

## OBJECTIVES

- Analyze the association of residual disease after neoadjuvant chemotherapy at radical cystectomy with overall survival among patients with muscle-invasive bladder cancer.
- Compare overall survival, stratified by pathological stage, between patients treated for muscle-invasive bladder cancer with neoadjuvant chemotherapy plus radical cystectomy, radical cystectomy alone, or radical cystectomy and adjuvant chemotherapy.

## INTRODUCTION

- Bladder cancer is one of the most commonly diagnosed malignancies of the genitourinary system with an expected 81,400 new cases and 17,980 deaths in the United States for 2020<sup>1</sup>.
- Approximately 25% of patients are diagnosed with muscle invasive bladder cancer (MIBC) at the time of presentation and progression to MIBC occurs in 20-40% of patients with non-invasive disease<sup>2</sup>.
- Radical cystectomy (RC) with neoadjuvant chemotherapy (NAC) is standard of care treatment for MIBC patients<sup>3</sup>.
- Despite the high level of evidence, the adoption of NAC prior to RC has been suboptimal.
- A commonly cited concern regarding the use of NAC is the difficulty in identifying which patients are most likely to benefit from treatment.
- Our objective was to evaluate differences in overall survival of patients with MIBC who were treated with NAC prior to RC compared to those who underwent RC alone or RC and adjuvant chemotherapy (AC) in a population-based analysis, using the National Cancer Data Base (NCDB).

## METHODS

- Study Design:** Retrospective analysis of patients undergoing RC for MIBC between 2004-2015 using the NCDB.
- Study Outcome:** Overall survival compared between patients with MIBC treated with NAC plus RC, RC alone, or RC plus AC.
- Statistical Analysis:**
  - Covariates were balanced using propensity-score (PS) weighting.
  - PS-adjusted Kaplan-Meier curves were calculated and stratified based on pathologic stage.
  - A Cox proportional hazards model, with a 6-month conditional landmark, was then used to assess hazard ratios in the fully weighted cohort.

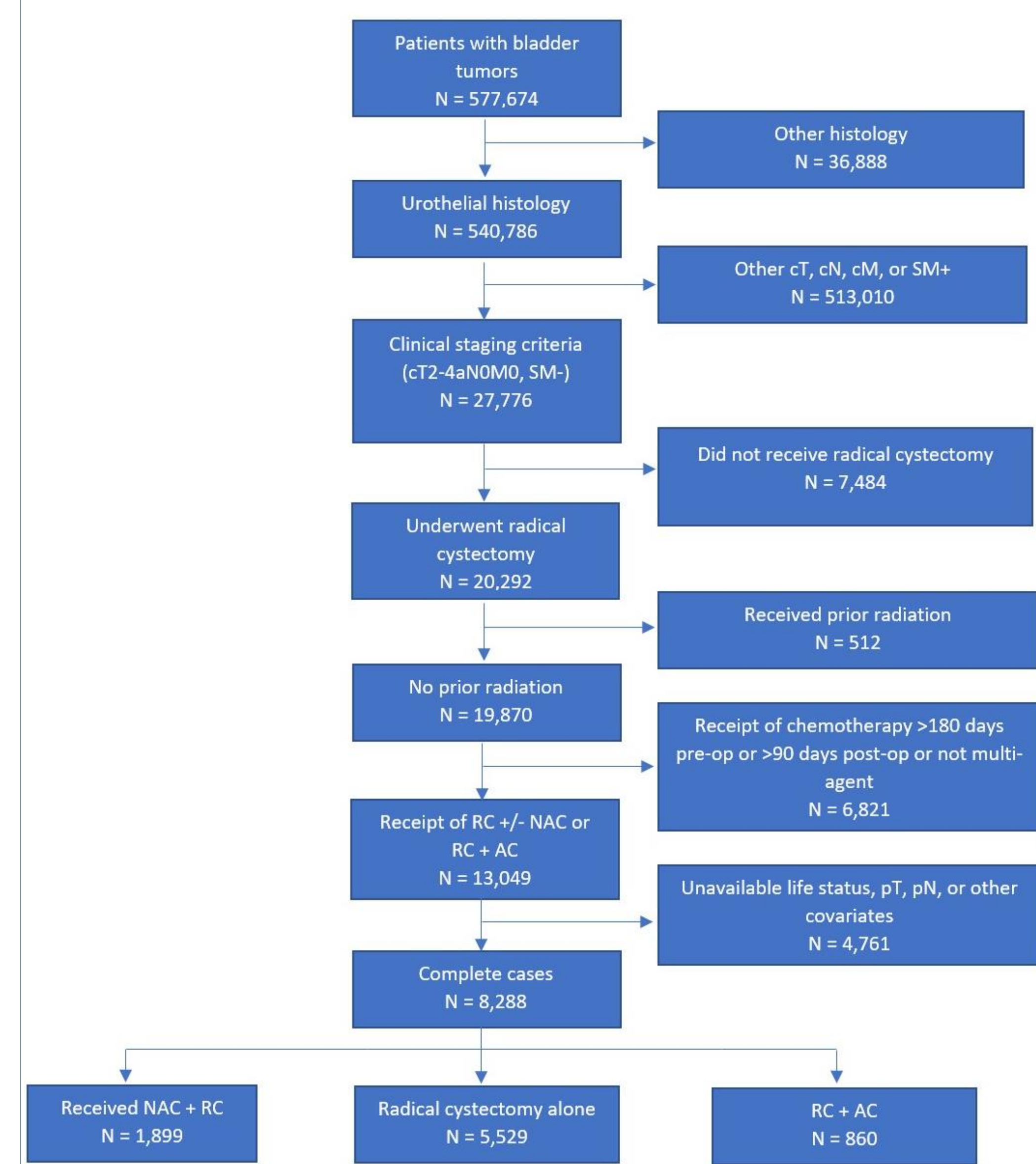


Figure 1. Schematic illustration of cohort inclusion and exclusion

## RESULTS

Group	Unweighted			Weighted			SMD
	RC Alone	NAC + RC	RC + AC	RC Alone	NAC + RC	RC + AC	
n	5529	1899	860	8198.4	7746.72	7722.35	
Age (median (IQR))	72 (64-78)	66 (59-72)	66 (59-73)	70 (62-77)	70 (62-76)	70 (62-76)	0.018
Sex (%)							
Female	1330 (24.1)	457 (24.1)	197 (22.9)	1952.8 (23.8)	1832.3 (23.7)	1712.0 (22.2)	0.026
Male	4199 (75.9)	1442 (75.9)	663 (77.1)	6245.6 (76.2)	5914.4 (76.3)	6010.3 (77.8)	
Race (%)							
White	5017 (90.7)	1715 (90.3)	793 (92.2)	7453.0 (90.9)	7071.4 (91.3)	7056.5 (91.4)	0.012
Black	302 (5.5)	103 (5.4)	37 (4.3)	432.6 (5.3)	385.1 (5.0)	379.3 (4.9)	
Other	210 (3.8)	81 (4.3)	30 (3.5)	312.9 (3.8)	290.2 (3.7)	286.6 (3.7)	
Insurance (%)							
Medicaid/Other Government	240 (4.3)	111 (5.8)	50 (5.8)	385.8 (4.7)	322.1 (4.2)	319.0 (4.1)	0.023
Medicare	3757 (68.0)	987 (52.0)	443 (51.5)	5162.5 (63.0)	4889.8 (63.1)	4872.2 (63.1)	
No insurance	121 (2.2)	43 (2.3)	18 (2.1)	176.2 (2.1)	148.0 (1.9)	149.7 (1.9)	
Private	1411 (25.5)	758 (39.9)	349 (40.6)	2473.9 (30.2)	2386.8 (30.8)	2381.5 (30.8)	
Income (%)							
High	3185 (57.6)	1212 (63.8)	540 (62.8)	4880.5 (59.5)	4672.0 (60.3)	4753.7 (61.6)	0.028
Low	2344 (42.4)	687 (36.2)	320 (37.2)	3317.9 (40.5)	3074.7 (39.7)	2968.6 (38.4)	
County (%)							
Metro	4390 (79.4)	1529 (80.5)	725 (84.3)	6580.7 (80.3)	6259.3 (80.8)	6249.8 (80.9)	0.021
Rural	161 (2.9)	35 (1.8)	16 (1.9)	208.4 (2.5)	163.4 (2.1)	161.4 (2.1)	
Urban	978 (17.7)	335 (17.6)	119 (13.8)	1409.3 (17.2)	1324.0 (17.1)	1311.1 (17.0)	
Distance to Facility (median (IQR))	17.2 (6.6-50.5)	20.2 (8.5-49.0)	13.4 (5.4-31.0)	17.4 (6.8-50.7)	17.4 (7.2-45.6)	15 (5.7-37.8)	0.042
Facility Type (%)							
Academic	2957 (53.5)	1213 (63.9)	406 (47.2)	4509.9 (55.0)	4323.2 (55.8)	4165.8 (53.9)	0.025
Nonacademic	2572 (46.5)	686 (36.1)	454 (52.8)	3688.5 (45.0)	3423.6 (44.2)	3556.6 (46.1)	
cT (%)							
cT2	4738 (85.7)	1483 (78.1)	693 (80.6)	6875.3 (83.9)	6494.9 (83.8)	6493.8 (84.1)	0.006
cT3	551 (10.0)	269 (14.2)	101 (11.7)	894.1 (10.9)	853.3 (11.0)	831.2 (10.8)	
cT4a	240 (4.3)	147 (7.7)	66 (7.7)	428.9 (5.2)	398.6 (5.1)	397.4 (5.1)	
pT (%)							
pT0	127 (2.3)	369 (19.4)	10 (1.2)	192.7 (2.3)	1434.7 (18.5)	89.6 (1.2)	0.829
pT1	327 (5.9)	319 (16.8)	14 (1.6)	516.1 (6.3)	1238.4 (16.0)	140.7 (1.8)	
pT2	2300 (41.6)	484 (25.5)	122 (14.2)	3417.0 (41.7)	2013.8 (26.0)	1167.1 (15.1)	
pT3	2190 (39.6)	538 (28.3)	546 (63.5)	3185.5 (38.9)	2367.5 (30.6)	4938.9 (64.0)	
pT4	585 (10.6)	189 (10.0)	168 (19.5)	887.2 (10.8)	692.3 (8.9)	1386.0 (17.9)	
pN (%)							
pN0	4733 (85.6)	1589 (83.7)	365 (42.4)	7057.5 (86.1)	6449.4 (83.3)	3159.8 (40.9)	0.704
pN+	796 (14.4)	310 (16.3)	495 (57.6)	1140.9 (13.9)	1297.3 (16.7)	4562.5 (59.1)	
Charlson (%)							
0-1	4920 (89.0)	1793 (94.4)	791 (92.0)	7419.0 (90.5)	7063.4 (91.2)	7047.6 (91.3)	0.018
2-3	609 (11.0)	106 (5.6)	69 (8.0)	779.4 (9.5)	683.4 (8.8)	674.8 (8.7)	
Overall Survival in Months (median (IQR))	28.1 (11.6-56.0)	27.8 (15.5-49.8)	27.8 (14.6-55.3)	29.2 (12.1-57.2)	26.3 (14.7-45.8)	27.0 (14.3-52.7)	0.106

Table 1. Demographic, clinical, and tumor characteristics between patients treated with radical cystectomy alone, NAC plus RC, and RC plus AC

	No Landmark			6-month Landmark		
	HR (Ref. RC Alone)	95% CI	p-value	HR (Ref. RC Alone)	95% CI	p-value
<b>No Stratification:</b>						
NAC + RC	0.889	0.850-0.930	<0.001	1.033	0.985-1.084	0.18
RC + AC	1.11	1.064-1.158	<0.001	1.274	1.274-1.333	<0.001
<b>Stratification by &lt;math&gt;\leq pT2&lt;/math&gt; vs. &lt;math&gt;&gt; pT2&lt;/math&gt;:</b>						
<b>&lt;math&gt;\leq pT2&lt;/math&gt;:</b>						
NAC + RC	0.848	0.787-0.914	<0.001	0.951	0.880-1.027	0.2
RC + AC	1.462	1.336-1.599	<0.001	1.508	1.372-1.658	<0.001
<b>&lt;math&gt;&gt; pT2&lt;/math&gt;:</b>						
NAC + RC	1.113	1.051-1.178	<0.001	1.336	1.256-1.42	<0.001
RC + AC	0.737	0.701-0.774	<0.001	0.872	0.827-0.92	<0.001
<b>Stratification by pT stage:</b>						
<b>pT0:</b>						
NAC + RC	0.743	0.549-1.007	0.056	0.759	0.556-1.036	0.082
RC + AC	1.773	1.102-2.854	0.018	1.914	1.184-3.04	0.008
<b>pT1/Tis:</b>						
NAC + RC	1.012	0.747-1.370	0.941	1.182	0.852-1.64	0.316
RC + AC	0.416	0.165-1.046	0.062	0.509	0.201-1.29	0.155
<b>pT2:</b>						
NAC + RC	1.800	1.359-2.385	<0.001	2.044	1.527-2.737	<0.001
RC + AC	0.965	0.588-1.583	0.888	1.087	0.659-1.794	0.745
<b>pT3:</b>						
NAC + RC	1.034	0.944-1.133	0.472	1.166	1.062-1.281	0.001
RC + AC	1.485	1.352-1.631	<0.001	1.517	1.374-1.676	<0.001
<b>pT4:</b>						
NAC + RC	1.134	1.062-1.211	<0.001	1.315	1.226-1.410	<0.001
RC + AC	0.731	0.690-0.774	<0.001	0.84	0.791-0.893	<0.001
<b>Overall</b>						
NAC + RC	1.022	0.909-1.149	0.718	1.383	1.215-1.573	<0.001
RC + AC	0.746	0.674-0.826	<0.001	0.983	0.876-1.102	0.767

Table 2. Cox regression analyses of the association between treatment regimen and overall survival, stratified by pathological stage

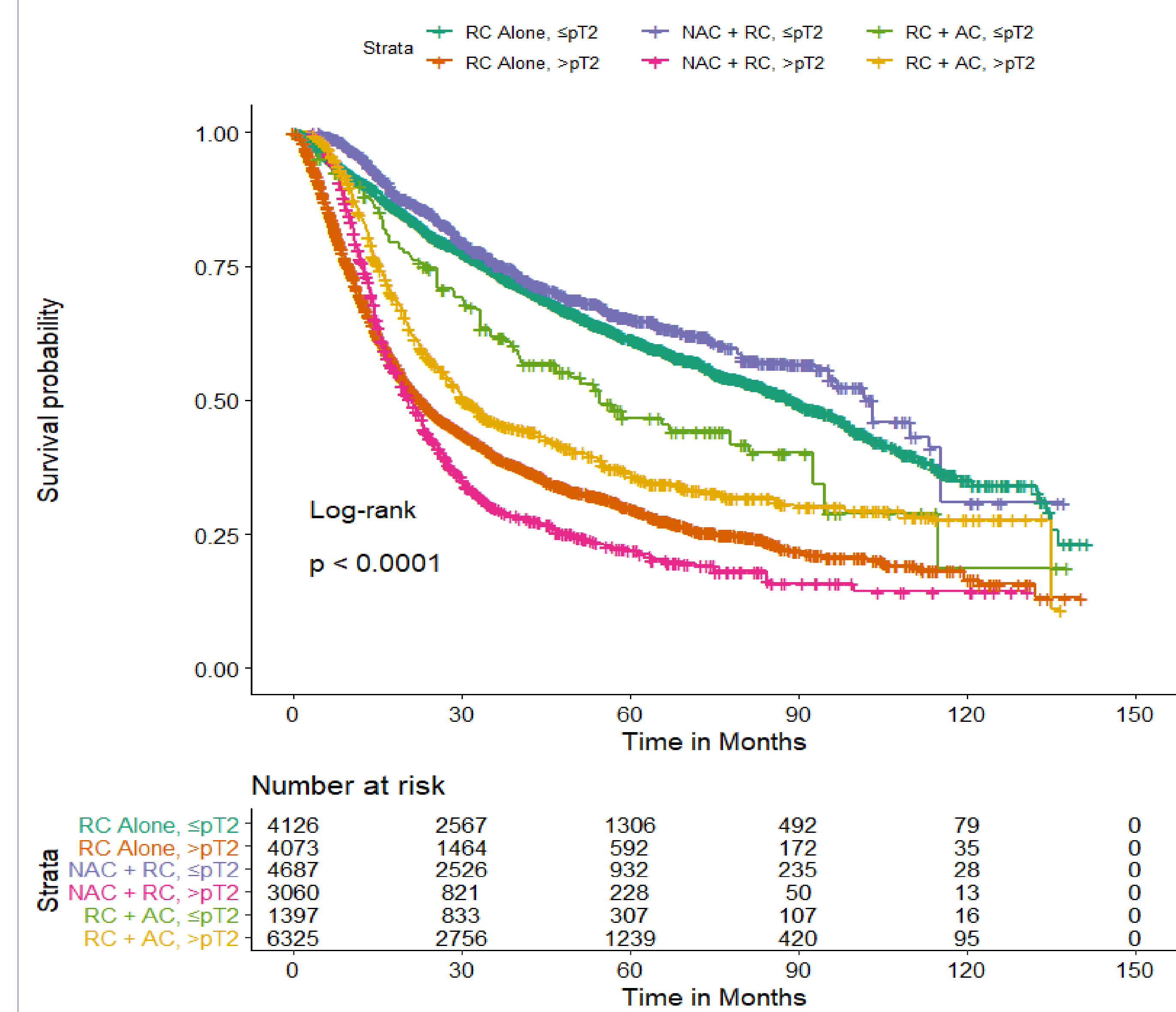


Figure 2. 6-month conditional landmark PS-adjusted Kaplan-Meier analysis of overall survival for patients treated with neoadjuvant chemotherapy prior to radical cystectomy in comparison to pathological stage-matched controls treated with radical cystectomy alone or radical cystectomy and adjuvant chemotherapy.

## CONCLUSIONS

- Overall, NAC is associated with improved OS in this comparative effectiveness analysis.
- Presence of >ypT2 disease is associated with particularly poor outcomes when compared with >pT2 disease in patients treated with cystectomy alone.
- Several factors may contribute to these findings, such as selective pressures of aggressive tumor clones.
- Biomarkers predictive of NAC resistance may be important to optimize individualized treatment regimens for patients with MIBC.

## LIMITATIONS

- Limited dataset lacking variables such as, cancer specific survival, chemotherapy agents used, and how many chemotherapy cycles, which would be useful for further analysis.

## REFERENCES

1. Siegel, R. L., Miller, K. D. & Jemal, A. Cancer statistics, 2019. CA Cancer J Clin 69, 7-34, doi:10.3322/caac.21551 (2019).  
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 3. Stein, J. P. et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol 19, 666-675, doi:10.1200/JCO.2001.19.3.666 (2001).