Original Article

Oncologic outcomes of neoadjuvant chemotherapy and lymph node dissection with partial cystectomy for muscle-invasive bladder cancer

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Contributions: (I) Conception and design: RM Antar, AK Smith, MJ Whalen; (II) Administrative support: All authors; (III) Provision of study materials or patients: RM Antar, MJ Whalen; (IV) Collection and assembly of data: RM Antar, VE Xu, MJ Whalen; (V) Data analysis and interpretation: RM Antar, VE Xu, MJ Whalen; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: Partial cystectomy (PC) offers potential benefits for select patients with muscle-invasive bladder cancer (MIBC). However, the oncologic efficacy of PC may be compromised due to the underutilization of standard-of-care modalities, such as neoadjuvant chemotherapy (NAC) and pelvic lymph node dissection (PLND). We aimed to assess factors influencing the incorporation of NAC and PLND with PC and evaluate their impact on overall survival (OS).

Methods: We identified 2,832 patients with cT2-4N0M0 bladder cancer (BCa) who underwent PC between 2004 and 2019 using the National Cancer Database (NCDB). The primary endpoint was OS. Kaplan-Meier analysis compared OS in treatment modalities in PC patients. Multivariate Cox Proportional Hazards (CPH) model assessed the impact of age, sex, race, insurance, income, Charlson-Deyo Index (CDI), clinical T-stage, facility type, histology, surgical margins, NAC, PLND adequacy [≥10 lymph node (LN) yield], and adjuvant radiation treatment on OS. Multivariate logistic regressions were performed to examine predictors of NAC and PLND receipt in PC patients.

Results: Two hundred and thirty-one patients received multi-agent NAC with PC. NAC treatment with PLND was associated with significantly improved OS (P<0.001). Median OS was 43.9 months in patients treated with PC alone, while median OS was not reached in PC patients treated with NAC & PLND. Furthermore, patients who received NAC without any PLND had a median OS of 50.6 months, while those treated with PLND without NAC had a median OS of 76.5 months. This persisted in the adjusted CPH model, where private insurance, NAC, and PLND significantly improved OS, especially when PLND yielded ≥10 LN. Conversely, age >80 years old, CDI >2, cT3-4, positive margins, and adjuvant radiation all increased adjusted mortality risk. After controlling for clinicopathologic variables, females were less likely to receive PLND [odds ratio (OR) 0.719, P=0.005], while NAC was more likely administered to PC patients diagnosed from 2016–2019 (OR 5.295, P<0.001). PC patients who received NAC were more likely to have PLND performed as part of their treatment regimen (OR 2.189, P<0.001). Additionally, patients treated at academic centers were more likely to have NAC administered and PLND performed (OR 1.745, P=0.003; OR 2.465, P<0.001, respectively).

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Conclusions: Despite guideline recommendations, the utilization of NAC and PLND with PC remains insufficient. Our analysis underscores the significant OS benefit of these recommended treatments as part of MIBC care. Importantly, we highlight a gradual increase in NAC and PLND receipt in recent years, centered largely at academic facilities. Notably, gender disparities exist in PLND receipt, emphasizing the need for further investigation.

Keywords: Partial cystectomy (PC); neoadjuvant chemotherapy (NAC); bladder cancer (BCa); pelvic lymph node dissection (PLND)

Submitted Apr 04, 2024. Accepted for publication Jul 27, 2024. Published online Aug 26, 2024.
doi: 10.21037/tau-24-165
View this article at: https://dx.doi.org/10.21037/tau-24-165

Introduction

Bladder cancer (BCa) is the sixth most common cancer in the United States, with an estimated 82,290 new cases and 16,710 deaths in 2023 (1). Muscle-invasive bladder cancer (MIBC), accounting for nearly 25% of these cases, presents a therapeutic challenge (2). The current standard of care for MIBC is multifaceted, combining cisplatin-based neoadjuvant chemotherapy (NAC), radical cystectomy (RC), pelvic lymph node dissection (PLND), and urinary diversion (3). However, RC's implications on a patients' quality of life, including the chronic sequelae of urinary diversion, potential sexual dysfunction, and a spectrum of other acute post-operative complications, are significant (4). Moreover, adherence to curative intent treatments remains suboptimal; studies indicate that over one-half of MIBC patients never receive such interventions, primarily due to poor tolerability (5). This underscores the need for alternative treatment modalities, such as bladder preservation, to optimize oncologic and functional outcomes (6).

Partial cystectomy (PC) is a potential bladder-sparing option for highly select patients with small (e.g., <5 cm), solitary, or diverticular cT2 lesions sparing the trigone and without hydronephrosis or carcinoma *in situ*. Additionally, it is recommended that a 2-cm surgical margin can be achieved. These criteria, unfortunately, apply to a mere 5–10% of MIBC cases (7,8). There is yet to be a clear consensus regarding the role of PC in treating MIBC, particularly with concerns regarding PC's effectiveness in oncologic control (9-11). Furthermore, contemporary data highlights an infrequent use of NAC and PLND in conjunction with PC. One study reported that only 7–11% of PC patients received NAC, compared to 17–28% in RC. Similarly, PLND was performed in 93% of RCs but only 59% of PCs (12,13). The disparity in adherence to NAC and PLND raises questions about the potential underestimation of PC's clinical efficacy. Indeed, after propensity-matching for tumor stage and NAC receipt, PC has shown comparable cancer-specific survival to RC (14).

Highlight box

Key findings

- Utilization trends of neoadjuvant chemotherapy (NAC) and pelvic lymph node dissection (PLND) with partial cystectomy (PC) for muscle-invasive bladder cancer (MIBC) show a gradual but inadequate increase over time.
- Implementation of NAC and adequate PLND—specifically yielding more than ten lymph nodes—significantly enhances survival outcomes.
- Notable gender disparities in the receipt of PLND underscore an area requiring further investigation.

What is known and what is new?

- While NAC and PLND are recommended for MIBC treatment, their integration as therapeutic modalities with PC remains suboptimal, with existing literature citing underutilization.
- Our contemporary study includes one of the largest PC cohorts over an extended study period, demonstrating the temporal adoption of standard-of-care modalities and the profound impact of NAC and PLND on overall survival.

What is the implication, and what should change now?

- This study's findings advocate for an enhanced role of partial cystectomy as a viable bladder-sparing approach when combined with rigorous NAC and PLND protocols in highly select patients, offering survival benefit.
- To facilitate this shift, there should be a concerted effort to improve guideline adherence, emphasizing the importance of NAC and PLND in partial cystectomy regimens. In addition to continued regionalization of urologic oncology care and further investigation into gender-based disparities in PLND receipt is crucial for equitable care.

Our study investigates the contemporary trends and factors influencing the use of NAC and PLND in conjunction with PC. Moreover, we aim to build upon limited literature to gauge the oncologic efficacy of PC with these multimodal treatments. Through this analysis, we hope to discern the potential viability of an "optimized" PC for non-metastatic MIBC. We present this article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-24-165/rc).

Methods

Study population

This study was conducted by querying the National Cancer Database (NCDB), a hospital-based cancer registry by the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. This database represents over 1,500 Commission-accredited cancer programs in the United States, collecting de-identified data on approximately 70% of all newly diagnosed cancer cases.

A retrospective cohort analysis of 2,832 patients with cT2-4N0M0 BCa who underwent PC [International Classification of Disease-O-3 (ICD-O-3) organ site codes C67.0-9] with curative intent (e.g., not palliative surgery) between 2004 and 2019 was conducted. Since the inclusion of variant histology is under debate and not an imperative contraindication for PC, patients with urothelial carcinoma and variant histology were included in our analysis, provided other criteria are fulfilled. We excluded patients who received single-agent chemotherapy and neoadjuvant radiation therapy, as these are not within the standard of care (15). Patients undergoing PC were differentiated by PLND receipt [binary variable with regional lymph node (LN) yield ≥1 or 0] and further stratified by nodal yield greater or less than ten regional nodes, a metric with established precedent in studying cystectomy outcomes (12,16). Additionally, this study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Furthermore, our study was exempt from institutional ethics review due to using de-identified data from a national database (i.e., NCDB).

Statistical analysis

Descriptive statistics (two-sided independent sample *t*-tests and Chi-squared tests) were used to compare patient characteristics and variables in our cohorts: patients undergoing PC that received multi-agent NAC (n=231) and those that did not (n=1,972) and PC patients that received PLND (n=1,501) and those that did not (n=1,264). The primary outcome was OS, defined as the time from diagnosis to the last follow-up with vital status. Kaplan-Meier analysis and multivariable Cox Proportional Hazards (CPH) regression model compared OS between groups. Multivariable models were adjusted for confounding variables that may impact mortality outcomes, including age, sex, race/ethnicity, insurance, income, Charlson-Deyo Index (CDI), clinical T-stage, home-to-facility distance, histology, surgical margins, NAC, extent of PLND, and adjuvant radiation treatment. Furthermore, binary logistic regression models were performed to examine variables that could predict the receipt of NAC and PLND in PC patients. All statistical calculations were performed in SPSS software (version 29.0; SPSS Inc., Chicago, IL, USA). All reported P values were based on two-sided hypotheses, with a P value of <0.05 considered statistically significant.

Results

Baseline characteristics

We identified 2,832 patients who underwent PC following our inclusion and exclusion criteria. In our cohort analysis, 231 (10.5%) received PC with NAC, and 1,972 (89.5%) received PC without NAC. Of the 231 PC patients receiving NAC, 176 (76.2%) had PLND performed. Additionally, our total PC cohort consisted of 1,501 (54.3%) patients who received PLND, while 1,264 (45.7%) did not. On demographic analysis, there were no differences in sex, facility location, and home region between NAC and non-NAC, as well as PLND and non-PLND cohorts. However, patients receiving NAC and those receiving PLND had significant associations with age, insurance status, facility type, home-to-facility distance, and year of diagnosis. Patients who received PLND during their PC surgery had higher incomes than those who did not receive PLND (61.7% *vs.* 57.4%, P=0.03). Patients receiving NAC were more often privately insured (44.5% *vs.* 29.1%, P<0.001) than those not receiving NAC. PC patients diagnosed in recent years received more NAC and PLND (P<0.001). Academic centers had increased NAC utilization (43.2% *vs.* 32.9%, P=0.003) and PLND utilization (42.9% *vs.* 23.6%, P<0.001). Of patients who did receive PLND with PC, 589 (39.2%) patients had greater than or equal to ten LNs removed. Finally, patients receiving NAC and PLND had lower cT stage (P<0.001). Baseline clinical and demographic characteristics are summarized in *Table 1*.

Tumor response to NAC

Patients treated with NAC had lower rates of positive surgical margins (9.3% *vs.* 16.2%, P=0.009). Additionally, NAC patients were more likely to be pN0 (71.4% *vs.* 47.4%, P<0.001). More patients treated with NAC before PC were downstaged at the time of surgery compared with those who received PC alone (31.2% *vs.* 5.9%, P<0.001). Furthermore, PC patients receiving NAC had greater rates of complete pathological response (pT0) (28.6% *vs.* 3.7%, P<0.001) and reclassification to non-muscle invasive BCa (i.e., "muscle response") (29.9% *vs.* 5.0%, P<0.001) (*Table 2*). When adjusting for clinical and demographic factors among PC patients, NAC was associated with improved odds of complete pathologic response [odds ratio (OR) 6.886, 95% confidence interval (CI): 4.349–10.903, P<0.001] by our logistic regression model.

Survival analysis

Kaplan-Meier analysis demonstrated that NAC treatment in conjunction with PLND for PC patients was associated with significantly improved OS (P<0.001). Median OS was 43.9 months (95% CI: 36.2–51.6) in patients who were treated with PC alone, while median OS was not reached in PC patients treated with NAC & PLND (*Figure 1*). Furthermore, patients who received NAC without any PLND had a median OS of 50.6 months, while those treated with PLND without NAC had a median OS of 76.5 months. The results from our multivariate CPH

Table 1 Baseline demographics of PC patients by NAC and PLND utilization

Variables	NAC			PLND		
	PC without NAC (n=1,972)	PC with NAC (n=231)	P value*	PC without PLND (n=1,264)	PC with PLND (n=1,501)	P value*
Age (years)			<0.001			<0.001
<65	596 (30.2)	100 (43.3)		310 (24.5)	540 (36.0)	
65–80	821 (41.6)	116 (50.2)		519 (41.1)	647 (43.1)	
>80	555 (28.1)	15 (6.5)		435 (34.4)	314 (20.9)	
Sex			0.70			0.30
Male	1,358 (68.9)	162 (70.1)		860 (68.0)	1,049 (69.9)	
Female	614 (31.1)	69 (29.9)		404 (32.0)	452 (30.1)	
Race/ethnicity			0.25			0.04
White	1,687 (86.1)	206 (90.0)		1,080 (86.0)	1,306 (87.6)	
Black	151 (7.7)	12 (5.2)		106 (8.4)	95 (6.4)	
Asian	34 (1.7)	6 (2.6)		18 (1.4)	39 (2.6)	
Hispanic	71 (3.6)	4 (1.7)		42 (3.3)	39 (2.6)	
Other	16 (0.8)	1 (0.4)		10 (0.8)	12 (0.8)	
Charlson-Deyo Index			0.07			0.21
0	1,338 (67.8)	176 (76.2)		848 (67.1)	1,050 (70.0)	
1	427 (21.7)	39 (16.9)		288 (22.8)	300 (20.0)	
2	141 (7.2)	11 (4.8)		91 (7.2)	98 (6.5)	
3+	66 (3.3)	5 (2.2)		37 (2.9)	53 (3.5)	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	NAC			PLND		
	PC without NAC (n=1,972)	PC with NAC (n=231)	P value*	PC without PLND (n=1,264)	PC with PLND (n=1,501)	P value*
Insurance			<0.001			<0.001
None	41 (2.1)	4 (1.8)		20 (1.6)	28 (1.9)	
Private	560 (29.1)	101 (44.5)		303 (24.5)	517 (35.3)	
Medicaid	70 (3.6)	7 (3.1)		40 (3.2)	56 (3.8)	
Medicare	1,253 (65.1)	115 (50.7)		875 (70.7)	863 (58.9)	
Income†			0.47			0.03
Low	704 (39.6)	77 (37.0)		487 (42.6)	509 (38.3)	
High	1,074 (60.4)	131 (63.0)		655 (57.4)	821 (61.7)	
Facility type			0.003			<0.001
Community	934 (48.2)	84 (37.0)		691 (55.4)	580 (39.6)	
Academic	637 (32.9)	98 (43.2)		295 (23.6)	628 (42.9)	
Integrated network	365 (18.9)	45 (19.8)		262 (21.0)	256 (17.5)	
Facility location			0.21			0.17
Northeast	432 (22.3)	63 (27.8)		283 (22.7)	337 (23.0)	
Southeast	417 (21.5)	39 (17.2)		287 (23.0)	293 (20.0)	
Midwest	770 (39.8)	90 (39.6)		492 (39.4)	582 (39.8)	
West	317 (16.4)	35 (15.4)		186 (14.9)	252 (17.2)	
Home-to-facility distance			0.02			<0.001
<10 miles	890 (52.3)	81 (41.3)		626 (57.8)	593 (46.6)	
10–20 miles	257 (15.1)	42 (21.4)		160 (14.8)	205 (16.1)	
20–30 miles	145 (8.5)	21 (10.7)		84 (7.8)	116 (9.1)	
>30 miles	411 (24.1)	52 (26.5)		213 (19.7)	358 (28.1)	
Home region			0.53			0.67
Metropolitan	1,526 (80.7)	180 (81.1)		995 (81.6)	1,150 (80.3)	
Urban	328 (17.3)	40 (18.0)		202 (16.6)	256 (17.9)	
Rural	37 (2.0)	2 (0.9)		23 (1.9)	27 (1.9)	
Year of diagnosis			<0.001			<0.001
2004–2009	627 (31.8)	29 (12.6)		477 (37.7)	369 (24.6)	
2010–2015	826 (41.9)	98 (42.4)		499 (39.5)	652 (43.4)	
2016–2019	519 (26.3)	104 (45.0)		288 (22.8)	480 (32.0)	

Data are presented as n (%). Due to variance among each variable having missing information within the cohorts isolated. *, statistical significance calculated with 2-sided independent sample *t*-test and Chi-square; †, income split by upper and lower two adjusted quartiles. PC, partial cystectomy; NAC, neoadjuvant chemotherapy; PLND, pelvic lymph node dissection.

Table 2 Clinical characteristics of PC patients by NAC and PLND utilization

Variables	NAC			PLND		
	PC without NAC (n=1,972)	PC with NAC (n=231)	P value*	PC without PLND (n=1,264)	PC with PLND (n=1,501)	P value*
Clinical stage			<0.001			<0.001
cT2	1,486 (75.4)	201 (87.0)		912 (72.2)	1,204 (80.2)	
cT3	420 (21.3)	21 (9.1)		300 (23.7)	261 (17.4)	
cT4	66 (3.3)	9 (3.9)		52 (4.1)	36 (2.4)	
Histology			<0.001			<0.001
Urothelial	1,367 (79.6)	210 (93.3)		936 (83.3)	1,061 (80.4)	
Small cell	41 (2.4)	12 (5.3)		33 (2.9)	34 (2.6)	
Squamous cell	73 (4.2)	2 (0.9)		55 (4.9)	42 (3.2)	
Adenocarcinoma	211 (12.3)	0 (0.0)		82 (7.3)	162 (12.3)	
Sarcomatoid	26 (1.5)	1 (0.4)		18 (1.6)	21 (1.6)	
Pathologic stage			<0.001			<0.001
pT0	73 (4.4)	66 (43.4)		39 (4.2)	128 (9.7)	
pT1	25 (1.5)	3 (2.0)		13 (1.4)	23 (1.7)	
pT2	699 (42.4)	35 (23.0)		435 (46.5)	463 (35.2)	
pT3	790 (48.0)	44 (28.9)		410 (43.9)	653 (49.7)	
pT4	60 (3.6)	4 (2.6)		38 (4.1)	48 (3.7)	
pN status			<0.001			<0.001
pNx	904 (47.0)	51 (22.5)		1,264 (100.0)	0 (0.0)	
pN0	913 (47.4)	162 (71.4)		0 (0.0)	1,338 (89.1)	
pN+	108 (5.6)	14 (6.2)		0 (0.0)	163 (10.9)	
Performance of PLND			<0.001			<0.001
No PLND	904 (47.0)	51 (22.5)		1,264 (100.0)	0 (0.0)	
PLND & <10 LN	628 (32.6)	85 (37.4)		0 (0.0)	912 (60.8)	
PLND & ≥10 LN	393 (20.4)	91 (40.1)		0 (0.0)	589 (39.2)	
Surgical margins			0.009			<0.001
Negative	1,514 (83.8)	186 (90.7)		851 (77.9)	1,214 (85.9)	
Positive	293 (16.2)	19 (9.3)		242 (22.1)	199 (14.1)	
Radiation treatment			0.18			<0.001
No radiation	1,803 (91.4)	206 (89.2)		1,059 (83.8)	1,369 (91.2)	
Adjuvant radiation	117 (5.9)	14 (6.1)		145 (11.5)	91 (6.1)	
Unknown	52 (2.6)	11 (4.8)		60 (4.7)	41 (2.7)	
Any downstaging			<0.001			<0.001
Was not downstaged	1,856 (94.1)	159 (68.8)		1,195 (94.5)	1,339 (89.2)	
Downstaged	116 (5.9)	72 (31.2)		69 (5.5)	162 (10.8)	

Table 2 *(continued)*

Table 2 (*continued*)

Variables	NAC			PLND		
	PC without NAC (n=1,972)	PC with NAC (n=231)	P value*	PC without PLND (n=1,264)	PC with PLND (n=1,501)	P value*
cPR (pT0)			<0.001			<0.001
No	1,899 (96.3)	165 (71.4)		1,225 (96.9)	1,373 (91.5)	
Yes	73 (3.7)	66 (28.6)		39 (3.1)	128 (8.5)	
Muscle response			<0.001			<0.001
MIBC	1,874 (95.0)	162 (70.1)		1,212 (95.9)	1,350 (89.9)	
NMIBC	98 (5.0)	69 (29.9)		52 (4.1)	151 (10.1)	

Data are presented as n (%). Due to variance among, each variable having missing information within the cohorts isolated. *, statistical significance calculated with 2-sided independent sample *t*-test and Chi-square. PC, partial cystectomy; NAC, neoadjuvant chemotherapy; PLND, pelvic lymph node dissection; cPR, complete pathological response; MIBC, muscle invasive bladder cancer; NMIBC, non-muscle invasive bladder cancer; LN, lymph node(s).

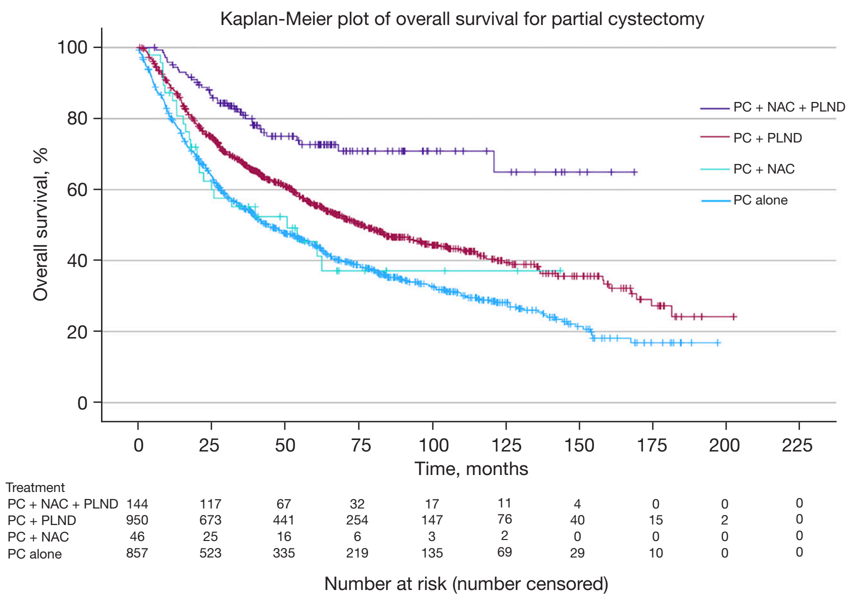

Figure 1 Kaplan-Meier plot of overall survival for partial cystectomy across treatment groups: PC alone, PC & PLND, PC & NAC, PC with both NAC & PLND. PC, partial cystectomy; NAC; neoadjuvant chemotherapy; PLND, pelvic lymph node dissection.

model assessing NAC and PLND's impact on PC patients' OS are provided in *Table 3*. NAC treatment in PC patients significantly reduced adjusted mortality hazard [adjusted hazard ratio (aHR) 0.657; 95% CI: 0.478–0.904; P=0.01]. Furthermore, a PLND yield of ≥10 nodes significantly decreased adjusted mortality risk compared to no PLND (aHR 0.586, P<0.001). However, PLND of <10 nodes reduced adjusted mortality risk, but this effect only trended towards significance (aHR 0.856, P=0.06). Since only ~6% of our cohort received both NAC and PLND, we could not perform a comprehensive survival analysis comparing both effects to those who did not undergo these interventions.

Predictors of NAC and LN dissection receipt

Our findings revealed that various clinicodemographic characteristics were independent predictors of NAC and PLND receipt, summarized in *Table 4*. Patients

Table 3 Cox Proportional Hazards model for overall survival in partial cystectomy patients

Covariate	Hazard ratio	95% CI	P value
Age (Ref.: <65 years old)			
65–80 years old	1.029	0.779–1.360	0.84
>80 years old	1.885	1.406–2.526	<0.001
Sex (Ref.: males)			
Female	1.027	0.874–1.206	0.75
Race/ethnicity (Ref.: White)			
Black	0.894	0.655–1.219	0.48
Asian	0.837	0.517–1.353	0.47
Hispanic	0.758	0.374–1.539	0.44
Other	1.768	0.831–3.761	0.14
Charlson-Deyo Index (Ref.: 0)			
1	1.102	0.925–1.313	0.28
2	1.946	1.508–2.512	<0.001
3+	1.567	1.069–2.297	0.02
Insurance (Ref.: uninsured)			
Private	0.515	0.300–0.885	0.02
Medicaid	1.111	0.579–2.132	0.75
Medicare	0.729	0.412–1.290	0.28
Income (Ref.: low)			
High	0.845	0.727–0.982	0.028
Clinical T stage (Ref.: cT2)			
cT3	1.358	1.134–1.626	0.001
cT4	2.575	1.727–3.838	<0.001
Facility type (Ref.: community)			
Academic	1.005	0.842–1.198	0.96
Integrated network	1.212	1.001–1.467	0.049
Histology (Ref: urothelial)			
Small cell	1.599	1.034–2.473	0.04
Squamous cell	1.552	1.147–2.099	0.004
Adenocarcinoma	0.579	0.424–0.792	<0.001
Sarcomatoid	1.204	0.657–2.204	0.55
Surgical margins (Ref: negative)			
Positive	1.711	1.421–2.062	<0.001
Chemotherapy (Ref: no NAC)			
NAC treatment	0.657	0.478–0.904	0.01
Performance of PLND (Ref: no PLND)			
PLND & <10 LN	0.856	0.730–1.004	0.06
PLND & ≥10 LN	0.586	0.465–0.740	<0.001
Radiation treatment (Ref: no radiation)			
Adjuvant radiation	1.492	1.128–1.974	0.005
Unknown	1.183	0.808–1.734	0.39

Ref., reference; NAC, neoadjuvant chemotherapy; PLND, pelvic lymph node dissection; LN, lymph node(s); CI, confidence interval.

Table 4 Effect of covariates on neoadjuvant chemotherapy and pelvic lymph node dissection utilization with partial cystectomy by binary logistic regressions

Variables[†]	Receiving NAC		Receiving PLND	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (Ref.: <65 years old)				
65–80 years old	0.670 (0.410–1.097)	0.11	0.834 (0.553–1.259)	0.84
>80 years old	0.135 (0.066–0.275)	<0.001	0.550 (0.349–0.868)	0.051
Sex (Ref.: male)				
Female	1.165 (0.812–1.671)	0.41	0.719 (0.570–0.905)	0.005
Race (Ref.: White)				
Black	0.765 (0.375–1.558)	0.46	0.716 (0.470–1.090)	0.12
Asian	0.766 (0.252–2.327)	0.64	0.624 (0.321–1.214)	0.17
Hispanic	1.865 (0.575–6.056)	0.30	2.048 (0.870–4.816)	0.10
Other	0.403 (0.050–3.251)	0.39	1.046 (0.306–3.570)	0.94
Charlson-Deyo Index (Ref.: 0)				
1	0.721 (0.468–1.110)	0.14	0.942 (0.728–1.218)	0.65
2	0.725 (0.354–1.483)	0.38	1.078 (0.721–1.611)	0.72
3+	0.773 (0.285–2.093)	0.61	1.349 (0.742–2.453)	0.33
Insurance (Ref.: uninsured)				
Private	1.508 (0.483–4.709)	0.48	1.167 (0.538–2.534)	0.70
Medicaid	1.087 (0.271–4.365)	0.91	0.807 (0.314–2.075)	0.66
Medicare	1.151 (0.349–3.797)	0.82	0.837 (0.372–1.882)	0.67
Income[‡] (Ref.: low)				
High	1.102 (0.779–1.559)	0.58	1.223 (0.983–1.521)	0.07
Facility type (Ref.: community)				
Academic	1.745 (1.214–2.509)	0.003	2.465 (1.934–3.142)	<0.001
Integrated network	1.234 (0.778–1.958)	0.37	1.049 (0.792–1.389)	0.74
Clinical stage (Ref.: cT2)				
cT3	0.637 (0.376–1.079)	0.09	0.711 (0.542–0.935)	0.01
cT4	1.052 (0.406–2.723)	0.92	0.566 (0.307–1.043)	0.07
Histology (Ref: urothelial)				
Small cell	2.026 (0.925–4.437)	0.08	0.799 (0.417–1.531)	0.50
Squamous	0.229 (0.054–0.978)	0.047	0.986 (0.579–1.679)	0.96
Adenocarcinoma	0.000 (0.000–0.000)	0.995	1.626 (1.120–2.361)	0.01
Sarcomatoid	0.237 (0.030–1.872)	0.17	0.764 (0.331–1.759)	0.53
Year of diagnosis (Ref.: 2004–2009)				
2010–2015	3.042 (1.877–4.931)	<0.001	1.474 (1.155–1.883)	0.002
2016–2019	5.295 (3.219–8.709)	<0.001	1.747 (1.319–2.315)	<0.001
Chemotherapy (Ref.: no NAC)				
NAC treatment			2.189 (1.505–3.184)	<0.001

[†], OR compared to reference category in parentheses; [‡], income split by upper and lower two adjusted quartiles. Ref., reference; NAC, neoadjuvant chemotherapy; PLND, pelvic lymph node dissection; OR, odds ratio; 95% CI, 95% confidence interval.

over 80 years old were less likely to receive NAC (OR 0.135, P<0.001). Patients with variant histologies such as squamous cell carcinoma were less likely to receive NAC (OR 0.229, P=0.047), while patients with adenocarcinoma were more likely to receive PLND (OR 1.626, P=0.01). Additionally, patients treated at academic centers were more likely to have NAC administered and PLND performed (OR 1.745, P=0.003; OR 2.465, P<0.001, respectively). Women undergoing PC were less likely to have PLND as part of their treatment (OR 0.719, P=0.005). Moreover, the year patients were diagnosed predicted NAC and PLND treatments.

Compared to patients diagnosed between 2004 and 2009, the likelihood of NAC receipt increased from an OR of 3.042 (P<0.001) to 5.295 (P<0.001) between the ranges of 2010–2015 and 2016–2019, respectively. Patients' likelihood of PLND receipt also increased from an OR of 1.474 (P=0.002) to 1.747 (P<0.001) from 2010–2015 and 2016–2019, respectively. Furthermore, PC patients who had received NAC were also more likely to have PLND performed as part of their treatment regimen (OR 2.189, P<0.001).

Other outcomes of interest

There were no significant differences between cohorts regarding 30-day mortality. However, patients who underwent PC and received NAC were shown to have a lower 90-day mortality rate, decreasing from 5.3% to 1.0% (P=0.009).

Discussion

Despite the recommendations from the National Comprehensive Cancer Network (NCCN) guidelines to incorporate NAC with PC for cT2 MIBC patients, previous studies have reported a clear underutilization of NAC and PLND. One study reported that patients undergoing PC were less likely to receive standard care, such as NAC (11.4% *vs.* 27.9%) and PLND (58.7% *vs.* 92.5%), than those in the RC group (13). Although a comprehensive NCDB study indicated improved OS with RC compared to PC (67.8 *vs.* 54.1 months), a subgroup analysis revealed similar survival outcomes between RC and highly selected PC patients, including cT2 patients with tumor size <5 cm, no carcinoma in situ (CIS), and cN0 (17). Considering the advantages of PC, like reduced morbidity and shorter hospital stays, there may be an expanded role for its utilization. Yet, it is worth noting that PC has been associated with greater rates of positive surgical margins (15.7% *vs.* 10.6%, P<0.001) (13). In our analysis, the rate of positive surgical margins was decreased in patients who received NAC (9.3% *vs.* 16.2%, P=0.009), suggesting that poor NAC utilization may contribute to the not-insubstantial positive surgical margin rate observed in prior studies. Moreover, the widely recognized underutilization of NAC and PLND in PC patients means that the perceived survival advantage of RC over PC may be attributable, in part, to the combined use of NAC and PLND.

The impact of NAC and LN dissection on PC outcomes

Our findings demonstrate that NAC independently reduces the risk of death by 34% amongst patients who received PC when adjusting for other significant predictors. However, only 8.1% of PC patients within our cohort received NAC, which aligns with prior studies (18,19). Our temporal analysis indicates that patients diagnosed in recent years [2016–2019] had a fivefold increased likelihood of receiving NAC and were twice as likely to have PLND during their PC. Notably, those who received NAC were twice as likely to have PLND performed. These observations align with updated multi-disciplinary guidelines published in 2017 by several associations that emphasized the role of NAC and PLND with PC (3). Even though NAC and PLND's integration into PC appears suboptimal, our results illustrate a promising upward trend in their inclusion in PC treatment protocols over time.

Additionally, the extent of the PLND was shown to impact OS. While there is no consensus in the literature for an optimal PLND yield, we found the most pronounced benefit when at least ten LNs were harvested. While it intuitively makes sense that examining more nodes increases the chances of identifying pN+ disease, our findings propose a benchmark of ten LNs as a potentially meaningful clinical target to enhance survival outcomes for patients undergoing PC.

We also found an association between NAC administration and improved pathologic response. There was a notable 25.3% increase in any downstaging among PC patients treated with NAC. Additionally, those treated with NAC demonstrated less muscle invasion (95.0% *vs.* 70.1%) and were more likely to experience a complete pathologic response to NAC (28.6% *vs.* 3.7%). We also identified a link between patients receiving PLND and complete pathological response or downstaging. This correlation likely stems from the increased likelihood of patients undergoing NAC and PLND treatments. When combined with other best practices like NAC, PLND, and prompt surgery, PC may indeed offer curative efficacy on par with RC in a subset of eligible patients.

Other associated factors

An intriguing observation from our study indicated that, when adjusted for demographic and clinical parameters, women had a nearly 30% lower likelihood of undergoing PLND. While there is no clear explanation for this disparity, the result could be related to a relative lack of experience in treating women with BCa, given that BCa is generally more common in men (20). It may be possible that women are understaged at the initial diagnosis of BCa as non-muscle invasive because of inadequate resection depth and the absence of muscularis propria in pathologic specimens. However, this hypothesis would undoubtedly impact NAC rates as well, not just PLND. When assessing women undergoing RC, Anderson *et al.* found that women were 21% less likely to receive PLND than men, even after adjusting for patient characteristics and higher-volume surgeons at high-volume facilities (21). Another plausible explanation could stem from any prior history of a hysterectomy, which frequently involves PLND. While a previous history of hysterectomy with PLND cannot be assessed in the NCDB, it lends an interesting consideration for women undergoing cystectomy and should be further investigated.

Of the variant histology assessed in our study, we observed a decreased mortality risk in patients with adenocarcinoma compared to other histological subtypes when accounting for clinicodemographic and treatment receipt (i.e., NAC and PLND). Adenocarcinoma of the bladder dome or urachus has long been a known indication for PC, explaining why it may have been the only variant histology with improved survival outcomes (8,22). In our analysis, the predominance of adenocarcinoma was observed in the bladder dome and urachus, together accounting for 75.8% of cases, with 37.5% in the dome and 38.3% in the urachus. Conversely, the remaining 24.2% of adenocarcinoma tumors were located in other regions of the bladder. Moreover, BCa patients with adenocarcinoma histology were also more likely to receive PLND in our cohort. This could be because adenocarcinoma, a recognized indication for PC, often sees a stricter adherence to the standard of care, including PLND. In contrast, other variants might lack well-established care guidelines. Not surprisingly, none of the adenocarcinoma BCa patients in our study received NAC, reflecting the treatment paradigm of PC with PLND rather than NAC for urachal and non-urachal adenocarcinoma (23). In contrast, other variants lack well-established guidelines concerning the use of perioperative chemotherapy. Therefore, the observed survival benefit of NAC in our entire cohort highlights the need for subsequent investigations in variant histological subtypes.

NAC and LN dissection utilization over time

While our study found that the utilization of NAC and PLND in PC is improving over time, both remain heavily underutilized. We observed an increase in NAC utilization from 0% in 2004 to nearly 23% in 2019, while PLND improved from 41% in 2004 to 63% in 2019 (*Figures 2,3*). Despite being standard treatment procedures, merely 6.2% of patients in our cohort received both NAC and PLND. Even further, our study demonstrated alarming discrepancies in utilization depending on which treatment facility a patient is treated at, with academic centers 75% more likely to utilize NAC and 147% more likely to perform PLND compared to community hospital centers, even when adjusting for other variables such as age, insurance, staging, variant histology, and year of diagnosis. Moreover, when patients had NAC as part of their care, their likelihood of also undergoing PLND increased by 119%, implying that many patients are either getting "all or nothing" regarding the standard of care.

Given the association between NAC and OS, our work reinforces the need for more detailed, population-level studies to better understand the determinants of MIBC outcomes and uptake of these treatment intensification modalities. One strategy to improve outcomes with PC is to reinforce the importance of National Comprehensive Cancer Network Guidelines in the multimodal treatment of BCa patients via national organizations such as the American Urological Association or the American Society of Clinical Oncology. Furthermore, regionalization of care with the encouragement of referral to high-volume centers of excellence (academic or otherwise) has been proposed to promote superlative, evidence-based care. As the adoption of these treatment modalities expands and care standardization is achieved across healthcare institutions, it is plausible that the efficacy of PC would commensurately improve over time to the point that bladder preservation treatment regimens utilizing PC become a better utilized

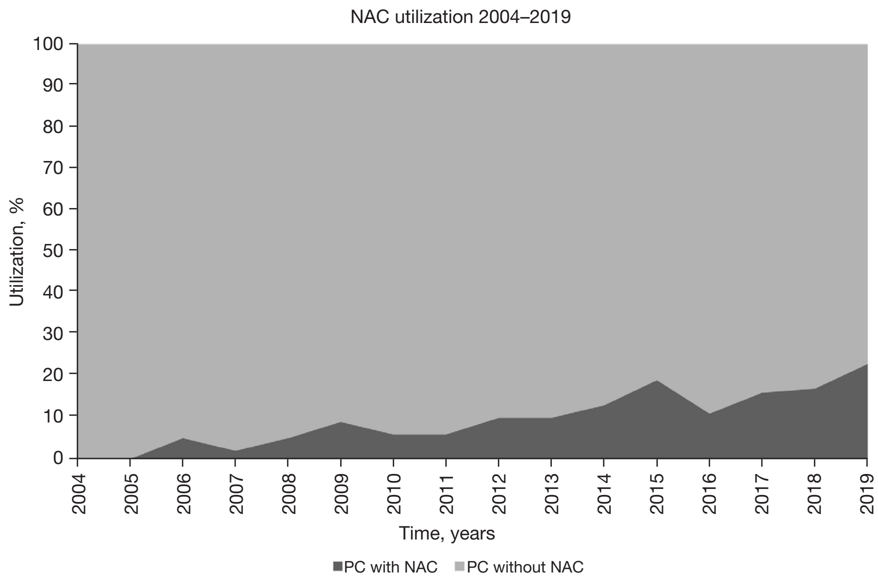

Figure 2 Temporal graph (years) displaying utilization of neoadjuvant chemotherapy with partial cystectomy from 2004 to 2019. NAC, neoadjuvant chemotherapy; PC, partial cystectomy.

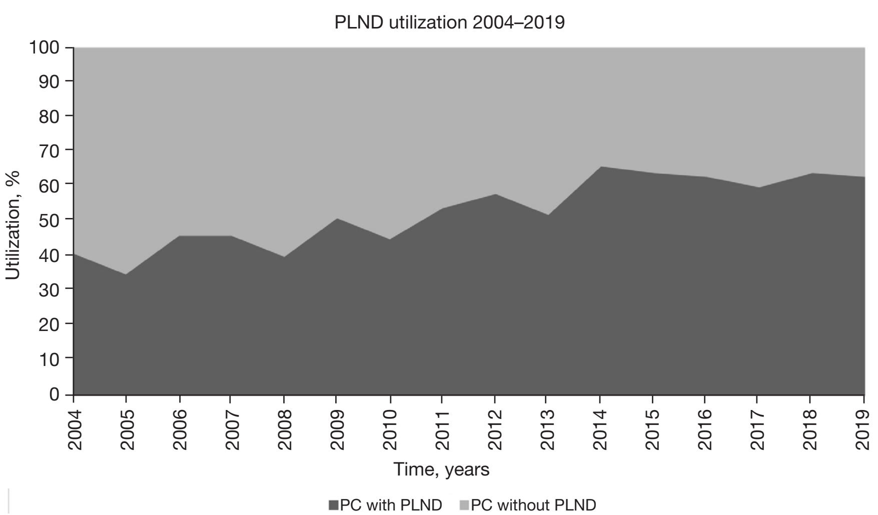

Figure 3 Temporal graph (years) displaying utilization of pelvic lymph node dissection with partial cystectomy from 2004 to 2019. PLND, pelvic lymph node dissection; PC, partial cystectomy.

first-line treatment option for carefully selected patients meeting the appropriate criteria.

Advantages and limitations

This study builds upon the foundation of other studies, such as Lenis *et al.*, further investigating the role of PC with a contemporary series encompassing one of the largest PC sample sizes to date and encapsulating the most recent treatment patterns up to 2019. Furthermore, with this expanded cohort, we conducted a comprehensive survival analysis between PC patients to assess NAC and PLND's impact on overall survival (OS). Our novel study reflects the current state of PC utilization and highlights increased recognition of bladder-sparing strategies and variables influencing the receipt of MIBC treatments, requiring further inquiry.

Moreover, our study is not without limitations. Firstly, the retrospective nature of this study must be acknowledged. Secondly, the exact rationale for PC selection is unknown, and our analysis is subject to the influence of unmeasured confounders. The inclusion criteria for PC have evolved over the last 15 years. This variability in patient selection criteria could introduce heterogeneity in our study population, impacting the generalizability of our survival analysis. Future studies should consider these evolving criteria and their potential effects on treatment outcomes to provide a more nuanced understanding of PC's effectiveness over different periods. Thirdly, the NCDB does not provide information on the experience and expertise of surgeons performing PC. Surgeon experience is a critical factor influencing surgical outcomes, including survival rates, complication rates, and overall treatment success. Unfortunately, the NCDB does not collect data on individual surgeon experience or surgical volume. This omission is a notable limitation, as it could account for variations in patient outcomes related to the treatment modalities themselves. Future research should aim to include surgeon-specific data better to understand the impact of surgical expertise on PC outcomes.

Moreover, the specifics of NAC regimens, including the types of chemotherapeutic agents and the number of cycles administered, were not available in the NCDB. While we excluded patients who received single-agent chemotherapy, the lack of detailed information on the NAC regimens limits our ability to analyze the impact of different chemotherapy protocols on patient outcomes. Additionally, the inability to assess why certain patients could not tolerate or complete NAC regimens adds another layer of complexity to our findings. This underscores the need for more granular data collection in future studies to evaluate the effectiveness of specific chemotherapy regimens and their tolerability in the PC patient population. Additionally, staging in the NCDB is reported as the highest stage, thereby making the determination of carcinoma *in-situ* in the presence of concomitant muscle-invasive disease not possible. Furthermore, we could not account for secondary malignancies (i.e., colorectal, gynecological, etc.) given the limitations of the NCDB, which could influence treatment decisions and outcomes.

Despite these limitations, our study captures a broad view of current treatment modalities, setting the stage for future, more granular investigations that could offer an improved understanding of the therapeutic landscape of PC. With regards to variant histology, there remains no clear consensus on the best management of BCa subtypes; therefore, we included these subtypes in our data to capture the current landscape of PC and its adjacent treatment modalities, acknowledging the necessity for subsequent studies to delve deeper into the nuanced management of these variants.

Conclusions

Our analysis underscores a gradual yet inadequate increase in the utilization of NAC and PLND with PC in recent years, centered largely at academic centers. The broader incorporation of NAC and PLND within the context of PC is essential, given that each variable was an independent predictor of OS. Additionally, we identified factors influencing the selection of patients for NAC and PLND, highlighting the need to investigate gender-based disparities in PLND receipt among women. The marked improvement in OS among NAC recipients reiterates the potential value of this modality as part of the comprehensive treatment regime for MIBC. To our knowledge, our study is one of the first to utilize a larger sample size to assess the impact of NAC use before PC on OS and investigate the determinants of NAC and PLND adoption. Our insights may serve as a foundation for future studies to optimize multimodal treatment for MIBC.

Acknowledgments

Both the CoC's NCDB and the affiliated hospitals serve as sources of the de-identified data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived from this study. Furthermore, this study's abstract was presented at the 2024 American Society of Clinical Oncology's Genitourinary Cancers Symposium.
Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-24-165/rc

Peer Review File: Available at https://tau.amegroups.com/

article/view/10.21037/tau-24-165/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-24-165/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was exempt from institutional ethics review due to using de-identified data from a national database (i.e., NCDB).

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Cite this article as: Antar RM, Xu VE, Farag CM, Lucero J, Drouaud A, Sundaresan V, Gordon OF, Azari S, Wynne M, Smith AK, Whalen MJ. Oncologic outcomes of neoadjuvant chemotherapy and lymph node dissection with partial cystectomy for muscle-invasive bladder cancer. Transl Androl Urol 2024;13(8):1349-1363. doi: 10.21037/tau-24-165