Neoadjuvant chemotherapy plus radical cystectomy versus radical cystectomy alone in clinical T2 bladder cancer without hydronephrosis

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Abstract

Objectives

To assess the efficacy of neoadjuvant chemotherapy (NAC) before radical cystectomy (RC) in a retrospective multicenter patient cohort of patients with cT2N0M0 BCa without preoperative hydronephrosis.

Materials and methods

This was a propensity-based analysis of 619 patients. Of these, 316 were treated with NAC followed by RC and 303 with upfront RC. After multiple imputations, inverse probability of treatment weighting (IPTW) was used to account for potential selection bias. Multivariable logistic regression analysis was performed to evaluate the impact of NAC on pathologic complete response and downstaging at RC, while IPTW-adjusted Kaplan-Meier curves and Cox regression models were built to evaluate the impact of NAC on overall survival (OS).

Results

After IPTW-adjusted analysis, standardized differences between groups were less than 15%. A complete response (pT0N0) at final pathology was achieved in 94 (30%) patients receiving NAC and 9 (3%) patients undergoing upfront RC. Downstaging to non-muscle invasive disease (<pT2N0M0) was observed in 174 (55%) patients after NAC and in 72 (24%) patients without NAC. On multivariable analysis, NAC was found to be an independent predictor of both pathologic complete response and downstaging. No significant difference with respect to OS was observed between groups with a median follow-up of 18 months.

Conclusions. In patients with cT2N0 BCa and no preoperative hydronephrosis, NAC increased the rate of pathologic complete response and downstaging.

Introduction

Cisplatin-based neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC) is the standard of care and recommended treatment for clinical T2-T4aN0M0 bladder cancer (BCa) [1]. NAC has proven to confer an approximately 8% overall survival (OS) advantage after 5 years compared to RC alone, with a number needed-to-treat to save one life of 12.5 [2]. However, despite high-level evidence in favor of NAC, compliance with this recommendation remains low; a recently published systematic review and meta-analysis reported an overall NAC utilization rate of 17% [3]. The perception of a modest OS gain, a potential delay in radical surgery or the false belief that the morbidity of RC may be greater after NAC may all contribute to the low compliance with level I evidence and guidelines recommendations.

The under-utilization of NAC is even greater in clinical T2 (cT2) disease, probably due to the fact that data coming from prospective randomized clinical trials showed a greater OS benefit for patients with ≥cT3 stage relatively over those with cT2 (median OS gain of 41 vs 30 months, respectively) [4,5]. These results have led to a debate regarding which patients are most likely to benefit from NAC, with the aim to find a balance between under and overtreatment.

Several attempts have been made with the aim to risk-stratify patients with muscle-invasive BCa based on the presence of different preoperative risk factors, such as clinical stage, preoperative hydronephrosis, presence of lymphovascular invasion (LVI), histological variants and carcinoma in situ (CIS) at the time of transurethral resection of bladder tumor (TURBT) [6,7]. Preoperative hydronephrosis, in particular, has proven one of the most common high-risk factors, independently predicting locally advanced and non-organ confined disease at the time of RC [8].

However, these retrospective studies have usually been conducted on patients who only underwent RC without NAC and, therefore, the results should be interpreted with caution. Given the complexity of conducting a new randomized trial and the lack of direct comparisons in patients with cT2 disease, the aim of our study was to compare the efficacy of NAC and RC vs RC alone in a large multicenter cohort of patients with cT2N0 BCa without preoperative hydronephrosis. We hypothesized that patients receiving NAC and RC would experience a higher rate of complete response and pathologic downstaging at the time of surgery compared to those treated with upfront RC.

Materials and methods

Patients with muscle-invasive BCa treated either with NAC and RC or RC alone between 2000 and 2018 were retrospectively identified from 21 centers across Europe, Canada and the USA, to form a comprehensive systematic database/registry. Patients with cT2N0M0 BCa and complete data regarding pathologic stage at RC were retained for the analysis. Clinical stage was assigned by the treating physician based on TURBT, bimanual exam, and/or cross-sectional imaging. Patients with preoperative hydronephrosis were excluded from the analysis. The presence of preoperative hydronephrosis was assessed through abdomen computed tomography/MRI performed with staging purpose at the time of TURBT.

NAC regimens usually consisted of cisplatin-based combination therapy. Chemotherapy regimen and number of cycles were administered at clinician discretion. For the purpose of this analysis, patients who received less than three cycles of NAC were excluded. All the included patients received RC and lymph-node dissection through an open surgical approach. The extent of lymph-node dissection and the type of urinary diversion were based on patient and tumor characteristics as well as on patient and surgeon preference. Histologic examination was performed by experienced genitourinary pathologists at each center. Tumor stage was assigned according to the 1998 TNM classification system while tumor grade was determined according to 1973 and/or 2004 WHO system.

Follow up and surveillance schedule was not standardized due to the retrospective nature of the study but usually complied with international guidelines and consisted of history and physical exam, labs, urine cytology, computed tomography or MRI of the abdomen/pelvis and computed tomography/X-ray of the chest at regular intervals. Usually, patients were followed every 6 months for the first 3 years and annually thereafter [1].

Endpoints and statistical analysis

The primary endpoint of the study was pathologic response at the time of RC. Complete response was defined as the absence of any tumor at surgery (pT0N0M0) while partial response (downstaging) as the presence of non-muscle invasive bladder cancer (NMIBC; pTa-Tis-T1N0M0) at RC. Objective response was defined as the evidence of either partial or complete response at RC. The impact of NAC on OS was taken as exploratory endpoint.

First, multiple imputation was used to handle missing data for preoperative variables that were assumed to be missing at random for all covariates. Fifteen new imputed data sets were generated using a sequential regression method. Rubin's rules were used to summarize the estimates and variances from the different analyses across the 15 imputed data sets. Second, to account for potential selection bias, observed differences in baseline characteristics between the two groups were controlled for with inverse probability of treatment weighting (IPTW) analysis. The following variables were included in the IPTW analysis: age, gender, smoking status, body-mass index (BMI), Eastern Cooperative Oncology Group (ECOG) score, Charlson Comorbidity Index (CCI), histological variant at TURBT, LVI at TURBT (Fig. 2). Standardized differences approach and Kernel density plots were used to evaluate the covariate balance. Third, IPTW-adjusted Kaplan-Meier curves were calculated to compare OS between patients who received NAC and those who directly underwent RC. IPTW-univariable logistic and cox regression analysis were performed to determine the independent predictive value of NAC on pathologic and survival outcomes, respectively. Multivariable logistic and cox regression analyses, that adjusted for the effect of standard prognosticators (age, gender, smoking habit, CCI, BMI, ECOG performance status, presence of histological variants, LVI and CIS at TURBT), were performed to evaluate how the different variables interact with each other. Statistical analyses were performed using STATA 13 (Stata Corp., College Station, TX, USA). All tests were two sided and $p < 0.05$ was considered as statistically significant.

Results

Baseline characteristics of study patients are depicted in Table 1. Overall, 1865 patients treated with NAC and RC and 798 treated only with RC formed the original dataset. After eligibility criteria were implemented, 619 patients with cT2N0 without preoperative hydronephrosis (316 receiving NAC and RC and 303 treated only with RC), and with complete data regarding final pathologic stage, were included in the study. A flow-diagram illustrating the patients' selection process is depicted in Figure 1. Patients receiving NAC were younger (median age of 64 vs 69 years), with less medical comorbidities (Charlson Comorbidity Index (CCI) significantly differed between groups), and with better ECOG performance status vs their counterparts undergoing upfront RC. Concomitant CIS and LVI at TURBT were more frequent in patients treated with NAC, while histological variants were seen more often in patients who underwent upfront RC.

After IPTW-adjusted analysis, all standardized differences were less than 15% (and mostly less than 10%, with the exception of age, BMI and CCI), which indicates that patients who received NAC and those who underwent upfront RC were subsequently relatively comparable (Figure 2). Propensity score distribution between the treatment groups achieved adequate balance after IPTW adjustment (Supplementary Figure 1).

Primary endpoint – pathologic response

Pathologic response data of the study population are depicted in Table 2 and represented in Figure 3. Overall, 94 (30%) patients receiving NAC and 9 (3%) patients treated with primary RC achieved a complete response (pT0N0M0). Partial response was observed in 80 (25%) patients treated with NAC and in 63 (21%) patients who did not receive NAC. Therefore, an objective response was observed in 174 (55%) patients who received NAC and in 72 (24%) patients who underwent upfront RC. Beyond lower tumor stage, patients who received NAC before RC had a lower rate of lymph node metastasis and LVI in the cystectomy specimen compared to those treated with upfront RC. On IPTW univariable logistic regression analysis, NAC was independently associated with both objective (HR 3.82, p<0.001) and complete response (OR 9.33, p<0.001). On multivariable logistic regression analysis that adjusted for the effect of standard prognosticators, NAC retained its independent association with both objective (OR 2.82, p=0.004) and complete response (OR 4.91, p=0.001) (Table 3).

Exploratory endpoint – overall survival

After a relatively short median follow up of 18 months (IQR 7-38), 123 patients experienced recurrence and 168 died. Of these, 93 (55%) died of BCa. Median time to recurrence was 16 months (IQR 6-37). Two-years OS rates were 73% and 60% for patients treated with NAC and those who underwent RC upfront, respectively. The IPTW-adjusted Kaplan-Meier curves showed no significant difference regarding OS between patients who received NAC vs those who did not (OR 0.78, 95%CI 0.50-1.23, p=0.3) (Figure 4). On multivariable cox regression analysis that adjusted for the effect of standard prognosticators, such as pathologic tumor stage, lymph-node status and positive surgical margin rate, NAC was not significantly associated with OS (HR 1.25, 95%CI 0.71-2.19, p=0.4) (Supplementary Table 1). Finally, on univariable IPTW-adjusted cox regression analysis, NAC was not associated

with recurrence-free survival (HR 1.03, 95%CI 0.61-1.73, p=0.9) nor with cancer-specific survival (HR 1.08, 95%CI 0.61-1.94, p=0.8).

Discussion

In this multicenter propensity score-based study we found that patients with cT2 BCa without hydronephrosis treated with NAC before RC had a significantly higher rate of pathologic response at surgery compared to patients who underwent upfront RC. Moreover, NAC was the only independent predictor of pathologic response. These findings provide additional corroborating evidence to support the role of NAC in this favorable subgroup of patients and reinforce the current recommendations regarding NAC in cT2-T4a MIBC. The lack of significant OS benefit in this study may be attributable to the relatively short follow-up and low number of events.

The evidence for cisplatin-based NAC is clearly established. Several randomized-controlled trials (SWOG-8710, BA06 30894, Nordic I-II) and systematic meta-analyses have proven the ability of NAC to downstage tumors at RC, with a subsequent significant OS advantage of around 6-8% at 5 years [2,4,5,9–11]. However, subgroup analyses have shown that this OS advantage may be driven by the proportion of cT3-4a stage. The SWOG-8710 trial reported a significantly prolonged median OS in patients receiving NAC of 77 vs 46 months in those undergoing RC only; the most dramatic improvement (from 24 to 65 months) was seen in patients with ≥cT3 stage [4]. Recently, the efficacy of NAC in terms of pathologic downstaging and OS in cT3-4aN0M0 vs cT2N0M0 has been evaluated in a population-based study from the Netherlands Cancer Registry [12]. Superior OS for patients receiving NAC was particularly evident in cT3-T4a stage, while no difference was found between groups in cT2 stage (5-year OS rates for NAC + RC vs upfront RC were 57% vs 51% in cT2 stage, and 55% vs 36% in cT3-T4a stage).

These findings, in addition to the non-negligible morbidity related to NAC [13], have raised the question regarding its utility in patients with more favorable risk MIBC. Culp et al. proposed a preoperative risk stratification model based on clinical stage, presence of hydronephrosis, LVI and histological variants [7]. The patients with “low-risk” experienced better survival outcomes compared to those with “high risk” undergoing RC alone (5-year OS of 65% vs 47%). The conclusion was that patients with “low-risk” cT2 should be treated with upfront RC, while the “high-risk" group should receive NAC before RC. However, in this

trial, 50% of “low risk” patients were upstaged to pT3-4 or pN+ at RC, with shorter OS rates compared to true “low-risk” group (58% vs 72%), but still superior to “high risk” patients who remained high risk after RC. The debate about NAC in cT2 stage continues, and current practice among clinicians reflects this uncertainty, with clinical stage T3-T4a being the most used indication for NAC, as revealed from a recent survey [14].

To the best of our knowledge, a direct definitive comparison of NAC + RC vs RC alone in patients with cT2 without risk factors is lacking. In our propensity-based study we demonstrated that one third of patients with cT2 without hydronephrosis treated with NAC achieved a complete response at final pathology (compared to 3% in patients treated with primary RC). NAC conferred a 9-fold increased probability of being cancer-free at the time of surgery. These findings have several practical implications and reinforce the role of NAC even in patients with more favorable features. It has been extensively demonstrated that pathologic downstaging at RC can be used as surrogate endpoint for OS [15]. By analyzing patients enrolled in the Nordic Cystectomy Trials 1 and 2, Rosenblatt et al. showed that survival benefits of NAC are reflected in downstaging of the primary tumor at surgery: the combination of NAC and complete downstaging revealed a hazard ratio for overall mortality of 0.32 compared with 1.0 for the combination of no NAC and no downstaging [16]. In our study, we were not able to prove a difference in OS between groups, probably due to the relatively short median follow-up and low number of deaths overall. Similar to previous observations [4, 14], we believe that the significant difference in pathologic downstaging should be taken as a proxy of the benefit of NAC in cT2 stage without hydronephrosis.

Our study is not devoid of limitations, mainly related to its retrospective nature. Despite the correction introduced with the IPTW-adjusted approach, our analyses are subject to selection bias and many unmeasurable confounders may have influenced the receipt of NAC and OS. A central pathologic review of the specimens was not provided. Pathological response rate may depend upon tumor volume and completeness of TURBT (other than NAC), factors that may also influence treatment choice that could not be recorded in the current study. Moreover, we were not able to differentiate between different NAC regimens due to the relatively limited sample size. As already mentioned, the short follow up and the low number of events (deaths) in our cohort could have limited the OS analysis. We were not able to assess the impact of NAC on recurrence-free and cancer-specific survival. Finally, the impact of adjuvant and salvage therapies after RC, as well potential variability in surveillance schedules could not be assessed. However, to the best of our knowledge and

despite the limitations, the present study represents a meaningful comparative effectiveness assessment of NAC + RC vs RC alone in cT2N0M0 BCa without hydronephrosis.

Conclusions

In our multicenter retrospective propensity score-based analysis, NAC was associated with pathologic complete and objective response in patients with cT2N0 BCa without preoperative hydronephrosis, further supporting the role of NAC in this subset.

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References

[1] Witjes JA, Bruins HM, Cathomas R, Compérat EM, Cowan NC, Gakis G, et al. European Association of Urology Guidelines on Muscle-invasive and Metastatic Bladder Cancer: Summary of the 2020 Guidelines. Eur Urol 2020. doi:10.1016/j.eururo.2020.03.055.

[2] Yin M, Joshi M, Meijer RP, Glantz M, Holder S, Harvey HA, et al. Neoadjuvant Chemotherapy for Muscle-Invasive Bladder Cancer: A Systematic Review and Two-Step Meta-Analysis. Oncologist 2016;21:708–15. doi:10.1634/theoncologist.2015-0440.

[3] Liu W, Tian J, Zhang S, Yang E, Shen H, Li F, et al. The utilization status of neoadjuvant chemotherapy in muscle-invasive bladder cancer: a systematic review and meta-analysis. Minerva Urol Nefrol 2020. doi:10.23736/S0393-2249.19.03648-8.

[4] Grossman HB, Natale RB, Tangen CM, Speights VO, Vogelzang NJ, Trump DL, et al. Neoadjuvant Chemotherapy plus Cystectomy Compared with Cystectomy Alone for Locally Advanced Bladder Cancer. N Engl J Med 2003;349:859–66. doi:10.1056/NEJMoa022148.

[5] Griffiths G. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: Long-term results of the BA06 30894 trial. J Clin Oncol 2011;29:2171–7. doi:10.1200/JCO.2010.32.3139.

[6] Moschini M, Soria F, Klatte T, Wirth GJ, Özsoy M, Gust K, et al. Validation of Preoperative Risk Grouping of the Selection of Patients Most Likely to Benefit From Neoadjuvant Chemotherapy Before Radical Cystectomy. Clin Genitourin Cancer 2017;15. doi:10.1016/j.clgc.2016.07.014.

[7] Culp SH, Dickstein RJ, Grossman HB, Pretzsch SM, Porten S, Daneshmand S, et al. Refining patient selection for neoadjuvant chemotherapy before radical cystectomy. J Urol 2014;191:40–7. doi:10.1016/j.juro.2013.07.061.

[8] Green DA, Rink M, Hansen J, Cha EK, Robinson B, Tian Z, et al. Accurate preoperative prediction of non-organ-confined bladder urothelial carcinoma at cystectomy. BJU Int 2013;111:404–11. doi:10.1111/j.1464-410X.2012.11370.x.

[9] Sherif A, Holmberg L, Rintala E, Mestad O, Nilsson J, Nilsson S, et al. Neoadjuvant cisplatinum based combination chemotherapy in patients with invasive bladder cancer: a combined analysis of two Nordic studies. Eur Urol 2004;45:297–303. doi:10.1016/j.eururo.2003.09.019.

[10] Winquist E, Kirchner TS, Segal R, Chin J, Lukka H. Neoadjuvant chemotherapy for transitional cell carcinoma of the bladder: A systematic review and meta-analysis. J Urol 2004;171:561–9. doi:10.1097/01.ju.0000090967.08622.33.

[11] Advanced Bladder Cancer Overview Collaboration. Advanced Bladder Cancer Meta-analysis Collaboration. Neo-adjuvant chemotherapy for invasive bladder cancer. Cochnrane Database Syst Rev 2004:CD005246. doi:10.1002/14651858.CD005246.

[12] Hermans TJN, Voskuilen CS, Deelen M, Mertens LS, Horenblas S, Meijer RP, et al. Superior efficacy of neoadjuvant chemotherapy and radical cystectomy in cT3-4aN0M0 compared to cT2N0M0 bladder cancer. Int J Cancer 2019;144:1453–9. doi:10.1002/ijc.31833.

[13] Black PC, Brown GA, Grossman HB, Dinney CP. Neoadjuvant chemotherapy for bladder cancer. World J Urol 2006;24:531–42. doi:10.1007/s00345-006-0113-z.

[14] Martini T, Gilfrich C, Mayr R, Burger M, Pycha A, Aziz A, et al. The Use of Neoadjuvant Chemotherapy in Patients With Urothelial Carcinoma of the Bladder: Current Practice Among Clinicians. Clin Genitourin Cancer 2017;15:356–62. doi:10.1016/j.clgc.2016.09.003.

[15] Zargar H, Zargar-Shoshtari K, Lotan Y, Shah JB, van Rhijn BW, Daneshmand S, et al. Final Pathological Stage after Neoadjuvant Chemotherapy and Radical Cystectomy for Bladder Cancer-Does pT0 Predict Better Survival than pTa/Tis/T1? J Urol 2015. doi:10.1016/j.juro.2015.10.133.

[16] Rosenblatt R, Sherif A, Rintala E, Wahlqvist R, Ullén A, Nilsson S, et al. Pathologic downstaging is a surrogate marker for efficacy and increased survival following neoadjuvant chemotherapy and radical cystectomy for muscle-invasive urothelial bladder cancer. Eur Urol 2012;61:1229–38. doi:10.1016/j.eururo.2011.12.010.

Table 1:

Baseline characteristics of the study patients

Variables	Unweighted Study Population [a]				Weighted Study population [b]			
	Overall (n=619)	Receipt of neoadjuvant chemotherapy		Standardized difference, %	Overall	Receipt of neoadjuvant chemotherapy		Standardized difference, %
		No (n=303)	Yes (316)			No	Yes	
Median age (IQR), years	66 (59-73)	69 (63-76)	64 (57-70)	-53.5	67 (59-73)	67 (61-74)	67 (59-73)	14.5
Gender				4.3				5.8
Female	113 (19)	63 (21)	50 (16)		16	15	17	
Male	496 (81)	240 (79)	256 (84)		84	85	83	
Median BMI (IQR)	26.5 (23.7-30.0)	25.9 (23.1-28.6)	27.8 (23.7-31.0)	30.7	26.5 (24.1-30.0)	26.4 (24.1-29.3)	27 (24-30.6)	11.5
ECOG score				83.9				1.2
0	288 (74)	56 (50)	232 (84)		71	72	71	
1	74 (19)	34 (30)	40 (15)		22	20	23	
2	25 (6)	21 (19)	4 (1)		6	8	6	
3	1 (1)	1 (1)	0 (0)		0	0	1	
4	0 (0)	0 (0)	0 (0)		0	0	0	
Charlson Comorbidity Index				17				10.6
2-3	291 (57)	188 (64)	103 (47)		60	64	54	
4-5	156 (31)	80 (27)	76 (35)		26	22	30	
>6	64 (12)	24 (8)	40 (18)		14	13	15	
Smoking status				-25.2				4.0
Never smoker	113 (28)	23 (23)	90 (29)		27	29	24	
Former smoker	191 (46)	45 (45)	146 (47)		48	44	51	
Actual smoker	107 (26)	32 (32)	75 (24)		26	27	25	

Concomitant CIS at TURB	128 (21)	32 (11)	96 (30)	30.7	29	32	27	-9.7
LVI at TURB	113 (18)	41 (14)	72 (23)	-12.4	23	23	23	-0.7
Histological variants at TURB	91 (21)	44 (33)	47 (16)	-28.2	21	21	22	2.1

IQR: interquartile range; BMI: body mass index; ECOG: Eastern Cooperative Oncology Group; CIS: carcinoma in situ; TURB: transurethral resection of bladder; LVI: lymphovascular invasion

[a] Data are presented as number (percentage) of patients unless otherwise indicated; [b] Data are presented as percentage of patients unless otherwise indicated

Table 2:

Pathologic outcomes after radical cystectomy among the study patients.

Variables	Overall (n=619)	Receipt of neoadjuvant chemotherapy		p value
		No (n=303)	Yes (316)	
Pathologic tumor stage, n (%)				<0.001
pT0	104 (16)	9 (3)	94 (30)	
pTa-Tis-T1	143 (23)	63 (21)	80 (25)	
pT2-T3-T4	373 (60)	231 (76)	142 (45)	
Lymph node metastases, n (%)	114 (20)	64 (24)	50 (16)	0.025
Pathologic LVI, n (%)	142 (33)	121 (41)	21 (16)	<0.001
Positive surgical margins, n (%)	48 (8)	26 (9)	22 (7)	0.5

LVI: lymphovascular invasion

Table 3:

Multivariable logistic regression analysis for prediction of complete (pT0N0M0), partial (pTa-Tis-T1N0M0) and objective (pT0-Tis-Ta-T1N0M0) response among the study population.

Variable	Complete response			Partial response			Objective response		
	OR	95%CI	p	OR	95%CI	p	OR	95%CI	p
NAC	4.91	1.87-12.94	0.001	1.07	0.47-2.39	0.8	2.83	1.41-5.69	0.004
Age (cont.)	1.01	0.97-1.06	0.6	0.97	0.93-1.01	0.1	0.98	0.95-1.02	0.4
Female gender	1.35	0.54-3.41	0.5	0.71	0.26-1.94	0.5	0.97	0.43-2.20	0.9
Smoking habit	1.42	0.82-2.48	0.2	0.97	0.58-1.63	0.9	1.27	0.81-2.00	0.3
CCI, Ref.: 2-3									
4-5	0.38	0.16-0.92	0.03	1.34	0.62-2.93	0.5	0.66	0.33-1.31	0.2
≥6	0.78	0.23-2.71	0.7	1.19	0.33-4.26	0.8	0.97	0.34-2.77	0.9
ECOG (cont.)	0.82	0.41-1.61	0.6	0.74	0.49-1.36	0.3	0.72	0.43-1.21	0.2
BMI (cont.)	1.01	0.95-1.07	0.8	1.00	0.94-1.06	0.9	1.00	0.95-1.06	0.9
Histological variants at TURB	0.46	0.17-1.24	0.3	1.15	0.52-2.53	0.7	0.70	0.34-1.44	0.3
LVI at TURB	1.06	0.48-2.37	0.9	0.78	0.35-1.73	0.5	0.88	0.45-1.73	0.7

Concomitant CIS at TURB	0.72	0.31-1.67	0.7	0.78	0.35-1.75	0.5	0.66	0.33-1.34	0.3

NAC: neoadjuvant chemotherapy; CCI: Charlson Comorbidity Index; ECOG: Eastern Cooperative Oncology Group; BMI: body mass index; TURB: transurethral resection of the bladder; LVI: lymphovascular invasion; CIS: carcinoma in situ

Figure 1

Flow diagram depicting the patients' selection process

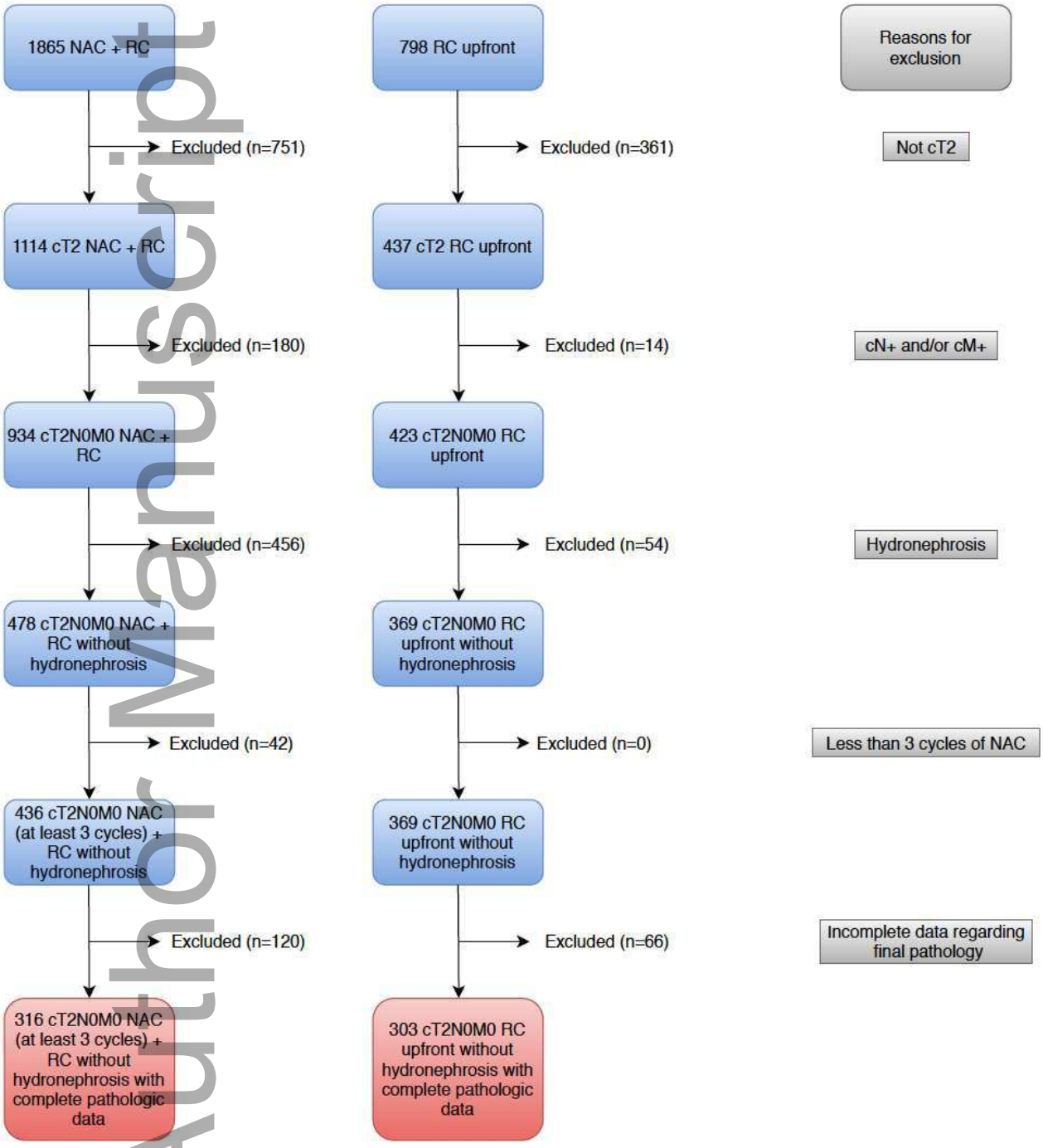

Figure 2

Effect of inverse probability of treatment weighting adjustment on the baseline characteristics distribution among the study population.

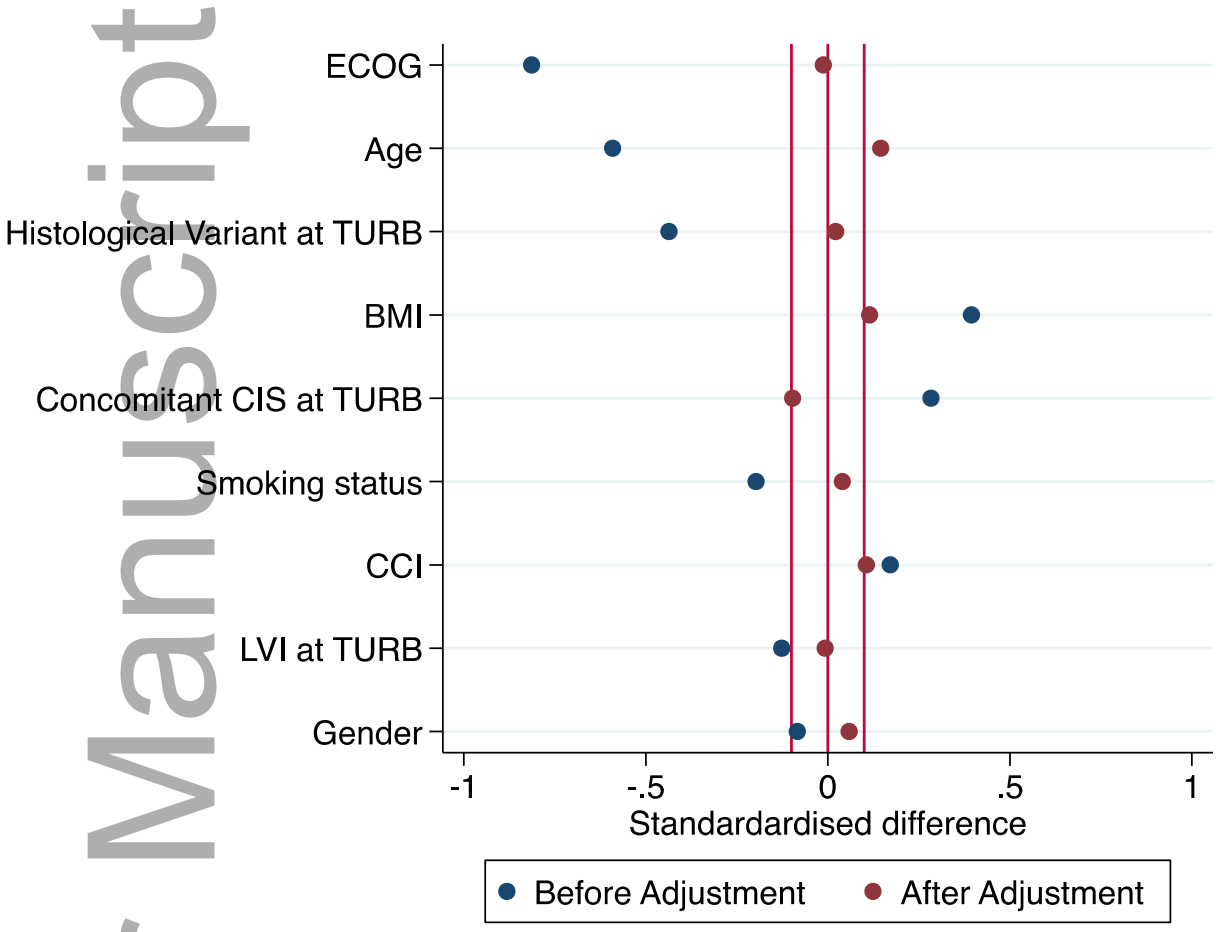

Figure 3

Pathologic response at radical cystectomy among the study population (%).

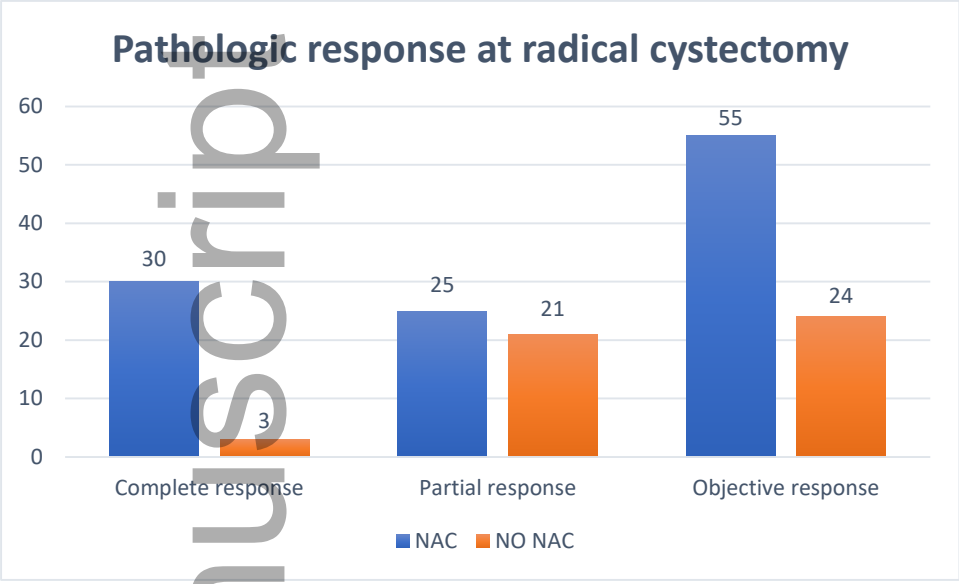

Figure 4

Inverse probability of treatment weighting–adjusted kaplan-meier analysis of overall survival for patients who received neoadjuvant chemotherapy and radical cystectomy vs those treated with radical cystectomy upfront for cT2N0M0 bladder cancer without preoperative hydronephrosis