Original Article

Neoadjuvant and adjuvant chemotherapy share equivalent efficacy in improving overall survival and cancer-specific survival among muscle invasive bladder cancer patients who undergo radical cystectomy: a retrospective cohort study based on SEER database

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Background: Although neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC) have been reported an 6% absolute improvement in 5-year overall survival (OS) for muscle invasive bladder cancer (MIBC), criticism still exists including the delay of surgery and the lack of accurate pathological evidence guidance. Trials have instead focused on adjuvant chemotherapy (AC) but encountered with many difficulties. Convincing data directly compared the treatment efficacy of these 2 strategies are lacking.

Methods: We conducted a retrospective cohort study to compare the effectiveness of NAC versus AC among patients with T2-4N0-3M0 bladder cancer using the Surveillance, Epidemiology, and End Results (SEER) database. OS and cancer-specific survival (CSS) were compared using Kaplan-Meier (KM) survival estimators and univariate Cox proportional hazards regression models adjusted for inverse probability of treatment weighting (IPTW). The baseline between groups were compared using standardized mean differences (SMD) approach and kernel density plot. Sensitivity analysis was performed to test the robustness of our results.

Results: In total, 1,620 (38.9%) of all eligible patients (4,169) received NAC and 2,549 (61.1%) received AC. After adjusted for propensity score, all baseline characteristics were balanced with SMD <10%. The IPTW-adjusted survival analyses revealed no significant difference in OS between the 2 groups [adjusted hazard ratio (AHR) 1.09, 95% confidence interval (CI): 0.99–1.20, P=0.1]. Exploratory subgroup analysis indicated longer OS among lymph node-negative patients treated with NAC (AHR 1.25, 95% CI: 1.1–1.4, P=0.001), whereas lymph node-positive patients were in favor of AC (AHR 0.85, 95% CI: 0.72–0.99, P=0.043). This treatment heterogeneity according to lymph node status is associated with better prognosis in Stage II (T2N0) patients receiving NAC (AHR 1.28, 95% CI: 1.1–1.6, P=0.014). Meanwhile, in stage III-IV (T3-T4 and/or N+) diseases, NAC shares similar treatment efficacy to AC (AHR 0.98, 95% CI: 0.87–1.1, P=0.762). The analyses of CSS yielded similar, robust results on the effect of potential unmeasured

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confounding variables.

Conclusions: Our population-based study suggests that NAC and AC might be interchangeable in MIBC management, especially in patients with Stage III-IV (T3-T4 and/or N+) diseases. However, this conclusion needs further validation from powerful, robust randomized trials.

Keywords: Surveillance, Epidemiology, and End Results (SEER); bladder cancer; chemotherapy; survival; epidemiology

Submitted Dec 01, 2022. Accepted for publication Feb 06, 2023. Published online Feb 27, 2023.
doi: 10.21037/tau-23-79
View this article at: https://dx.doi.org/10.21037/tau-23-79

Introduction

Bladder cancer is the most common malignant tumor originating from urothelial cells, which accounted for 3% of all malignancy cases and caused 212,536 deaths in 2020 (1). Approximately 20–30% of bladder cancer patients present with muscle invasive bladder cancer (MIBC) (2). Established standard management of MIBC requires thorough local therapy, including radical cystectomy (RC), pelvic lymphadenectomy, and urinary diversion (3-7). However, when treated with surgical procedures alone, approximately 40% of patients develop recurrence within 5 years (8,9). Multiple complementary therapies, including systemic cisplatin-based chemotherapy, immunotherapy, and radiotherapy, are applied to optimize MIBC management and yield better oncological outcomes.

To date, neoadjuvant chemotherapy (NAC) is the only combination therapy proven by solid level 1 evidence to be beneficial in postoperative survival. Chemotherapy administered in the preoperative setting has demonstrated superior overall survival (OS) in randomized controlled trials (RCTs) as well as meta-analyses (10-13). Meanwhile, comparing with adjuvant chemotherapy (AC), NAC was proven to be more tolerable with higher completion rate for assigned treatment cycle (14). For advanced MIBC, Primary chemotherapy might shrink the tumor therefore improving the tumor resectability (10,12). However, arguments exist that the delay of surgery may confer a risk for progression brought by micrometastasis especially among those who are chemoresistance. In addition, AC could be more precise and personalized under the guidance of accurate tumor staging as well as pathological result. Theoretically, minimizing tumor burden through surgical resection before systemic treatment might improve the efficacy of chemotherapy. Even though NAC and AC have their own strengths and limitations, the central concerning regarding the selection between NAC and AC is the comparison of their treatment efficacy.

In this case, multiple prospective studies focusing on AC tried to answer the question but remained less robust. A series of phase III RCTs investigating the treatment efficacy of RC plus AC versus RC alone or delayed chemotherapy at relapse reported conflicting results and were criticized as underpowered because of slow accrual along with early termination, methodological flaws, and small sample sizes (15-24). The lack of level 1 evidence imposes tight restrictions on AC administration, and it is only recommended if patients with locally advanced features

Highlight box

Key findings

- In our cohort study based on 4,169 patients with T2-4N0-3M0 muscle invasive bladder cancer (MIBC), adjuvant chemotherapy following radical cystectomy shows an equivalent survival benefit to that of pre-operative chemotherapy.

What is known and what is new?

- Neoadjuvant chemotherapy has been established as the standard of care for MIBC supported by multiple level 1 evidences. However, efficacy of post-operative chemotherapy remains uncertain owing to setbacks encountered by randomized trials.
- Our cohort study provides one of the largest real-world evidences based on the widely accepted SEER database across a wide time frame. Propensity score adjustment was utilized to guarantee comparable groups which has been ignored by many previous cohort studies.

What is the implication, and what should change now?

- Our study implies that radical cystectomy following adjuvant chemotherapy may also considered as a first-line strategy for localized MIBC. Further validation is required from robust randomized trials.

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(pT3/4 and/or pN +) have received no chemotherapy before surgery. In contrast, inspired by powerful evidence, routine administration of NAC among MIBC patients has been gradually established over the past decades (3-5). The latest updated meta-analysis based on individual patient data (IPD) from 11 trials, with a large sample size and improved methodology, demonstrated a relatively convincing reduction in recurrence as well as 6% absolute improvement in 5-year OS driven from AC utilization, which is comparable with the 5% achieved with NAC (13,25). However, to the best of our knowledge, a direct comparison of NAC and AC among MIBC patients who undergo definitive surgery has never been fully evaluated by convincing RCTs which might be difficult to perform considering multiple setbacks encountered with the AC arm.

Based on the above considerations, in the present cohort study, we compared the treatment efficacy between NAC and AC among patients diagnosed with locally advanced urothelial carcinoma of the bladder (T2-4N0-3M0) who were also treated with RC using the latest updated Surveillance, Epidemiology, and End Results (SEER) database, one of the largest cancer incidence database, aiming to fill in the blanks left by RCTs and provide complementary references regarding the treatment selection among different stages of MIBC in a real-world setting. We present the following article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-23-79/rc).

Methods

Data source

All case-level information regarding patients' epidemiologic features, essential clinical variables including tumor histology, stage, surgical management, and combination therapy, as well as follow-up information were collected from the SEER incidence database, which collects the data on the incidence of cancer covering roughly half of the US population.

Study design and population

This retrospective cohort study aimed to compare NAC with AC in their impact on OS and cancer-specific survival (CSS) among RC-managed MIBC patients extracted from SEER database. A total of 58,870 individuals pathologically diagnosed with stage II–IV bladder cancer from 2004 to 2019 were identified using SEER*Stat software (version 8.4.0.1; https://seer.cancer.gov/seerstat/) based on a private ID. The sampling criteria from SEER were as following: (I) Derived AJCC Stage Group, 6th ed (2004-2015)/7th edition Derived SEER Cmb Stg Grp (2016–2017)/8th edition Derived EOD 2018 Stage Group (2018+) = II-IV; (II) Diagnostic Confirmation = Microscopically confirmed; (III) site recode ICD-0-3/WHO 2008 = Urinary Bladder; (IV) behavior cod ICD-0-3 = Malignant. We selected only patients with T2-4N0-3M0 transitional cell carcinoma who received RC as local treatment combined with either NAC or AC. Those who underwent no/unknown surgical procedures or primary local treatment other than RC, those who received combination therapy with any radiation therapy or any form of systemic treatment other than NAC or NC, and those with nontransitional cell histology were excluded. In consideration of the various staging rules SEER applied according to the diagnosis year, the assignment of tumor stage grouping for all cases according to the American Joint Committee on Cancer (AJCC) staging system (8th edition) (26). Therefore, we excluded patients for whom tumor/node/metastasis (T/N/M) information was not available. Patients were also excluded if they had an ambiguous cause of death, which precluded the calculation of CSS (*Figure 1*). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Covariates and endpoints

Characteristics regarding patients' epidemiological information were extracted from the SEER database including age at diagnosis, sex, race, and year of diagnosis. Histology as well as clinical features including grade, T stage, N stage, and AJCC stage were also collected. Staging information can be obtained from derived AJCC stage categories. Cases with unknown values for all variables including covariates as well as follow-up information were excluded according to eligible criteria, except for those with unknown tumor grade. Therefore, tumor grade was handled as a dummy variable and missing values regarding grade were recorded as unknown. Follow up information for each individual was extracted from SEER database according to relevant claims including Survival months, SEER cause-specific death classification and SEER other cause of death classification.

The primary and secondary outcomes of interest were OS and CSS. We defined OS and CSS as the time from

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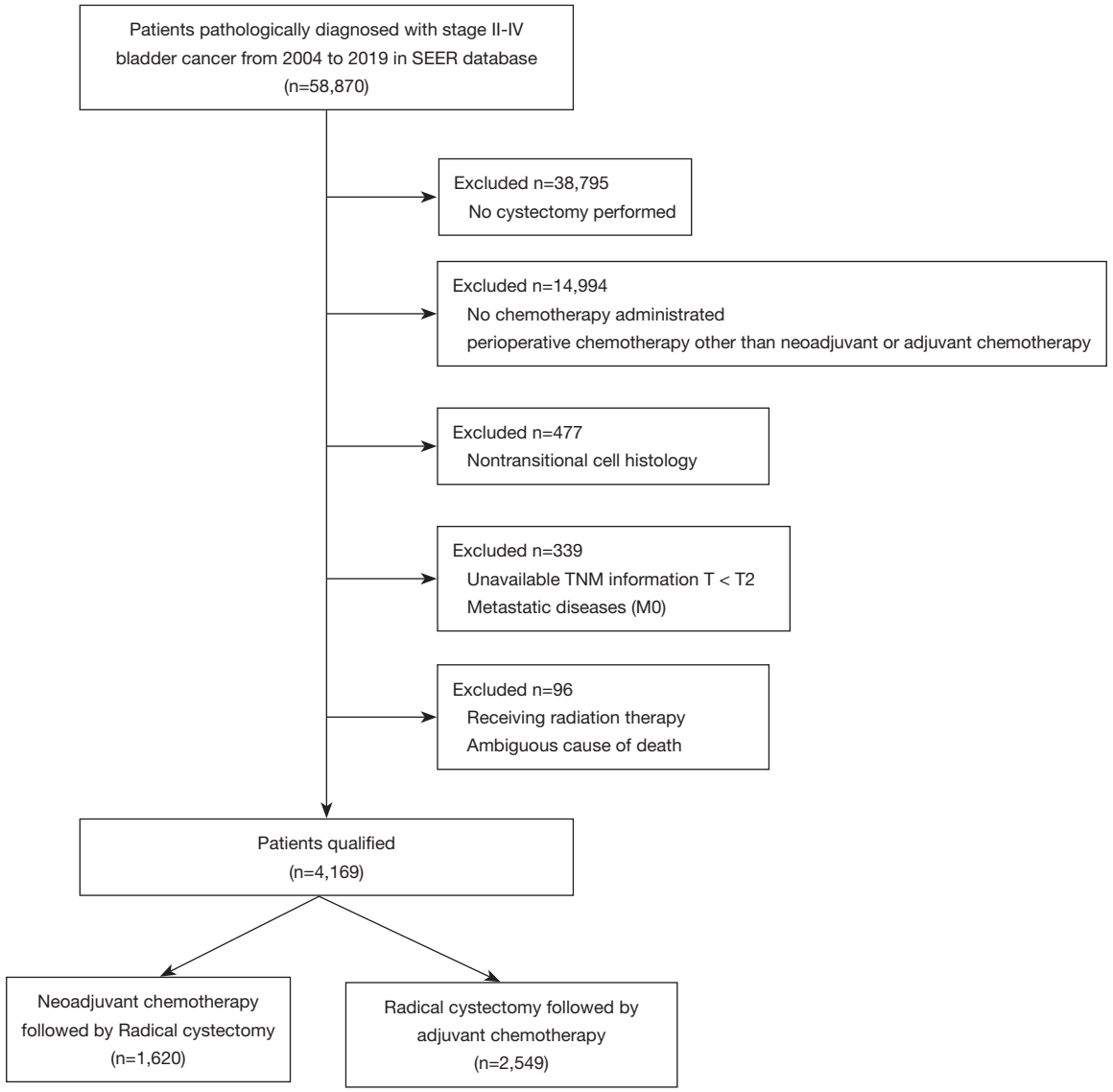

Figure 1 Flowchart of patient selection. SEER, Surveillance, Epidemiology, and End Results.

diagnosis to the last date of follow-up and the date of death from any cause or cancer, respectively. The SEER cause-specific death classification, other cause of death classification, and survival month categories extracted for SEER were used to identify the follow-up information mentioned above.

Statistical analyses

All variables were categorized except for year of diagnosis, which was coded as a nonnormal discrete quantity. Considering differences in baseline characteristics, inverse probability of treatment weighting (IPTW) was utilized to account for confounding between groups, which is a statistical method based on propensity score (27). To estimate the propensity score representing the conditional probability of receiving AC after RC versus receiving NAC followed by RC, we constructed a multivariate logistic regression model for each individual. To identify variables significantly associated with the receipt of different chemotherapy strategies, we included all covariables in a univariate logistic regression. Only variables with a P value ≤0.1 in the univariate analysis were allowed to remain in the multivariate model. To reduce large variances brought

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by the extreme distribution of propensity scores, stabilized weights targeting the average treatment effect among all eligible patients in the study population (ATE) were calculated for each individual as Pt/PS for the NAC group and (1-Pt)/(1-PS) for the AC group (Pt: the proportion of individuals in the AC group) (28). We assessed covariate balance both before and after weighting using a standardized differences approach and kernel density plot, which graphically illustrated the overlap of propensity score distribution.

To compare the OS and CSS between patients treated with NAC versus AC, we calculated IPTW-adjusted Kaplan-Meier (KM) survival curves and performed an IPTW-adjusted log-rank test. Furthermore, univariate IPTW-adjusted as well as unadjusted univariate Cox proportional hazards regression model was fitted to compute the corresponding hazard ratios (HRs) and explore the potential heterogeneity of treatment effects with tests of interaction and subgroup analyses according to all covariates.

In the absence of random assignment, it was difficult to construct comparable treated and control groups at baseline by controlling all potential confounding variables. Given that, we performed a sensitivity analysis developed by Lin *et al.* to evaluate the robustness of our conclusion by introducing an unmeasured confounding factor related to the receipt of combination chemotherapy and treatment effect (29). We varied the HRs of this confounding factor as well as its prevalence in the 2 groups to compute the corresponding adjusted HRs for OS and CSS.

A 2-sided P value <0.05 in all statistical hypothesis testing was considered statistically significant. We conducted all statistical analyses in R version 4.1.1 software (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

After screening, we included 4,169 patients with T2-4N0-3M0 MIBC diagnosed from 2006 to 2019 using the SEER database who had RC as primary local treatment and received combination NAC or AC. The majority of the study population were white (88%), male (76%) patients older than 65 years (58%, range from 17–98), and had lymph node-negative (N0, 66%) diseases. Few individuals developed tumors spreading through the bladder wall into the pelvic or abdominal wall (stage IV, 2%). Patients with low-grade cancer were in the minority (1%), which might be related to the large proportion of unknown grade information (39%). In total, 1,620 (38.9%) of all eligible patients received initial chemotherapy before RC, whereas 2,549 (61.1%) had initiated RC followed by postoperative chemotherapy. The baseline patient characteristics are synthesized in *Table 1*. Standardized differences before weighting showed that the NAC and AC groups differed significantly with respect to most characteristics of interest except for age, gender, and race.

Characteristics associated with chemotherapy receipt

The univariate logistic regression revealed that most covariables, except for age [<65 *vs.* ≥65 y: odds ratio (OR) 1, 95% confidence interval (CI): 0.93–1.2, P=0.45], sex (female *vs.* male: OR 0.96, 95% CI: 0.83–1.1, P=0.63), and AJCC stage, which was strongly correlated with T/N stage, were included in the multivariate model we utilized to estimate the propensity score. According to the multivariate logistic regression analysis, race, grade, T stage, N stage and year of diagnosis were significantly associated with different modes of chemotherapy administration. Patients with a race other than white, higher T stage and positive lymph nodes were more like to receive AC than NAC (*Table 2*). From 2006 to 2019, we found increasing popularity of NAC utilization in patients who underwent RC in clinical practice (17.7% in 2006 to 36.1% in 2019, P<0.001, *Figure 2A*, Figure S1). Meanwhile, we observed a higher ratio of AC administration among patients with stage III-IV diseases (*Figure 2B*). After IPTW, the standardized mean differences were less than 10% for all covariates, including age, sex, and AJCC stage (*Figure 3A*). The propensity distribution also achieved adequate balance after weighting (*Figure 3B*,*3C*), which indicated that the patients treated with RC in combination with NAC versus AC were subsequently comparable.

Survival analysis

The median follow-up was 68 months for the entire study cohort. A total of 1,958 deaths occurred during the follow-up period, including 1,511 cancer-specific deaths and 447 deaths from other causes. Patients lost to follow-up were recorded as censored during subsequent survival analysis.

The unadjusted 5-year OS was 60% (95% CI: 0.57–0.63) for patients receiving NAC which was significantly better than the 47% (95% CI: 0.44–0.49) in the AC group (P<0.001, *Figure 4A*). The unadjusted 5-year CSS rate

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Table 1 Baseline characteristics of the study cohort

Characteristics	Crude population				Weighted population			
	NAC [n=1,620, %]	AC [n=2,549, %]	Overall [n=4,169, %]	SMD	NAC (%)	AC (%)	Overall (%)	SMD
Age, years				0.024				0.072
<65	698 [43]	1,068 [42]	1,766 [42]		45	41	44	
≥65	922 [57]	1,481 [58]	2,403 [58]		55	59	56	
Gender				0.015				0.006
Female	345 [21]	559 [22]	904 [22]		22	22	22	
Male	1,275 [79]	1,990 [78]	3,265 [78]		78	78	78	
Race				0.063				0.001
Others	175 [11]	327 [13]	502 [12]		12	12	12	
White	1,445 [89]	2,222 [87]	3,667 [88]		88	88	88	
Year of diagnosis	2014 (2011, 2017)	2012 (2009, 2016)	2013 (2010, 2016)	0.469	2013 (2010, 2016)	2013 (2010, 2017)	2013 (2010, 2016)	0.033
Grade[a]				0.158				0.027
Low grade	26 [2]	16 [1]	42 [1]		1	1	1	
High grade	1,023 [63]	1,468 [58]	2,491 [60]		61	60	61	
Unknown	571 [35]	1,065 [42]	1,636 [39]		38	39	38	
T stage				0.45				0.009
T2	952 [59]	939 [37]	1,891 [45]		46	46	46	
T3	427 [26]	1,047 [41]	1,474 [35]		35	35	35	
T4	241 [15]	563 [22]	804 [19]		19	19	19	
N stage				0.475				0.02
N0	1,277 [79]	1,460 [57]	2,737 [66]		67	66	67	
N+[b]	343 [21]	1,089 [43]	1,432 [34]		33	34	33	
AJCC stage				0.539				0.064
II	850 [52]	691 [27]	1,541 [37]		39	37	38	
III	742 [46]	1,810 [71]	2,552 [61]		59	62	60	
IV	28 [2]	48 [2]	76 [2]		2	2	2	

In crude population, data are shown as count [percentage] while in weighted population, only percentages are shown; Year of diagnosis is shown as median (interquartile range). [a], tumor grade is based on World Health Organization (WHO) or International Society of Urological Pathology (ISUP) grading criteria. [b], N+ including all patients with N1-N3 diseases. NAC, neoadjuvant chemotherapy; AC, adjuvant chemotherapy; SMD, standardized mean difference; T, tumor; N, node; AJCC, American Joint Committee on Cancer.

was also higher when patients received NAC instead of AC (NAC+RC group: 67%, 95% CI: 0.64–0.70; RC+AC group: 53%, 95% CI: 0.51–0.55; P<0.001, *Figure 4B*). The unadjusted multivariate Cox Analysis also revealed that NAC and AC have no significant difference in OS (HR 1.06, 95% CI: 0.95–1.17, P=0.288) and CSS (HR 1.06, 95% CI: 0.94–1.19, P=0.375) (Table S1).

However, when adjusted for IPTW, individuals receiving NAC showed no significant difference in OS when comparing with those receiving AC. The 5-year adjusted OS was 53% (95% CI: 0.50–0.56) in the NAC group versus 50% (95% CI: 0.48–0.53) in the AC group (P=0.291), with

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Table 2 Characteristics associated with the receipt of perioperative chemotherapy

Characteristics	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
Race						
Others	Ref			Ref		
White	0.82	0.68–1	0.050	0.84	0.68–1	0.088
Year of diagnosis	0.88	0.87–0.9	<0.001	0.9	0.89–0.92	<0.001
Grade						
Low grade	Ref					
High grade	2.3	1.2–4.4	0.008	1.7	0.89–3.3	0.110
Unknown	3	1.6–5.7	<0.001	2	1–3.8	0.043
T stage						
T2	Ref			Ref		
T3	2.5	2.2–2.9	<0.001	1.9	1.7–2.3	<0.001
T4	2.4	2–2.8	<0.001	1.7	1.4–2	<0.001
N stage						
N0	Ref			Ref		
N+	2.8	2.4–3.2	<0.001	2.1	1.8–2.5	<0.001
AJCC stage						
II	Ref					
III	3	2.6–3.4	<0.001			
IV	2.1	1.3–3.4	0.002			
Age, years						
<65	Ref					
≥65	1	0.93–1.2	0.450			
Gender						
Female	Ref					
Male	0.96	0.83–1.1	0.630			

OR, odds ratio; CI, confidence interval; T, tumor; N, node; AJCC, American Joint Committee on Cancer.

corresponding median OS times of 81 months (95% CI: 57–94 months) and 63 months (95% CI: 55–70 months) (P=0.083, *Figure 4C*), respectively. A comparison of CSS between the 2 groups yielded similar results. The 5-year adjusted CSS was 59% (95% CI: 0.56–0.53) in the NAC group versus 57% (95% CI: 0.55–0.60) in the AC group (P=0.329). The median CSS was not reached (95% CI: 121–not reached) for NAC, and it was 125 months (95% CI: 89–not reached) for AC (P=0.146, *Figure 4D*).

In the IPTW-adjusted univariate Cox model, receiving NAC or AC was not associated with a significant difference in OS (HR 1.09, 95% CI: 0.99–1.20, P=0.1, *Figure 5A*) or CSS (HR 1.09, 95% CI: 0.97–1.22, P=0.166, *Figure 5B*).

Further subgroup analyses were performed to explore whether the treatment effect varied according to patients' baseline characteristics with respect to age, sex, race, tumor grade, T stage, N stage, and AJCC stage among the weighted population. For both OS and CSS, the analysis of interaction revealed that significant treatment heterogeneity existed only among the subgroups defined by N stage and

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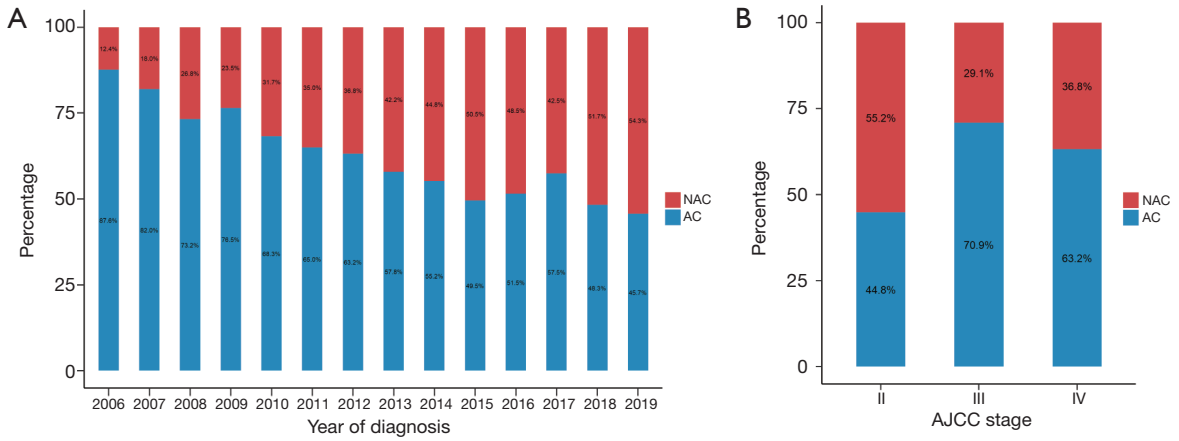

Figure 2 Proportion of different perioperative chemotherapies with the year of diagnosis (A) and AJCC stage (B) in patients with T2-4N1-3M0 bladder cancer who underwent RC. NAC, neoadjuvant chemotherapy; AC, adjuvant chemotherapy; AJCC, American Joint Committee on Cancer; RC, radical cystectomy.

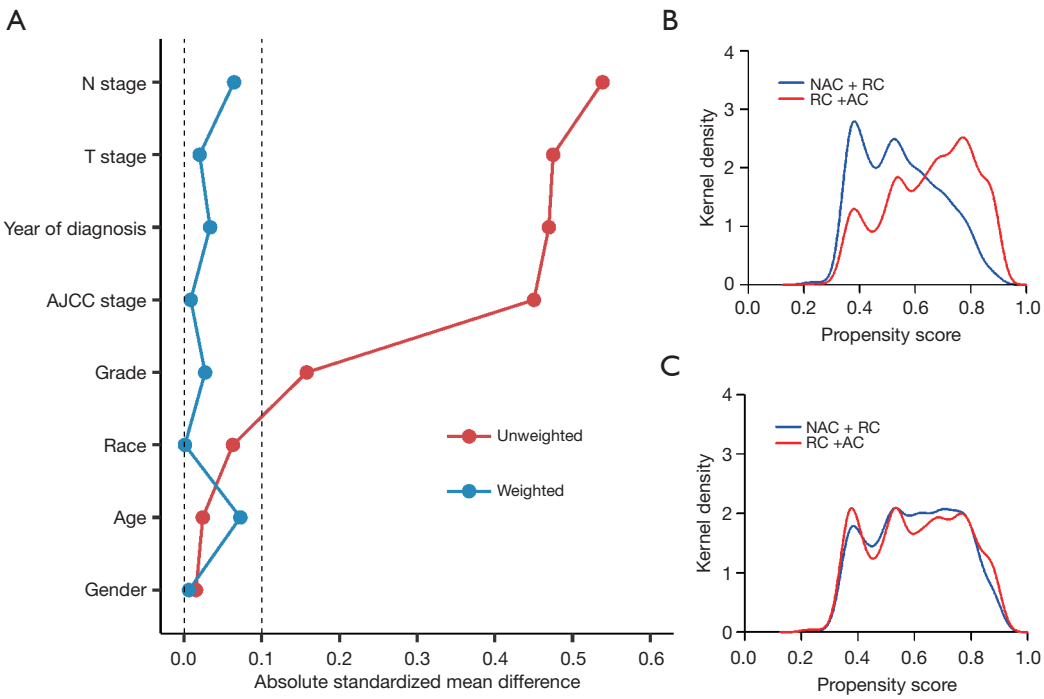

Figure 3 The balance between patients who received different chemotherapy strategies was evaluated by SMD as well as overlap of propensity score distribution before and after the IPTW adjustment. With IPTW adjustment, the SMD are less than 10% for all covariates. (A) And kernel density plots show that the distribution of propensity scores achieved adequate balance between neoadjuvant group and adjuvant group. (B) Before weighting. (C) After weighting. AJCC, American Joint Committee on Cancer; NAC, neoadjuvant chemotherapy; RC, radical cystectomy; AC, adjuvant chemotherapy; SMD, standardized mean difference; IPTW, inverse probability of treatment weighting.

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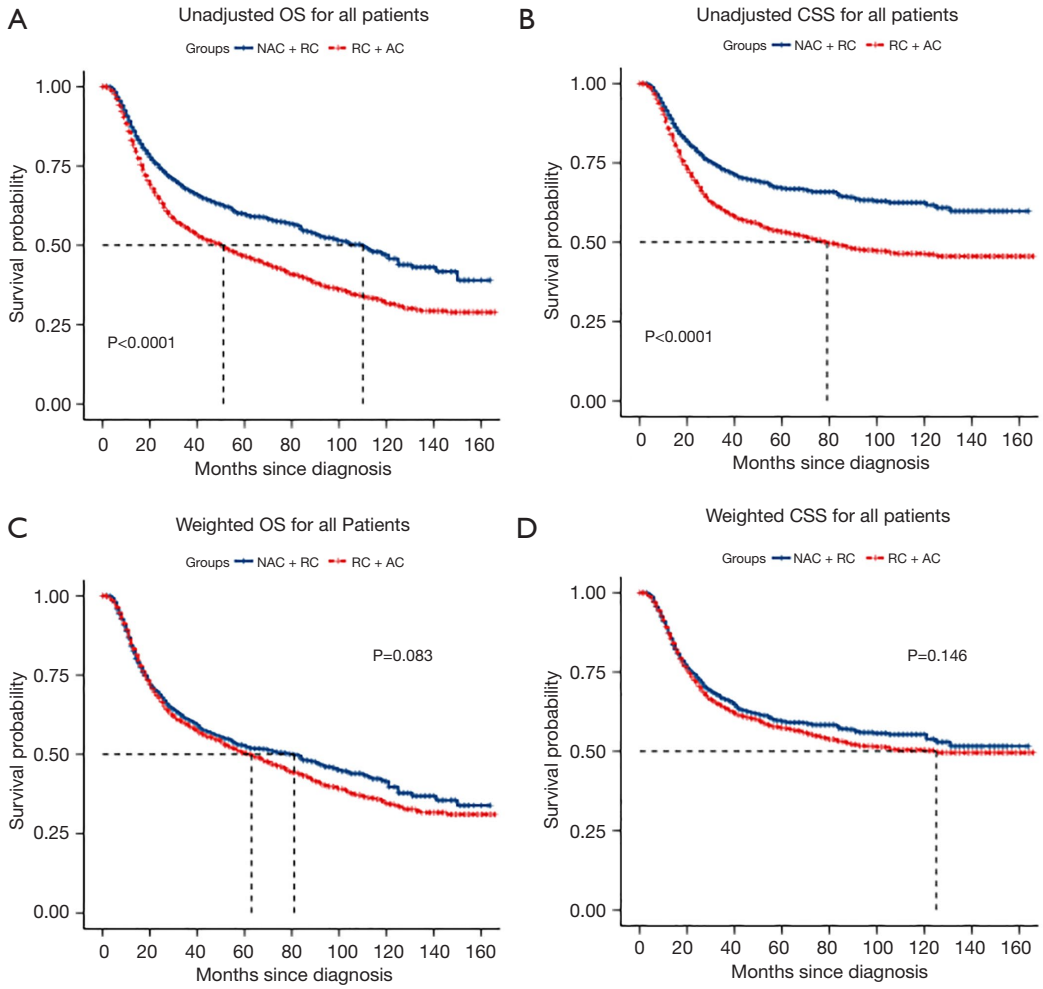

Figure 4 Unadjusted and inverse probability of treatment weighting–adjusted Kaplan–Meier curves of OS (A,C) and CSS (B,D) for patients with T2-4N1-3M0 transitional cell carcinoma of the bladder who underwent RC and received combination neoadjuvant chemotherapy versus adjuvant chemotherapy. OS, overall survival; NAC, neoadjuvant chemotherapy; RC, radical cystectomy; AC, adjuvant chemotherapy; CSS, cancer-specific survival.

AJCC stage (*Figure 5*).

In patients without lymph node involvement (N0), NAC was superior to AC in terms of both OS (65%, 95% CI: 0.62–0.68 in the NAC group versus 60%, 95% CI: 0.57–0.63 in the AC group; HR 1.25, 95% CI: 1.1–1.4, P=0.001) and CSS (73%, 95% CI: 0.70–0.76 in the NAC group versus 67%, 95% CI: 0.65–0.70 in the AC group; HR 1.28, 95% CI: 1.1–1.5, P=0.002) (*Figure 5* and *Figure 6A*,*6B*), whereas in patients with lymph node-positive diseases (N+), receiving AC instead of NAC was associated with longer 5-year OS (28%, 95% CI: 0.23–0.35 in the NAC group versus 34%, 95% CI: 0.31–0.37 in the AC group; HR 0.85, 95% CI: 0.72–0.99, P=0.043) and CSS (32%, 95% CI: 0.27–0.39 in the NAC group versus 39%, 95% CI: 0.36–0.43 in AC group; HR 0.83, 95% CI: 0.7–0.98, P=0.029) (*Figure 5* and *Figure 6C*,*6D*).

Regarding different AJCC stages, we observed significant improvements in OS and CSS attributed to receiving NAC in patients with stage II disease (5-year OS: 74%, 95% CI: 0.71–0.78 in the NAC group versus 72%, 95% CI: 0.68–0.76 in the AC group, HR 1.28, 95% CI: 1.1–1.6, P=0.014; 5-year CSS: 84%, 95% CI: 0.79–0.85 in the NAC group versus 78%, 95% CI: 0.75–0.82 in the AC group, HR 1.32, 95% CI: 1–1.7, P=0.028, *Figure 5* and *Figure 6E*,*6F*). Meanwhile, individuals diagnosed with stage III-IV disease had similar OS or CSS between NAC and AC (5-year OS: 39%, 95% CI: 0.35–0.44 in the NAC group versus 40%, 95% CI: 0.37–0.42 in the AC group, HR: 0.98, 95% CI:

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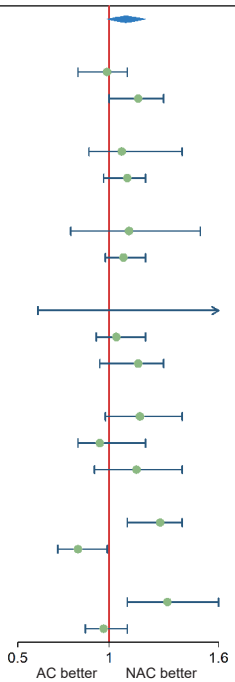
A

Characteristics	NAC+RC(%)	RC+AC(%)	Hazard ratio(95%CI)	P value	P for interaction
All Patients	**39**	**61**	**1.09(0.99-1.20)**	**0.1**	
Age					**0.072**
<65y	45	41	0.97(0.83-1.1)	0.712	
≥65y	55	59	1.18(1-1.3)	0.014	
Gender					**0.977**
Female	22	22	1.1(0.89-1.4)	0.387	
Male	78	78	1.09(0.97-1.2)	0.142	
Race					**0.891**
Others	12	12	1.07(0.79-1.5)	0.663	
White	88	88	1.09(0.98-1.2)	0.102	
Grade					**0.500**
Low Grade	1	1	2.09(0.61-7.2)	0.239	
High Grade	61	60	1.06(0.93-1.2)	0.373	
Unknown	38	39	1.13(0.95-1.3)	0.158	
T stage					**0.370**
T2	46	46	1.17(0.98-1.4)	0.078	
T3	35	35	0.98(0.83-1.2)	0.791	
T4	19	19	1.12(0.92-1.4)	0.26	
N stage					**<0.001**
N0	67	66	1.25(1.1-1.4)	0.001	
N+	33	34	0.85(0.72-0.99)	0.043	
AJCC stgae					**0.037**
II	39	37	1.28(1.1-1.6)	0.014	
III-IV	61	63	0.98(0.87-1.1)	0.762	



B

Characteristics	NAC+RC(%)	RC+AC(%)	Hazard ratio(95%CI)	P value	P for interaction
All Patients	**39**	**61**	**1.09(0.97-1.22)**	**0.166**	
Age					**0.206**
<65y	45	41	0.99(0.83-1.2)	0.935	
≥65y	55	59	1.16(0.99-1.4)	0.06	
Gender					**0.825**
Female	22	22	1.07(0.85-1.3)	0.586	
Male	78	78	1.1(0.96-1.3)	0.183	
Race					**0.872**
Others	12	12	1.11(0.79-1.6)	0.54	
White	88	88	1.08(0.96-1.2)	0.21	
Grade					**0.430**
Low Grade	1	1	2.21(0.55-8.8)	0.261	
High Grade	61	60	1.04(0.9-1.2)	0.636	
Unknown	38	39	1.16(0.95-1.4)	0.151	
T stage					**0.280**
T2	46	46	1.17(0.95-1.4)	0.15	
T3	35	35	0.95(0.79-1.1)	0.583	
T4	19	19	1.15(0.93-1.4)	0.206	
N stage					**<0.001**
N0	67	66	1.28(1.1-1.5)	0.002	
N+	33	34	0.83(0.7-0.98)	0.029	
AJCC stgae					**0.038**
II	39	37	1.32(1-1.7)	0.028	
III-IV	61	63	0.97(0.85-1.1)	0.655	

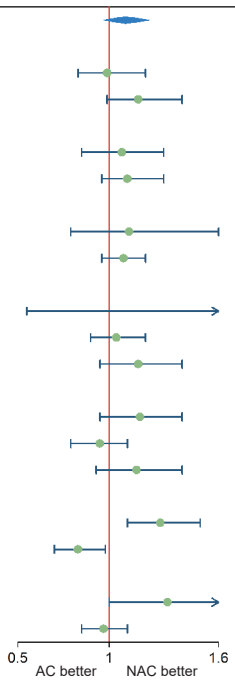


Figure 5 Forest plot summarized the results of subgroup analyzes for OS (A) and CSS (B) which depicting the HR of adjuvant chemotherapy versus neoadjuvant chemotherapy for radical cystectomy managed T2-4N1-3M0 transitional cell carcinoma of the bladder after inverse probability of treatment weighting. NAC, neoadjuvant chemotherapy; RC, radical cystectomy; AC, adjuvant chemotherapy; OS, overall survival; CSS, cancer-specific survival; RC, radical cystectomy; HR, hazard ratio.

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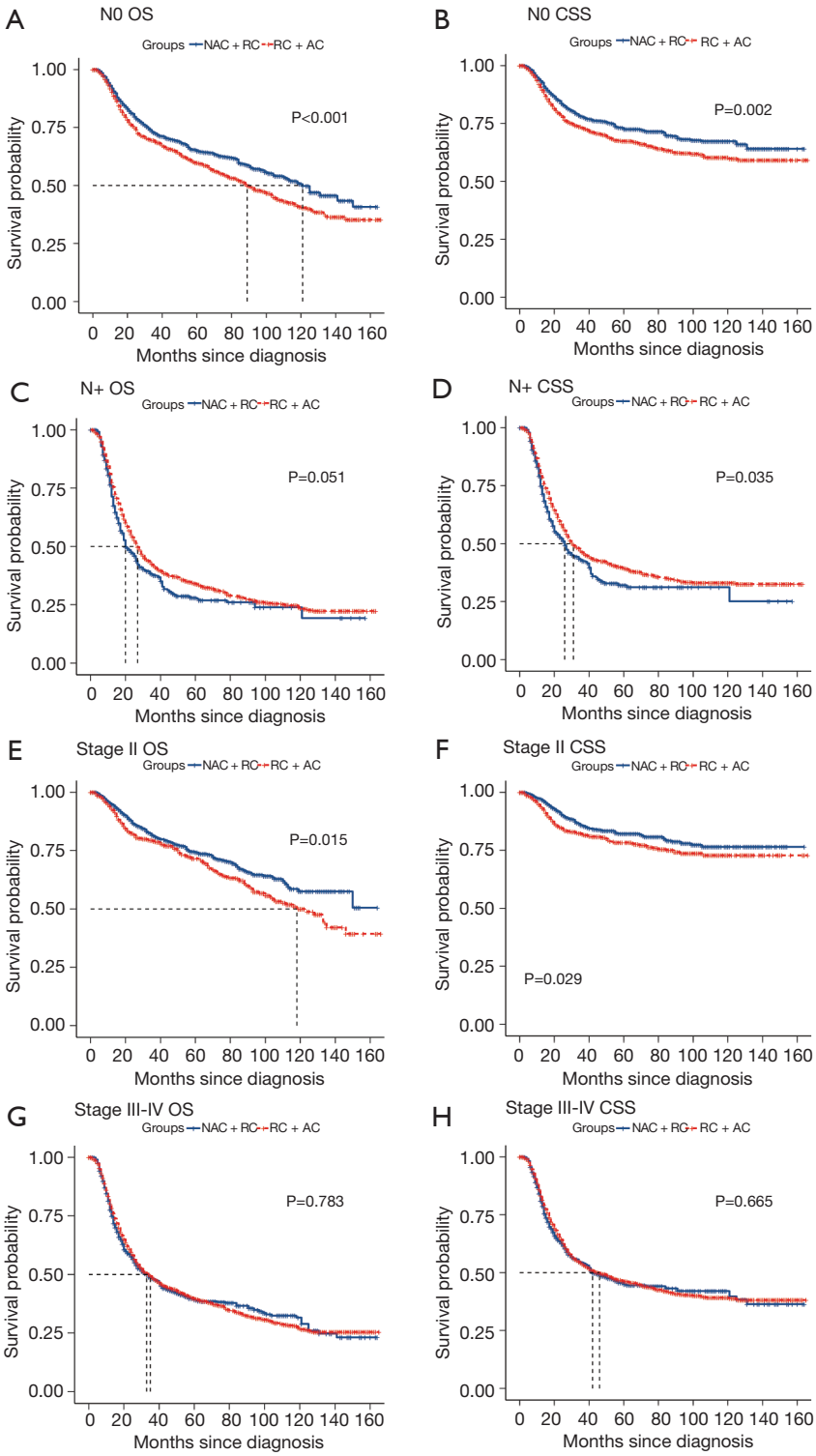

Figure 6 Subgroup inverse probability of treatment weighting–adjusted Kaplan–Meier curves for OS and CSS according to N stage and AJCC stage. Overall survival: patients without lymph node involvement (A), patients with lymph node positive diseases (C), patients with stage II diseases (E), patients with stage III-IV diseases (G); CSS: patients without lymph node involvement (B), patients with lymph node positive diseases (D), patients with stage II diseases (F), patients with stage III-IV diseases (H). OS, overall survival; NAC, neoadjuvant chemotherapy; RC, radical cystectomy; AC, adjuvant chemotherapy; CSS, cancer-specific survival; AJCC, American Joint Committee on Cancer.

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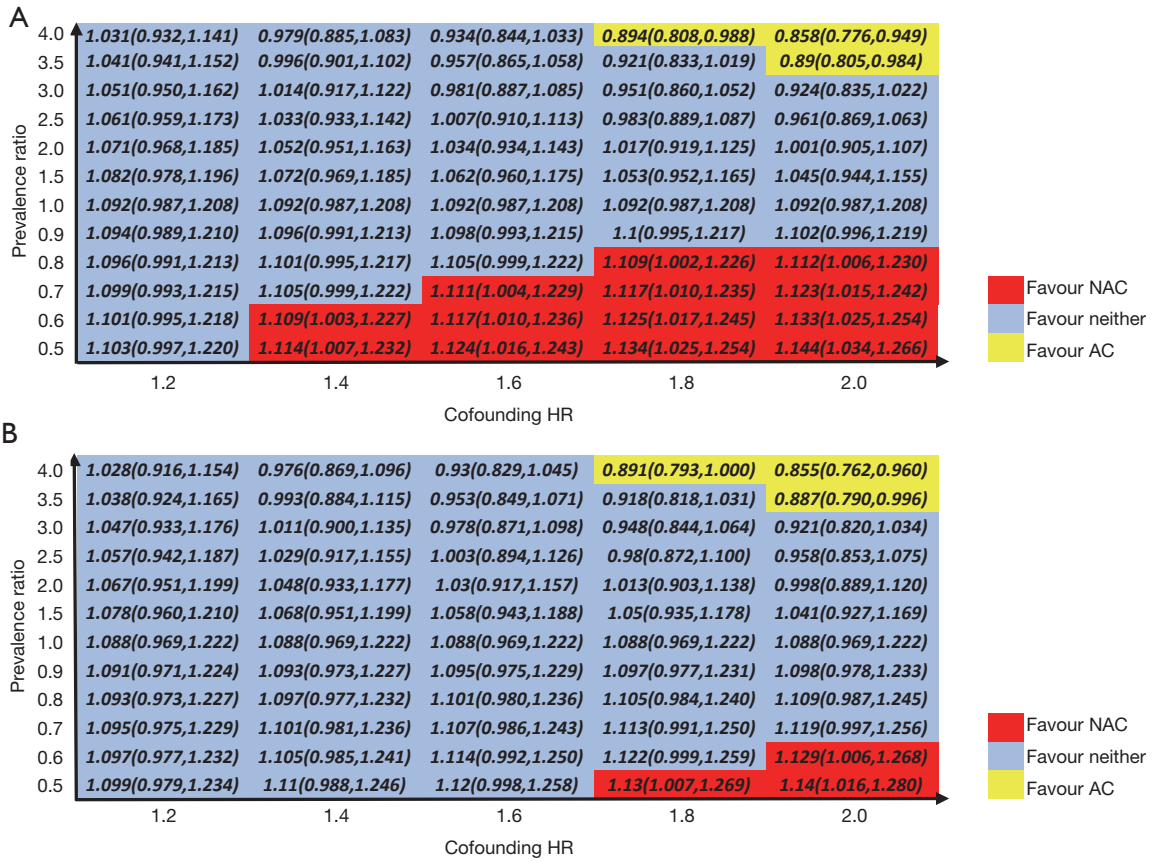

Figure 7 Sensitivity analysis for the impact of unmeasured confounding factors. With different HRs (x-axis) as well as prevalence ratios in the adjuvant chemotherapy group versus neoadjuvant group (y-axis) of this confounding factor, corresponding adjusted hazard ratios of adjuvant chemotherapy compared with neoadjuvant chemotherapy for MIBC patients were computed for OS (A) and CSS (B). HRs, hazard ratios; NAC, neoadjuvant chemotherapy; AC, adjuvant chemotherapy; MIBC, muscle invasive bladder cancer; OS, overall survival; CSS, cancer-specific survival.

0.87–1.1, P=0.762; 5-year CSS: 45%, 95% CI: 0.41–0.50 in the NAC group versus 46%, 95% CI: 0.44–0.49 in the AC group, HR: 0.97, 95% CI: 0.85–1.1, P=0.655, *Figure 5* and *Figure 6G,6H*).

Sensitivity analysis

Without fully controlling for potential covariates, the comparison of NAC versus AC may be influenced by unknown or unmeasured confounding variables. We assumed that there was an unmeasured confounding factor associated with both the receipt of different chemotherapy strategies and survival and varied the HR of this confounding factor as well as its prevalence ratio between the 2 groups to compute the corresponding adjusted HR for OS and CSS. Our sensitivity analysis showed that with an HR of 2 this confounder needed to have a prevalence ratio of 0.8 or 4 in the AC groups compared with the NAC group to fully explain the OS benefit of NAC or AC covered by this unmeasured confounding variable (*Figure 7A*). The sensitivity analysis targeting CSS showed similar results (*Figure 7B*). Therefore, our conclusion that receiving NAC or AC was not related to a significant difference in OS or CSS among MIBC patients who underwent RC was relatively robust.

Discussion

The role of neoadjuvant cisplatin-based chemotherapy before RC to help improve outcomes among MIBC patients has been fully illustrated in several RCTs and meta-analyses conducted in the late 1990s. From 1989 to 1995, the

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largest prospective trial of NAC (BA06-30894 trial), which randomized 976 patients diagnosed with advanced bladder cancer (T2-T4aN0-NXM0) to 3 courses of CMV (cisplatin, methotrexate, vinblastine) or no chemotherapy before radical radiotherapy or cystectomy, was performed. This study initially reported a nonsignificant OS benefit toward NAC when the result was first published in 1999. However, with longer follow-up, the updated result demonstrated a significant improvement in 10-year OS for NAC at 6% (30–36%, P=0.037) (10,11). Another RCT randomizing 307 patients with cT2-T4aN0M0 diseases to 3 courses of MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) followed by RC or RC alone was performed (SWOG-8710 trial) in 2003. After a follow-up of 11 years, although the result reported a marginal improvement in 5-year OS attributed to MVAC preceding RC according to a 2-sided log-rank test (43% to 57%, P=0.06), this trial was still considered evidence in favor of NAC because its original definition of a significant difference as a 1-sided P<0.05 was reached (12). In 2005, a meta-analysis of 11 RCTs on the basis of IPD originating from 3,005 patients demonstrated a 5% improvement in 5-year OS (HR 0.86, 95% CI: 0.77–0.95, P=0.003) among patients treated with cisplatin-based multiagent NAC, and it was widely accepted as the most powerful evidence favoring the addition of NAC in MIBC management (13).

Randomized studies of AC have been performed almost simultaneously with NAC but laden with difficulties. In 1988, Logothetis *et al.* first reported a significant progression-free survival improvement among high-risk MIBC patients who developed extravesicular, lymphatic/vascular permeation, or lymph node metastatic diseases and received adjuvant CISCA (cyclophosphamide, doxorubicin, and cisplatin) chemotherapy after cystectomy in a small-sample retrospective study (30). In 1991, Skinner *et al.* performed the first RCT investigating the treatment efficacy of adjuvant CISCA chemotherapy versus observation and demonstrated a 24% longer 3-year disease-free survival (DFS) (P<0.001) as well as a 2-year improvement in OS attributed to AC (15). Nevertheless, along with most subsequent early clinical trials, this study encountered problems including small sample sizes, inappropriate methodology, and poor compliance to assigned AC and was thus too underpowered for definitive clinical conclusions to be drawn (16-19). There were 3 contemporary RCTs conducted to further investigate whether there was a potential advantage of AC to MIBC patients (20,22,23). However, all of these trials suffered from poor recruitment and prematurely closed, reducing their power. The most recent RCT recruited 100 patients with pT3-4 and/or N+ MIBC to evaluate the treatment effect of 2 cycles of GC (gemcitabine and cisplatin) after RC and found no difference in OS, CSS, or DFS. Despite no early termination due to poor accrual, this trial remained underpowered because of low treatment intensity in the AC arm (24). The latest updated meta-analysis consisting of IPD derived from 10 RCTs found a significant improvement in OS (improvement of 6% at 5-year, HR =0.82, 95% CI: 0.70–0.96, P=0.02) and recurrence-free survival (improvement of 11% at 5-year, HR =0, 95% CI: 0.70–0.96, P=0.02) attributed to cisplatin-based AC. Compared with a prior review in 2005, this meta-analysis remarkably increased the sample capacity (1,183 patients/610 events *vs.* 491 patients/283 events) and adopted a more rational methodology. However, 7 out of 10 trials included in this study were terminated early. The low quality of the included RCTs, such as heterogeneity in clinical characteristics and low compliance with treatment, with almost one-third of the patients not completing all AC assignments, may lower the power of this meta-analysis (25,31).

The reason why most prospective trials over the past 30 years have been plagued by poor accrual, low compliance, and/or tolerability to AC, as mentioned above, may be strongly related to endogenous characteristics of postoperative MIBC patients. On the one hand, extensive surgical procedures might cause postoperative complications that could preclude or delay the administration of AC. At Memorial Sloan-Kettering Cancer Center, a retrospective review of 1,145 RC-managed patients found that up to 30% of patients developed a grade 2–5 complication within the optimal time for AC (32). On the other hand, a high proportion of elderly patients, poor performance status, and renal dysfunction due to primary tumors all contributed to the delay of AC as well as the impaired tolerability to chemotherapy in MIBC patients (33). Thus, conducting a well-designed RCT with full accrual to compare NAC with AC in MIBC management may be very difficult, or even impossible. In this case, observational studies could provide suggestive but feasible conclusions regarding the choice of NAC or AC in the absence of convincing trials. Moreover, although RCTs were regarded as a cornerstone by many in evidence-based clinical practice, there was criticism that the conclusions of many RCTs were based on a highly selected population, leading to poor extensibility (34). In

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contrast, population-based observational studies enable us to investigate the treatment efficacy of NAC versus AC in a real-world setting that usually cannot be fully reflected in aV clinical trial.

According to existing treatment paradigms recommended by authoritative guidelines, AC is considered only in patients who have developed stage III-IV (T3-T4 and/or N+) diseases and have not undergone NAC, serving as an alternative treatment that is secondary to NAC. However, our study implied that AC shows benefit equivalent to that of NAC, especially in locally advanced patients (stage III-IV). In addition, the delay of RC due to NAC administration contributes to higher disease-specific and all-cause mortality (35) and confers a risk for progression if micrometastatic disease does not respond to systemic chemotherapy. Therefore, initiating RC followed by AC might also be preferred in the management of MIBC. In addition to patients' clinical features, the characteristics of the chemotherapy itself are also important factors affecting the choice between NAC and AC. Previous trials have found chemotherapy before RC to be more tolerable than postoperative chemotherapy. In a phase III trial conducted by Millikan *et al.*, which randomized 140 patients to 2 cycles of neoadjuvant MVAC plus 3 after RC versus 5 cycles after RC, 97% of individuals in the NAC arm underwent at least 2 courses of therapy compared with only 77% of patients in the AC arm (14). Another point to note is that NAC has a remarkably downstaging effect, which may improve tumor resectability and improve survival. In the BA06-30894 trial and SWOG-8710 trial, pT0 rates of 33% and 38% were achieved, respectively (10,12). Notably, the downstaging effect of NAC can be influenced by adverse-events during chemotherapy (36). Our subgroup analysis also suggests that lymph node status should be considered in the selection of perioperative chemotherapy. Patients without lymph node-positive diseases tend to have a better prognosis when receiving NAC, which is associated with better outcomes in stage II (T2N0) diseases. This finding favors NAC as the first choice in stage II (T2N0) patients, which is consistent with guideline recommendations.

Although several observational studies have previously compared the treatment efficacy of the 2 perioperative chemotherapies, they have reported different results. Two single-institution, small-sample-size studies found no significant difference between NAC and AC among patients with T2-T4N0-N2M0 bladder cancer in terms of OS, disease-specific survival (DSS), and DFS (37,38). One population-based study analyzing 656 MIBC patients obtained from the RISC database (Retrospective International Study of Cancers of the Urothelial Tract) found no significant difference in OS (HR 1.08, 95% CI: 0.83–1.39, P=0.57) and CSS (HR 1.06, 95% CI: 0.79–1.43, P=0.70) (39). However, the confidence intervals of this study were wide as the population was still relatively small. At the ASCO meeting in 2016, Sonpavde *et al.* reported a cohort study using the National Cancer Database (NCDB) that demonstrated a significantly longer OS of NAC than AC (HR 1.19, 95% CI: 1.05–1.36, P=0.008) by retrospectively analyzing 2,463 patients diagnosed with cT2-T4N0M0 bladder cancer from 2004–2013 (40). The results of this study were published as a supplement, and detailed information was unavailable. Another study compared NAC versus AC among 1,768 bladder cancer patients from the South Korea National Health Insurance Service database demonstrated that patients receiving NAC had better OS than AC (HR 0.77, 95% CI: 0.65–0.92, P=0.003). Nevertheless, this conclusion should be interpreted cautiously because this study did not include essential clinical features such as histology or stage (41). A cohort study compared the impact of NAC versus AC on OS among MIBC patients using the SEER-Medicare database. This study had a relatively small population and adopted confusing methodology and terminology that lower the strength of the conclusion (42). Our research, adding to this body of literature, is one of the largest cohort studies focusing on the treatment efficacy of NAC versus AC in MIBC patients who underwent RC based on a widely accepted SEER database across a wide time frame. We used a well-established propensity score method to control for confounding variables between groups and sensitivity analysis to guarantee a robust result. A subgroup analysis was also performed to draw more subdivided and characteristics-based conclusions. The present study hopes to shed new light on the selection between NAC and AC in MIBC management and provide the most contemporary reference for further definitive clinical trials.

Limited by the nature of the retrospective design, despite the implementation of statistical methods to stimulate randomized assignment as well as the test of robustness, the present study remained susceptible to selection bias and unmeasured cofounding. In addition, the SEER database does not capture detailed information regarding chemotherapy, such as regimen, courses, adverse events, and salvage treatment at relapse. The lack of these data makes it difficult to comprehensively evaluate the pros and cons between these 2 perioperative chemotherapies. Finally,

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there is a risk of bias due to inaccurate staging as the T/N/M/AJCC stage obtained from the SEER database was derived from the combination of pathological and clinical information.

Conclusions

Our cohort study using the latest updated SEER database targeting OS and CSS suggests no significant difference in survival between NAC and AC among MIBC patients who undergo RC, which indicates that these 2 chemotherapeutic strategies may be interchangeable in MIBC management, especially in those with stage III-IV diseases. Based on powerful prospective evidence, NAC followed by RC remains the preferred approach among individuals without lymph node involvement (Stage II). Nevertheless, our findings should be interpreted as supplementary data to add insight into the selection between NAC and AC in MIBC management, which still calls for further validation from robust RCTs.

Acknowledgments

We thank the SEER database for providing valuable original data and our colleagues in the Department of Medical Statistics at Sun Yat-sen University for their statistics consultation.
Funding: This study was supported by the National Natural Science Foundation of China (Nos. 81725016, 81872094, 81772718, 81602219, 82272862, 81902576) and Guangzhou Science and Technology Projects (No. 202201010910).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-23-79/rc

Peer Review File: Available at https://tau.amegroups.com/article/view/10.21037/tau-23-79/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-23-79/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).

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Cite this article as: Tan Z, Chen Z, Yao G, Mumin MA, Wang Y, Zhu J, Xu Q, Chen W, Liang H, Wang Z, Deng Q, Luo J, Wei J, Cao J. Neoadjuvant and adjuvant chemotherapy share equivalent efficacy in improving overall survival and cancer-specific survival among muscle invasive bladder cancer patients who undergo radical cystectomy: a retrospective cohort study based on SEER database. Transl Androl Urol 2023;12(2):330-346. doi: 10.21037/tau-23-79

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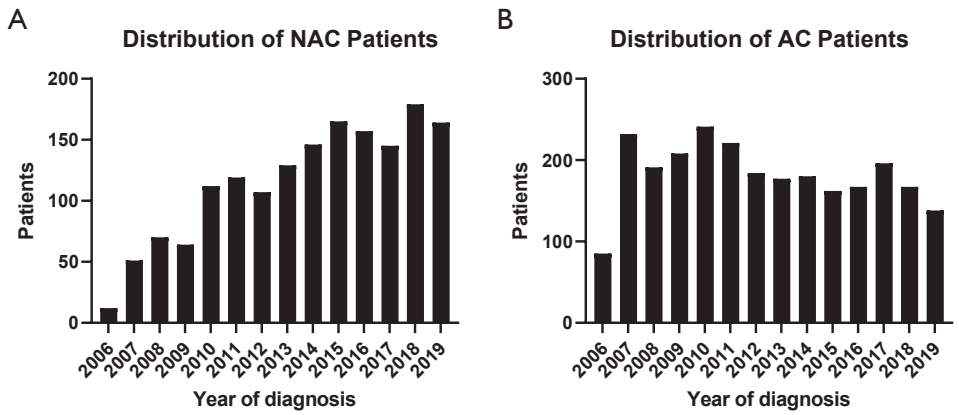

Figure S1 Histograms demonstrate the distribution of patients received NAC (A) and AC (B) according to year of diagnosis. NAC, neoadjuvant chemotherapy; AC, adjuvant chemotherapy.

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Table 1 Unadjusted Multivariate Cox Analysis for Overall Survival and Cancer-specific Survival.

Variables	OS		CSS	
	HR (95% CI)	P value	HR (95% CI)	P value
Age, years				
<65	Ref			
≥65	1.3(1.19-1.43)	<0.001	1.14(1.03-1.26)	0.014
Gender				
Female	Ref			
Male	0.93(0.83-1.03)	0.155	0.82(0.73-0.93)	0.001
Race				
Others	Ref			
White	1.09(0.95-1.25)	0.232	1.07(0.91-1.24)	0.423
Year of diagnosis	0.97(0.95-0.99)	0.001	0.97(0.95-0.99)	0.001
Grade				
Low grade	Ref			
High grade	1.13(0.62-2.04)	0.695	0.99(0.51-1.91)	0.975
Unknown	1.07(0.59-1.96)	0.818	0.97(0.5-1.89)	0.923
T stage				
T2	Ref			
T3	1.86(1.66-2.07)	<0.001	2.05(1.8-2.33)	<0.001
T4	2.69(2.38-3.04)	<0.001	3.17(2.75-3.65)	<0.001
N stage				
N0	Ref			
N+	1.75(1.59-1.92)	<0.001	1.99(1.79-2.22)	<0.001
Chemotherapy				
NAC	Ref			
AC	1.06(0.95-1.17)	0.288	1.06(0.94-1.19)	0.375

NAC, neoadjuvant chemotherapy; AC, adjuvant chemotherapy; T, tumor; N, node

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