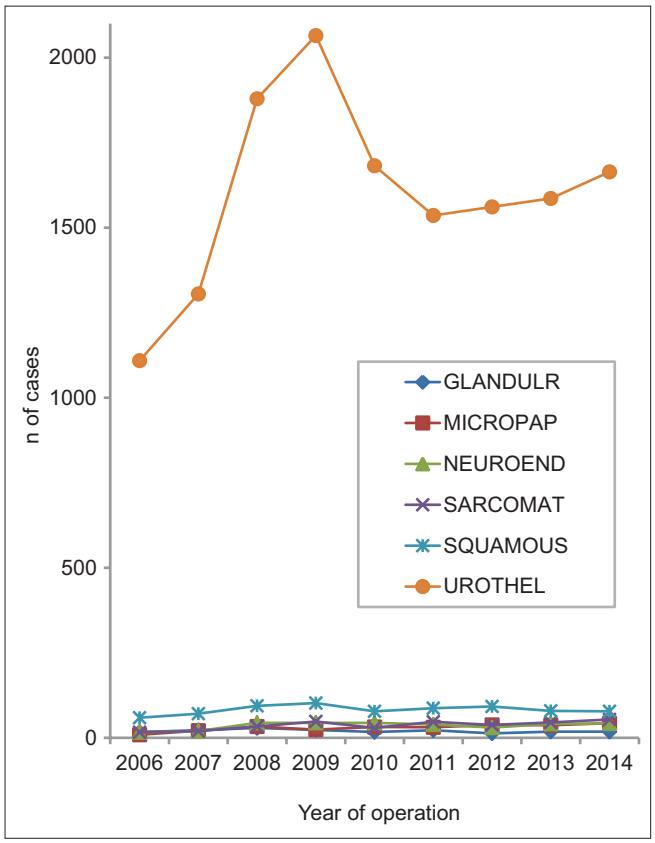

Figure 2: Number of cases × histology × year. There were far more urothelial cases than any other histology, each year

pN0 (63.2% vs. 60.5%, P =0.0008); were less likely to be readmitted within 30 days (8.9% vs. 10.6%, P = 0.0005); and were less likely to have 30-day (1.4% vs. 3%, $P < 0.0001$) or 90-day (5% vs. 8.3%, $P < 0.0001$) mortality. NAC was significantly positively associated with overall survival, after adjusting for covariates (adjusted hazard ratio: 0.77 [0.74–0.81], $P < 0.0001$)[Supplementary Table 3]. Those with urothelial histology had a trend toward fewer pN+ (36% vs. 64%, $P = 0.07$), were in fact more likely to have pT0 (4.8% vs. 5.7%, $P = 0.0039$), and had decreased 90-day mortality (7.3% vs. 8.3%, $P = 0.01$) [Supplementary Table 4]. We compared clinical outcomes by individual variant histology as well. Compared to UC, squamous and sarcomatoid histologies had an increase in 90-day mortality (7.26% vs. 13.19% and 16.67%, $P \leq 0.0001$). Compared to UC, micropapillary and glandular were less likely to be pN0 (60.71% vs. 34.7%, $P \leq 0.0001$, and 53%, $P = 0.038$, respectively). Compared to UC, glandular, micropapillary, and squamous were less likely to have a negative surgical margin (86.87% vs. 73.26%, $P < 0.0001$; 73.33%, $P \leq 0.0001$; and 81.7%, $P = 0.0002$). Compared to UC, neuroendocrine was more likely to be downgraded to T0 at the time of surgery (4.75% vs. 10.14%, $P \leq 0.0001$). Furthermore, patients with neuroendocrine histology were less likely to be readmitted at 30 days postoperative (4.6% vs. 10.7%, $P = 0.0005$).

We compared the overall survival of patients receiving NAC stratified by histology using multivariable logistic regression. Patients receiving NAC with urothelial histology had a statistically significant increase in overall survival ($P \leq 0.0001$) [Figure 4]. Similarly, patients receiving NAC with neuroendocrine histology also showed an increase in overall survival ($P = 0.014$). The other variant histologies

Table 1: Association of patient and hospital variables with adjuvant chemotherapy

Variable	All patients (*n*=22,320), *n* (column %)	No NAC (*n*=17,267), *n* (row %)	Had NAC (*n*=5053), *n* (row %)	*P*
Age	67.8±10.4	68.7±11.4	64.7±9.8	<0.0001
Sex female	5053 (23)	3850 (23)	1203 (22)	0.03
Race				
Asian	296 (1)	227 (77)	69 (23)	0.96
Black	1243 (6)	973 (78)	270 (22)	
White	20,383 (91)	15,763 (77)	4620 (23)	
Unknown/other	389 (2)	298 (77)	91 (22)	
Hispanic	547 (2)	415 (76)	132 (3)	0.40
Insurance				
None	595 (3)	451 (76)	144 (24)	<0.0001
Private	7108 (32)	5077 (71)	2031 (29)	
Medicaid	1055 (5)	771 (73)	284 (27)	
Medicare	13,035 (58)	10,583 (81)	2452 (19)	
Other governments	230 (1)	167 (73)	63 (27)	
Unknown	297 (1)	218 (73)	79 (27)	
Year of diagnosis				
2006	1685 (8)	1509 (90)	176 (10)	<0.0001
2007	2014 (9)	1685 (84)	329 (16)	
2008	2867 (13)	2386 (83)	481 (17)	
2009	3211 (14)	2582 (80)	629 (20)	
2010	2520 (11)	1955 (78)	565 (22)	
2011	2411 (11)	1818 (75)	593 (25)	
2012	2422 (11)	1764 (72)	678 (28)	
2013	2524 (11)	1789 (71)	735 (29)	
2014	2646 (12)	1779 (67)	867 (33)	
Grade				
1	207 (1)	182 (88)	25 (12)	<0.0001
2	1014 (5)	876 (86)	138 (14)	
3	9701 (49)	7791 (80)	1910 (20)	
4	8930 (45)	6722 (75)	2208 (25)	
Unknown	2468			
Regional nodes positive				
0	13,593 (61)	10,334 (76)	3259 (24)	<0.0001
1	2337 (10)	1839 (79)	498 (21)	
2-10	3298 (15)	2624 (80)	674 (20)	
11 or more	411 (2)	313 (76)	98 (24)	
Positive nodes found	93 (0.4)	79 (85)	14 (15)	
No nodes examined	2437 (11)	1962 (81)	475 (19)	
Unknown	151 (0.7)	116 (77)	35 (23)	
Regional nodes examined				
0	2437 (11)	1962 (81)	475 (19)	<0.0001
1-10	7568 (34)	6177 (82)	1391 (18)	
11 or more	11,743 (53)	8655 (74)	3088 (26)	
Nodes were examined	465 (2)	390 (84)	75 (16)	
Unknown	107 (0.5)	83 (78)	24 (22)	
Histology				
Urothelial	14,387 (89)	11,104 (77)	3283 (23)	<0.0001
Neuroendocrine	320 (2)	179 (56)	141 (44)	
Glandular	179 (1)	160 (89)	19 (11)	
Micropapillary	268 (2)	204 (76)	64 (24)	
Sarcomatoid	330 (2)	261 (79)	69 (21)	
Squamous	740 (5)	658 (89)	82 (11)	
AJCC clinical T stage				
2	16,757 (75)	13,116 (78)	3641 (22)	<0.0001
3	3121 (14)	2337 (75)	784 (16)	
4	2442 (11)	1814 (74)	628 (26)	
AJCC pathologic T stage				

Contd...

Table 1: Contd...

Variable	All patients (*n*=22,320), *n* (column %)	No NAC (*n*=17,267), *n* (row %)	Had NAC (*n*=5053), *n* (row %)	*P*
pT0	1049 (5)	435 (41)	614 (59)	<0.0001
pT1	644 (3)	412 (64)	232 (36)	
pT2	6114 (27)	4975 (81)	1139 (19)	
pT3	8046 (36)	6655 (83)	1391 (17)	
pT4	4031 (18)	3224 (80)	807 (20)	
pTa	167 (0.8)	88 (53)	79 (47)	
pTis	598 (3)	289 (48)	309 (52)	
Unknown	1671 (7)	1189 (71)	482 (29)	
Rural/urban				
Large metro area	16,837 (78)	12,982 (77)	3855 (23)	0.17
Urban	4097 (19)	3210 (78)	887 (22)	
Rural	551 (3)	434 (79)	117 (21)	
Income 2000 ($)				
<30 k	2497 (12)	1986 (80)	511 (20)	<0.0001
30 k-<35 k	4035 (19)	3225 (80)	810 (20)	
35 k-<46 k	6309 (29)	4930 (78)	1379 (22)	
≥46 k	8623 (40)	6476 (75)	2147 (25)	
Income 2008-2012 ($)				
<38 k	3438 (16)	2719 (79)	719 (21)	<0.0001
38 k-<48 k	5602 (25)	4467 (80)	1135 (20)	
48 k-<63 k	6167 (28)	4753 (77)	1414 (23)	
≥63 k	6769 (31)	5056 (75)	1713 (25)	
Facility type				
CCP	1431 (6)	1165 (81)	266 (19)	<0.0001
CCCP	7205 (32)	6010 (83)	1195 (17)	
ARP	11,531 (52)	8517 (74)	3014 (26)	
INCP	2010 (9)	1478 (74)	532 (26)	
Other/unknown	143			
Charlson/Deyo score				
0 condition	15,570 (70)	11,790 (76)	3780 (24)	<0.0001
1 condition	5140 (23)	4116 (80)	1024 (20)	
2 or more conditions	1610 (7)	1361 (85)	249 (15)	
pN0	13,646 (61)	10,454 (77)	3192 (23)	0.0008
Radiation after surgery[a]	591 (86)	476 (96)	115 (60)	<0.0001

[a]Only cases where radiation was for bladder cancer are examined (*n*=689). CCP=Community cancer program, CCCP=Comprehensive Community Cancer Program, ARP=Academic/Research Program, INCP=Integrated Network Cancer Program, NAC=Neoadjuvant chemotherapy, AJCC=American Joint Committee on Cancer

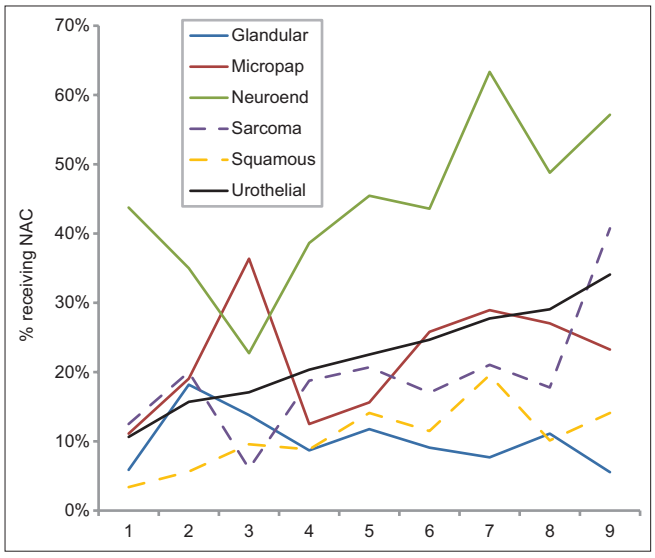

Figure 3: Percentage of cases receiving neoadjuvant chemotherapy by histology by year. There was a linear increase in percentage receiving neoadjuvant chemotherapy for urothelial histology across years. For the other histologies, the increase was more irregular. This is likely due to small *n*, which leads to increased error in the estimate of percentage neoadjuvant chemotherapy. In general, neuroendocrine histology had higher percentage neoadjuvant chemotherapy than other histologies

had an insufficient number of cases to adequately power a multivariable regression analysis.

DISCUSSION

The incidence of UC with variant histology of the bladder has been reported in 10%–44% of radical cystectomy specimens, and pure nonurothelial histology comprises <10% of cases.[10-13] The 2017 update to the AUA guidelines on MIBC recommends that bladder cancer specimens should be reviewed by an experienced genitourinary pathologist when variant histology is suspected. Re-review of cystectomy specimens by experienced genitourinary pathologists may identify variants that alter treatment in up to 33% of patients.[14,15] The present study shows that variant histology was found in over one-third of the patients and is increasing over time, which perhaps reflects growing appreciation by pathologists of the features of these histologies. Variant histology has been associated with an advanced tumor stage at presentation, node-positive disease, positive surgical margins, and higher cancer-specific mortality in patients undergoing radical cystectomy without NAC.[16] Specifically,

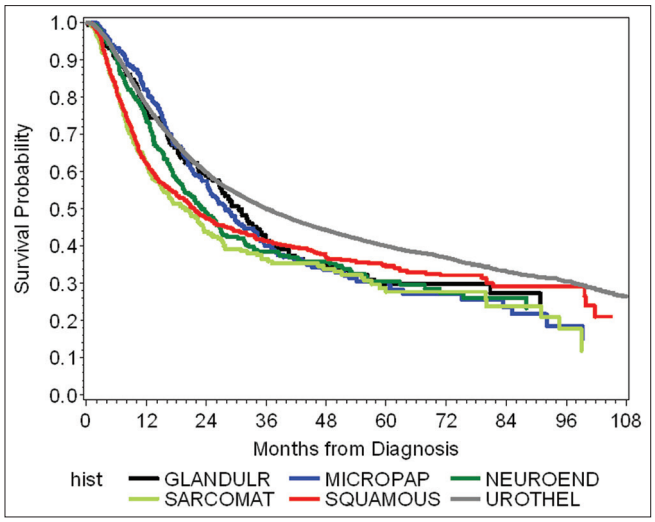

Figure 4: Kaplan–Meier curve for overall survival comparing urothelial carcinoma with each variant histology. Significant difference with every variant histology except glandular

both plasmacytoid and micropapillary variants have been shown to have higher rate of perivesical positive surgical margins and positive lymph nodes in 64%–72% of the cases[16] Furthermore, clear cell UC has been associated with node-positive disease.[17] These findings highlight the importance of consideration of NAC in the setting of UC with variant histology.

The role of NAC in the nonurothelial setting is less clear. Historically, pure squamous cell carcinoma and adenocarcinoma of the bladder have been thought to be chemoresistant.[18,19] In spite of this, there have been small studies recently looking at NAC in both histological types, with rate of downstaging at cystectomy up to 67%.[9,20]

Despite being considered the new standard of care, the use of NAC has not reached 100% in all eligible patients. A recent study by Krabbe *et al.* determined that ~41% of eligible patients actually received NAC from 2008 to 2012, and this was associated with a higher rate of pathologic downstaging after RC (21% vs. 7%).[4] Many previous studies on the use of NAC have not specifically examined the influence of variant histology on the receipt of NAC, however. The influence of variant histology on the chemosensitivity of UC has been controversial, with early reports suggesting diminished response to systemic chemotherapy.[21,22] More recently, in 2010, secondary analysis of the seminal Southwest Oncology Group-Directed Intergroup Study (8710) showed that patients with UC with squamous and glandular differentiation had a greater survival benefit when treated with NAC versus patients with pure UC carcinoma.[23] Another recently published study including $n = 126$ with 16% squamous or glandular dedifferentiation demonstrated increased rates of downstaging to pT0 after neoadjuvant cisplatin-based chemotherapy on multivariable logistic regression (60% vs. 32%, $P = 0.02$).[24] The effectiveness of NAC may depend on the specific variant histology, however, and benefits have been reported for small cell carcinoma and even micropapillary disease, which had been previously thought to be best treated with immediate RC.[25-27] Molecular genotyping tests in the future may help distinguish those patients with specific subsets of variant histology that would benefit from NAC in the future.

Previous studies using the NCDB have shown that NAC use between 2003 and 2007 increased from 6% to 13%.[28] Studies by Vetterlein. have looked at the breakdown of histologic variants among cystectomy patients but did not look at the trends in NAC in those patients.[29] A subsequent paper by the same group looked at NAC use in NUVH patients through 2011 but did not directly compare them to urothelial cell histology.[30] Their paper also included perioperative radiation patients, which could include salvage cystectomy patients or trimodal bladder-preserving patients. The present study demonstrates that the percentage of patients receiving NAC continues to increase year after year as NAC becomes integrated into multimodal treatment approaches for MIBC. The overall use of NAC in the present study was somewhat lower (33%) than other contemporary studies, perhaps because we were unable to identify all patients who would be eligible for NAC based on incomplete comorbidity data in the NCDB. However, the trend over time shows the increased use of NAC in all bladder cancer patients. We did notice a large spike in the number of patients receiving NAC in 2008 and 2009, a drop the following year, and then a steady climb from 2011 to 2014. We do not have a good explanation for this spike other than expansion of the NCDB-included hospitals, but the overall trend has continued to rise. Patients were more likely to receive NAC if they had private insurance or were younger, which is consistent with previous studies.[3] The increased use of NAC at academic centers was also corroborated by the present study. The increased use of NAC argues for treating more MIBC patients at centers of excellence where the use of NAC may lead to better outcomes.

The present study specifically looked at patients with non-UC and variant histology and showed the increased use of NAC in these patients over the past 8 years as well. A strength of the present study is the substantial proportion of the patients categorized as nonurothelial and variant histology (35.5%). The higher than traditionally thought prevalence of variant histology is being increasingly recognized. The rise in use of NAC in NUVH patients mirrors that in patients with UC. However, with the exception of neuroendocrine variant patients, the rate of NAC in patients with variant histology still lags behind those of urothelial cancer despite the fact that patients with variant histology often present at a higher stage and may derive more benefit from NAC, as mentioned previously [Figure 2]. While not statistically significant, there does appear to be a trend toward an increased use of NAC in the micropapillary variant. This may represent

changing attitudes as the use of NAC for micropapillary becomes more accepted. Figure 2 also demonstrates that patients with glandular histology rarely receive NAC. This may reflect that the pure adenocarcinoma patients are usually treated with immediate cystectomy given the aggressive nature of the disease and the historical lack of responsiveness to NAC.

We found that patients receiving NAC were more often downstaged to pT0 at the time of surgery compared to patients treated with immediate RC; this effect was observed for both urothelial and NUVH patients. We tested whether the NAC association with OS differed for those with urothelial versus neuroendocrine versus other histologies. The present study did not have enough patients to power overall survival for any histology except urothelial and neuroendocrine histologies but did show an increase in overall survival for both. It is interesting that the increase in the rate of pT0 for neuroendocrine histology did not translate into improved survival, but perhaps longer follow-up beyond 90 days would demonstrate improvement.

Limitations related to this study relate to the NCDB as a large administrative database with limited data points. For patients receiving NAC, we are unable to track the specific type of chemotherapy received, the number of cycles, or the associated toxicities. The NCDB does not include cancer-specific mortality data but only overall survival. We are unable to track intraoperative and postoperative complications as a result of the chemotherapy. The NCDB also has a limited follow-up. Furthermore, we were unable to precisely distinguish between UC with variant histology and pure nonurothelial histologies (such as pure squamous or pure adenocarcinoma). Although this may represent a heterogeneous group, the incidence of these variant histologies is much more common than pure nonurothelial cancers. Pure adenocarcinoma and squamous cell carcinoma only make up approximately 2%[31] and 2%–5%,[18] respectively, of bladder cancer patients per year. Therefore, this does not alter our recommendation for NAC in eligible patients with NUVH.

CONCLUSION

The present study shows that NAC continues to slowly increase in use in patients with MIBC. Patients with variant histology lag behind in terms of receiving NAC but appear to derive some benefit. Furthermore, patients with neuroendocrine variant histology have even higher rates of downstaging to pT0. Further prospective studies may help elucidate which variants have the best outcomes with neoadjuvant treatment prior to cystectomy.

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Note: Supplementary tables are available online at www.indianjurol.com

Supplementary Table 1: Raw percentage of patients each year receiving neoadjuvant chemotherapy by histology

Years	Glandular	Micropap	Neuroend	Sarcoma	Squamous	Urothelial
2006	0.059	0.111	0.438	0.125	0.034	0.106
2007	0.182	0.190	0.350	0.200	0.056	0.157
2008	0.138	0.364	0.227	0.061	0.096	0.171
2009	0.087	0.125	0.386	0.188	0.088	0.203
2010	0.118	0.156	0.455	0.207	0.141	0.225
2011	0.091	0.258	0.436	0.170	0.115	0.247
2012	0.077	0.289	0.633	0.211	0.196	0.277
2013	0.111	0.270	0.488	0.178	0.101	0.291
2014	0.056	0.233	0.571	0.407	0.141	0.341

Supplementary Table 2: Association of urothelial histology with patient and hospital variables

Variable	*n* (row %)		*P*
	Nonurothelial histology (*n*=7931)	Urothelial histology (*n*=14,389)	
Age	67.1±10.8	68.2±10.2	<0.0001
Sex female	2008 (36)	3566 (64)	0.38
Race			
Asian	127 (43)	169 (57)	0.033
Black	462 (37)	781 (63)	
White	7212 (35)	13,171 (65)	
Unknown/other	125 (32)	264 (68)	
Hispanic	214 (39)	333 (61)	0.08
Insurance			
None	238 (40)	357 (60)	0.0018
Private	2561 (36)	4547 (64)	
Medicaid	414 (39)	641 (61)	
Medicare	4517 (35)	8518 (65)	
Other governments	93 (40)	137 (60)	
Unknown	108 (36)	189 (64)	
Year of diagnosis			
2006	576 (34)	1109 (66)	0.048
2007	709 (35)	1305 (65)	
2008	987 (34)	1880 (66)	
2009	1146 (36)	2065 (64)	
2010	837 (33)	1683 (67)	
2011	875 (36)	1536 (64)	
2012	881 (36)	1561 (64)	
2013	938 (37)	1586 (63)	
2014	982 (37)	1664 (63)	
Grade			
1	133 (64)	74 (36)	<0.0001
2	699 (69)	315 (31)	
3	3267 (34)	6434 (66)	
4	2954 (33)	5976 (67)	
Unknown	2468		
Regional nodes positive			
0	4893 (36)	8700 (64)	<0.0001
1	761 (33)	1576 (67)	
2-10	1100 (33)	2198 (67)	
11 or more	157 (38)	254 (62)	
Positive nodes found	928 (38)	1509 (62)	
No nodes examined	28 (30)	65 (70)	
Unknown	64 (42)	87 (58)	
Regional nodes examined			
0	928 (38)	1509 (62)	0.0037
1-10	2590 (34)	4978 (66)	
11 or more	4203 (36)	7540 (64)	
Nodes were examined	164 (35)	301 (65)	
Unknown	46 (43)	61 (57)	
AJCC clinical T stage			
2	5920 (35)	10,837 (65)	0.10
3	1161 (37)	1960 (63)	
4	850 (35)	1592 (65)	

Contd...

Supplementary Table 2: Contd...

Variable	*n* (row %)		*P*
	Nonurothelial histology (*n*=7931)	Urothelial histology (*n*=14,389)	
AJCC pathologic T stage			
pT0	414 (39)	635 (61)	<0.0001
pT1	319 (50)	325 (50)	
pT2	2316 (38)	3798 (62)	
pT3	2539 (32)	5507 (68)	
pT4	1375 (34)	2656 (66)	
pTa	106 (63)	61 (37)	
pTis	224 (37)	374 (63)	
Unknown	638 (38)	1033 (62)	
Rural/urban			
Large metro area	6041 (36)	10,796 (64)	0.025
Urban	1384 (34)	2713 (66)	
Rural	184 (33)	367 (67)	
Median income 2000 ($)			
<30 k	927 (37)	1570 (63)	<0.0001
30 k-<35 k	1431 (35)	2604 (65)	
35 k-<46 k	2095 (33)	4214 (67)	
≥46 k	3174 (37)	5449 (63)	
Median income 2008-2012 ($)			
<38 k	1222 (36)	2216 (64)	0.013
38 k-<48 k	1923 (34)	3679 (66)	
48 k-<63 k	2162 (35)	4005 (65)	
≥63 k	2506 (37)	4263 (63)	
Facility type			
CCP	487 (34)	944 (66)	0.031
CCCP	2478 (34)	4727 (66)	
ARP	4189 (36)	7342 (64)	
INCP	702 (35)	1308 (65)	
Other/unknown	143		
Charlson/Deyo score			
0 conditions	5573 (36)	9997 (64)	0.45
1 condition	1800 (35)	3340 (65)	
2 or more conditions	558 (35)	1052 (65)	
pN0	4911 (36)	8735 (64)	0.07
Radiation after surgery[a]	238 (84)	353 (87)	0.39

[a]Only cases where radiation was for bladder cancer are examined (*n*=689). CCP=Community Cancer Program, CCCP=Comprehensive Community Cancer Program, ARP=Academic/Research Program, INCP=Integrated Network Cancer Program, AJCC=?American Joint Committee on Cancer

Supplementary Table 3: Outcomes × neoadjuvant chemotherapy

Outcome	Number of cases with data		*n* (% with outcome)		*P*
	No NAC	NAC	No NAC	Had NAC	
30-day mortality	15,367	4143	457 (3.0)	58 (1.4)	<0.0001
90-day mortality	15,261	4105	1269 (8.3)	206 (5.0)	<0.0001
Readmit within 30 days	16,926	4921	1790 (10.6)	437 (8.9)	0.0005
pN0	17,267	5053	10,454 (60.5)	3192 (63.2)	0.0008
pT0 (downstaging T0)	16,078	4571	435 (2.7)	614 (13.4)	<0.0001
Surgical margin 0	16,353	4800	14,067 (86.0)	4275 (89.1)	<0.0001
0 regional nodes positive	17,151	5018	10,334 (60.3)	3259 (65.0)	<0.0001

NAC=Neoadjuvant chemotherapy

Supplementary Table 4: Outcomes × urothelial histology

Outcome	Number of cases with data		*n* (% with outcome)		*P*
	Not urothelial	Urothelial	Not urothelial	Urothelial	
30-day mortality	6886	12,624	193 (2.8)	322 (2.6)	0.29
90-day mortality	6836	12,530	566 (8.3)	909 (7.3)	0.01
Readmit within 30 days	7760	14,087	722 (9.3)	1505 (10.7)	0.0013
pN0	7931	14,389	4911 (61.9)	8735 (60.7)	0.075
pT0	7293	13,356	414 (5.7)	635 (4.8)	0.0039
Surgical margin 0	7474	13,679	6486 (86.8)	11,856 (86.7)	0.83
0 regional nodes positive	7867	14,302	4893 (62.2)	8700 (60.8)	0.046