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Neoadjuvant Chemotherapy as a Risk Factor for Urinary Anastomotic Leak in Patients Undergoing Radical Cystectomy

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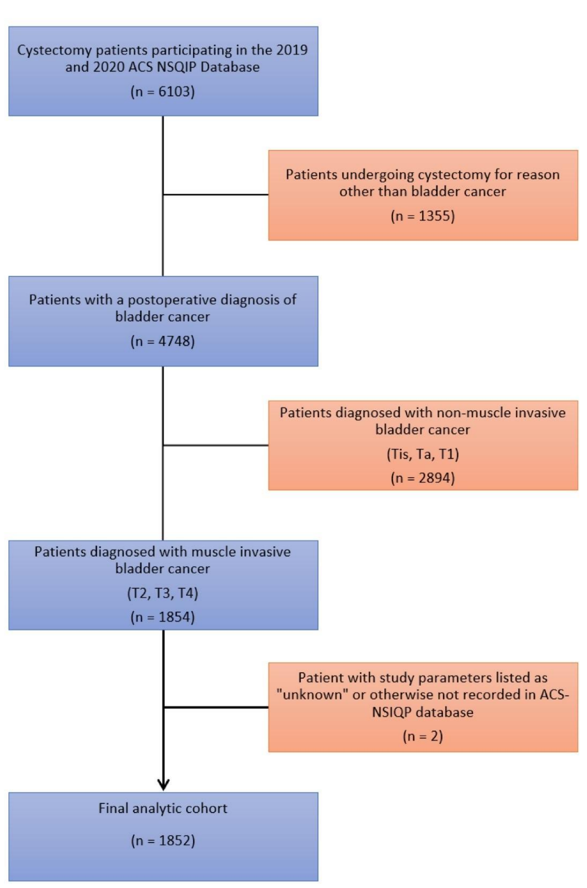
Background

Muscle-invasive bladder cancer (MIBC) represents approximately 25% of all bladder cancer and carries a significant risk of mortality[1]. Neoadjuvant chemotherapy (NAC) and radical cystectomy (RC) is the standard of care for MIBC[2]. One complication associated with RC is ureteral anastomotic leak with a predicted rate of 3%[3]. The objective of this National Surgical Quality Improvement Project (NSQIP) database analysis is to determine if correlations exist between radiation (RAD) and/or NAC before RC and anastomotic leak in the treatment of MIBC.

Methods

The 2019 and 2020 NSQIP data was analyzed for cystectomy patients. A total of 6103 patients were evaluated with 1852 meeting inclusion criteria of MIBC (T Stage = T2, T2a, T2b, T3, T3a, T3b, T4, T4a, T4b) treated with RC. Patients were divided into 4 groups: RC only, RC+NAC, RC+RAD, RC+NAC+RAD with NAC being given within 90 days of RC.



Additional variables such as age, comorbidities, operative time, and others were also analyzed (Table 1). One tailed two proportion Z test was used to calculate the rate of urinary leaks between the different groups

Results

Table 1. Patient Demographics and Post Operative Outcomes, Groups A – D

Cofactor	Total Cohort	Group A RC Only	Group B RC + Rad	Group C RC + NAC	Group D RC + NAC + Rad	p Value
Total No. (%)	1852	1075 (58%)	102 (5.5%)	613 (33%)	62 (3.34%)	
Pt Characteristics:						
Mean yrs. age (Range)	69.57 (22-89)	69.57 (30 – 90)	69.58 (41-87)	69.53 (22-85)	71.90 (53-88)	
No. Pt gender male (%)	1495 (80.72%)	856 (79.63%)	88 (86.27%)	502 (81.89%)	49 (79.03%)	
Non-Caucasian race (%)	526 (28.40%)	324 (30.14%)	26 (25.49%)	166 (27.08%)	10 (16.13%)	
Current smoker (%)	412 (22.25%)	217 (20.19%)	11 (10.78%)	169 (27.57%)	15 (24.19%)	p < 0.01
Pre-Op Non-Functional Health Status (%)	1820 (98.3%)	1053 (97.95%)	99 (97.06%)	606 (98.86%)	62 (100%)	
10 % Weight Loss (in past 6 months) (%)	90 (4.9%)	58 (5.39%)	1 (0.98%)	29 (4.73%)	2 (3.23%)	
Bleeding Disorder (%)	54 (2.9%)	23 (2.14%)	2 (1.96%)	27 (4.40%)	2 (3.23%)	
Currently on Dialysis (%)	10 (0.5%)	9 (0.84%)	0 (0%)	1 (0.16%)	0 (0%)	
Prior pelvic surgery (%)	904 (48.81%)	512 (47.63%)	63 (61.76%)	284 (46.33%)	45 (72.58%)	p < 0.01
Comorbid Conditions:						
Diabetes mellitus (%)	336 (18.14%)	182 (16.93%)	23 (22.55%)	115 (18.76%)	16 (25.81%)	
Congestive heart failure (%)	11 (0.59%)	7 (0.65%)	2 (1.96%)	1 (0.16%)	1 (1.61%)	
History of severe COPD (%)	139 (7.51%)	95 (8.84%)	8 (7.84%)	32 (5.22%)	32 (51.61%)	
HTN controlled w/ medication (%)	1073 (57.94%)	657 (61.12%)	65 (63.73%)	318 (51.88%)	33 (53.23%)	p < 0.01
Steroid use for chronic condition (%)	59 (3.19%)	31 (2.88%)	3 (2.94%)	21 (3.43%)	4 (6.45%)	
TNM Classification:						
Class T2 (T2, pT2a, pT2b) (%)	621 (33.53%)	340 (31.63%)	25 (24.51%)	234 (38.17%)	22 (35.48%)	p = 0.01
Class T3 (T3, pT3a, pT3b) (%)	860 (46.44%)	502 (46.70%)	51 (50.00%)	283 (46.17%)	24 (38.71%)	
Class T4 (T4, pT4a, pT4b) (%)	73 (3.94%)	40 (3.72%)	8 (7.84%)	21 (3.43%)	4 (6.45%)	
Class M0 (%)	1050 (56.70%)	620 (57.67%)	62 (60.78%)	332 (54.16%)	36 (58.06%)	
Class M1 (%)	11 (0.59%)	5 (0.47%)	2 (1.96%)	4 (0.65%)	0 (0.00%)	
Class Nx (%)	77 (4.16%)	48 (4.47%)	14 (13.73%)	10 (1.63%)	5 (8.06%)	p < 0.01
Class N0 (%)	1166 (62.96%)	681 (63.35%)	71 (69.61%)	377 (61.50%)	37 (59.68%)	
Class N1 (%)	220 (11.88%)	127 (11.81%)	6 (5.88%)	80 (13.05%)	7 (11.29%)	
Class N2 (%)	311 (16.79%)	183 (17.02%)	8 (7.84%)	110 (17.94%)	10 (16.13%)	
Class N3 (%)	60 (3.24%)	25 (2.33%)	2 (1.96%)	30 (4.89%)	3 (4.84%)	p = 0.03
Outcome Variables:						
Mean minutes operating time (Range)	327.12 (26-899)	316.51 (26-841)	320.49 (41-735)	342.59 (46-899)	368.58 (103-689)	p < 0.01
Mean length of stay (Range)	7.82 (0-67)	8.18 (0-67)	7.85 (3-27)	7.17 (0-28)	7.8 (1-23)	p < 0.01
Pt requiring blood product transfusion (%)	577 (31.16%)	300 (27.91%)	30 (29.41%)	227 (37.03%)	20 (32.26%)	
Bowel Anastomosis Leak (%)	50 (2.7%)	20 (1.86%)	4 (3.92%)	24 (3.92%)	2 (3.23%)	
Superficial Surgical site infection (%)	87 (4.70%)	54 (5.02%)	5 (4.90%)	21 (3.43%)	7 (11.29%)	p = 0.04
Deep Incisional Surgical Site Infection (%)	15 (0.8%)	10 (0.93%)	2 (1.96%)	2 (0.33%)	1 (1.61%)	
Organ Space Surgical Site Infection (%)	134 (7.2%)	70 (6.51%)	13 (12.74%)	43 (7.01%)	8 (12.90%)	
Post-operative sepsis (%)	141 (7.61%)	73 (6.79%)	9 (8.82%)	54 (8.81%)	5 (8.06%)	
Post-operative AKI (%)	24 (1.30%)	15 (1.40%)	1 (0.98%)	4 (0.65%)	4 (6.45%)	p < 0.01
Pneumonia occurrences (%)	60 (3.24%)	38 (3.53%)	4 (3.92%)	14 (2.28%)	4 (6.45%)	
Pulmonary embolism occurrence (%)	21 (1.13%)	15 (1.40%)	1 (0.98%)	5 (0.82%)	0 (0.00%)	
DVT occurrence (%)	41 (2.21%)	24 (2.23%)	2 (1.96%)	14 (2.28%)	1 (1.61%)	
Pt discharged to care facility (%)	260 (14.04%)	163 (15.16%)	24 (23.53%)	62 (10.11%)	11 (17.74%)	p < 0.01
Drains (%)	72 (3.9%)	52 (4.91%)	0 (0%)	19 (3.10%)	1 (1.61%)	P = 0.04
Rectal injury (%)	32 (1.73%)	13 (1.21%)	7 (6.86%)	11 (1.79%)	1 (1.61%)	p < 0.01
Unplanned readmission (%)	377 (20.36%)	209 (19.44%)	24 (23.53%)	125 (20.39%)	19 (30.65%)	
Unplanned re-operation (%)	98 (5.29%)	55 (5.12%)	9 (8.82%)	30 (1.79%)	4 (6.45%)	

P Value represents tests for significant variation from chi-square analysis of categorical variables and ANOVA analysis for continuous factors.
COPD = Chronic Obstructive Pulmonary Disease, HTN = Hypertension, AKI = Acute Kidney Injury, DVT = Deep Vein Thrombosis

Table 2. Comparison of Anastomotic Urinary Leak Rate Between Groups A - D

	No. Pt with Urinary Anastomosis Leak (%)	No. Pt Without Urinary Anastomosis Leak (%)	p Value
RC Only	31 (2.88%)	1044 (97.11%)	p = 0.98
RC + Rad	2 (1.96%)	100 (98.03%)	p = 0.82
RC + NAC	30 (4.89%)	583 (95.10%)	**p = 0.02**
RC + NAC + Rad	5 (8.06%)	57 (91.93%)	**p = 0.03**

P Value represents two sample proportion z-test, normal distribution (right-tailed), significant values are bolded.

Overall urinary leak rate was 3.67%. 1,057 patients underwent RC alone, 102 patients received RC + RAD, 613 patients received RC + NAC, and 62 patients received RC + NAC + RAD; anastomotic leak rates were 2.88% (p = 0.98), 1.96% (p = 0.83), 4.89% (p = 0.02), and 8.06% 9 p = 0.03), respectively (Table 2). In the cohort (mean [SD] age, 69.6 [9.56]) and there was an association with diabetes (p = 0.03) and congestive heart failure (p = 0.01) with the anastomosis leak group.

Discussion

RC+NAC and RC+NAC+RAD are associated with higher anastomotic leak rates in MIBC. A plausible factor driving this observation is the age of our patient population in conjunction with the tendency of MVAC therapy to induce leukopenia, which has an increased incidence in the elderly[5,6]. Leukopenia is associated with poor postoperative wound healing, and this may lead to increased rates of dehiscence and subsequent anastomotic leakage[7]. Additionally, diabetes is a known contributor to increased risk of dehiscence and was significantly associated with increased leak risk in this study[8]. Compounding with the effect of MVAC therapy on wound healing and anastomosis failure in the elderly is the detrimental effect of radiation therapy on wound healing[9]. The intended radiation-induced cell injury utilized to reduce tumor burden has the predictable side effect of injuring normal tissue, again reducing wound healing capacity with effects that may last months to years[10]. Much like MVAC-induced leukopenia, the incidence of these radiation-induced side effects are exaggerated in elderly populations.[11] When dealing with high risk patients, such as the elderly, it is of utmost importance to weigh the risk and benefit of anti-cancer therapies as they carry serious side effects. However, RAD alone was not associated with increase leak incidence. Further research is needed to elucidate the influence of NAC on anastomosis leak. Although RC+NAC+RAD had an increased risk compared to other groups, our sample size was limited and presents the possibility of sampling bias in this context.

Conclusion

In patient populations described here, RAD was not associated with increased incidence of anastomotic leaks following RC while populations whose treatment included NAC was associated. Although the inclusion of NAC is shown to increase the rate of this postoperative complication, its efficacy in improving primary cancer outcomes does not preclude its utility in this context. Knowing this, our data suggest that patients undergoing this treatment modality would benefit from more frequent and comprehensive postoperative follow up and monitoring.

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