BJU Int 2021; **128:** 79–87 doi:10.1111/bju.15289

BJUI
BJU International

Original Article

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

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Objectives

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

Patients 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 pathological 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, standardised differences between groups were <15%. A complete response (pT0N0) at final pathology was achieved in 94 (30%) patients receiving NAC and nine (3%) undergoing upfront RC. Downstaging to non-muscle-invasive disease (<pT2N0M0) was observed in 174 (55%) patients after NAC and in 72 (24%) without NAC. On multivariable analysis, NAC was found to be an independent predictor of both pathological complete response and

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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 pathological complete response and downstaging.

Keywords

neoadjuvant chemotherapy, bladder cancer, clinical T2, hydronephrosis, downstaging, #BladderCancer, #blcsm, #uroonc, #utuc

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 been shown to confer an ~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 favour of NAC, compliance with this recommendation remains low; a recently published systematic review and meta-analysis reported an overall NAC utilisation rate of 17% [3]. The perception of a modest OS gain, a potential delay in RC 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-utilisation of NAC is even greater in clinical T2 (cT2) disease, probably due to the fact that data coming from prospective randomised 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 over-treatment.

Several attempts have been made with the aim to risk-stratify patients with muscle-invasive BCa (MIBC) 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 tumour (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 randomised trial and the lack of direct comparisons in patients with cT2 disease, the aim of our present study was to compare the efficacy of NAC and RC vs RC alone in a large multicentre cohort of patients with cT2N0 BCa without preoperative hydronephrosis. We hypothesised that patients receiving NAC and RC would experience a higher rate of complete response and pathological downstaging at the time of surgery compared to those treated with upfront RC.

Patients and Methods

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

NAC regimens usually consisted of cisplatin-based combined 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 (LND) through an open surgical approach. The extent of LND and the type of urinary diversion were based on patient and tumour characteristics, as well as on patient and surgeon preference. Histological examination was performed by experienced genitourinary pathologists at each centre. Tumour stage was assigned according to the 1998 TNM classification system, while tumour grade was determined according to 1973 and/or 2004 WHO system.

Follow-up and surveillance schedule was not standardised due to the retrospective nature of the study, but usually complied

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with international guidelines and consisted of history and physical examination, laboratory measurements, urine cytology, CT or MRI of the abdomen/pelvis and CT/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 pathological response at the time of RC. Complete response was defined as the absence of any tumour at surgery (pT0N0M0), while partial response (down-staging) as the presence of non-MIBC (NMIBC; pTa-Tis-T1N0M0) at RC. Objective response was defined as the evidence of either a partial or complete response at RC. The impact of NAC on OS was taken as the 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. In all, 15 new imputed data sets were generated using a sequential regression method. Rubin's rules were used to summarise 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) Performance Status (PS), Charlson Comorbidity Index (CCI), histological variant at TURBT, and LVI at TURBT (Fig. 2). Standardised 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 analyses were performed to determine the independent predictive value of NAC on pathological 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 PS, 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 a $P < 0.05$ was considered as statistically significant.

Results

Baseline characteristics of study patients are listed 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 pathological stage were included in the study. A flow diagram illustrating the patients' selection process is shown in Fig. 1. Patients receiving NAC were younger (median age of 64 vs 69 years), with less medical comorbidities (CCI significantly differed between groups), and with better ECOG PS 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 standardised differences were <15% (and mostly <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 (Fig. 2). Propensity score distribution between the treatment groups achieved adequate balance after IPTW adjustment (Fig. S1).

Primary Endpoint – Pathological Response

Pathological response data of the study population are depicted in Table 2 and represented in Fig. 3. Overall, 94 (30%) patients receiving NAC and nine (3%) treated with primary RC achieved a complete response (pT0N0M0). Partial response was observed in 80 (25%) patients treated with NAC and in 63 (21%) who did not receive NAC. Therefore, an objective response was observed in 174 (55%) patients who received NAC and in 72 (24%) who underwent upfront RC. Beyond lower tumour stage, patients who received NAC before RC had a lower rate of LN metastasis and LVI in the RC specimen compared to those treated with upfront RC. On IPTW univariable logistic regression analysis, NAC was independently associated with both objective [odds ratio (OR) 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 (IQR) follow-up of 18 (7–38) months, 123 patients had recurrence and 168 died. Of these, 93 (55%) died from BCa. The median (IQR) time to recurrence was 16 (6–37) months. The 2-year 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, $P = 0.3$) (Fig. 4).

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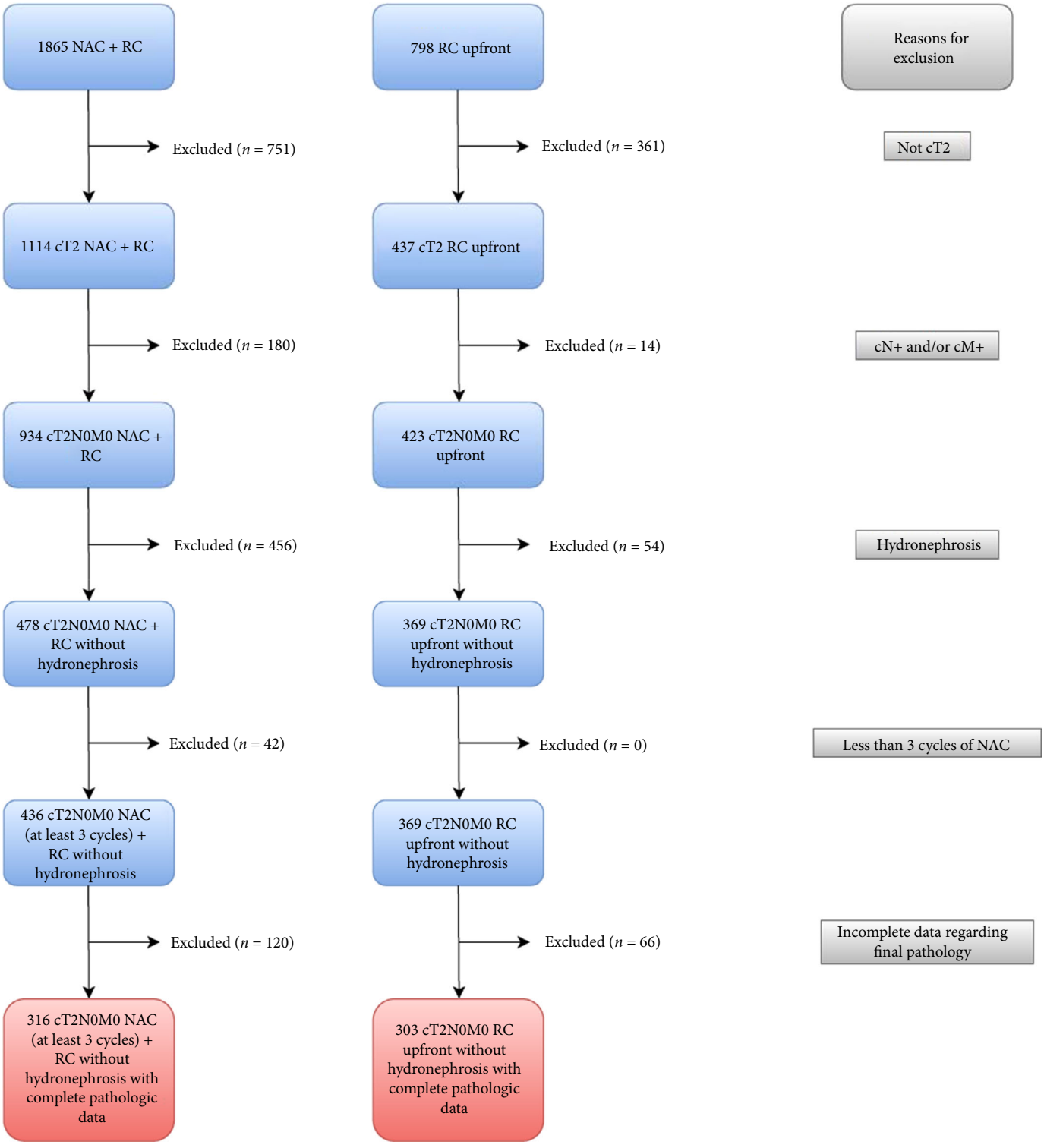
Table 1 Baseline characteristics of the study patients.

Variable	Unweighted study population*				Weighted study population†			
		Receipt of NAC				Receipt of NAC		
	Overall (*n* = 619)	No (*n* = 303)	Yes (*n* = 316)	Standardised difference, %	Overall	No	Yes	Standardised difference, %
Age, years, median (IQR)	66 (59–73)	69 (63–76)	64 (57–70)	−53.5	67 (59–73)	67 (61–74)	67 (59–73)	14.5
Gender, *n* (%)								
Female	113 (19)	63 (21)	50 (16)	4.3	16	15	17	5.8
Male	496 (81)	240 (79)	256 (84)		84	85	83	
BMI, kg/m^2, median (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 PS score, *n* (%)								
0	288 (74)	56 (50)	232 (84)	83.9	71	72	71	1.2
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	
CCI, *n* (%)								
2–3	291 (57)	188 (64)	103 (47)	17	60	64	54	10.6
4–5	156 (31)	80 (27)	76 (35)		26	22	30	
>6	64 (12)	24 (8)	40 (18)		14	13	15	
Smoking status,*n* (%)								
Never	113 (28)	23 (23)	90 (29)	−25.2	27	29	24	4.0
Former	191 (46)	45 (45)	146 (47)		48	44	51	
Actual	107 (26)	32 (32)	75 (24)		26	27	25	
Concomitant CIS at TURBT,*n* (%)	128 (21)	32 (11)	96 (30)	30.7	29	32	27	–9.7
LVI at TURBT,*n* (%)	113 (18)	41 (14)	72 (23)	−12.4	23	23	23	–0.7
Histological variants at TURBT,*n* (%)	91 (21)	44 (33)	47 (16)	−28.2	21	21	22	2.1

**Data are presented as number (percentage) of patients unless otherwise indicated; †Data are presented as percentage of patients unless otherwise indicated.*

Fig. 1 Flow diagram depicting the patients' selection process.



On multivariable Cox regression analysis that adjusted for the effect of standard prognosticators, such as pathological tumour stage, LN status and positive surgical margin rate, NAC was not significantly associated with OS (HR 1.25, 95% CI 0.71–2.19, $P = 0.4$) (Table S1). Finally, on univariable IPTW-adjusted Cox regression analysis, NAC was not

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Fig. 2 Effect of IPTW adjustment on the baseline characteristics distribution among the study population.

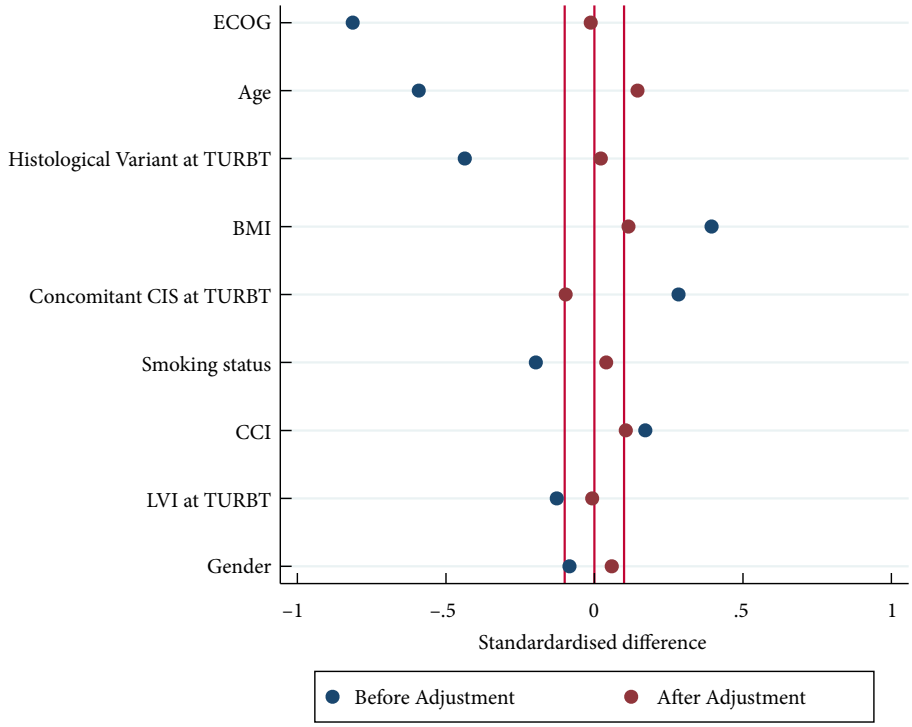

Table 2 Pathological outcomes after RC among the study patients

Variable, *n* (%)	Overall (*n* = 619)	Receipt of NAC		*P*
		No (*n* = 303)	Yes (*n* = 316)	
Pathological tumour stage				
pT0	104 (16)	9 (3)	94 (30)	<0.001
pTa–Tis–T1	143 (23)	63 (21)	80 (25)	
pT2–T3–T4	373 (60)	231 (76)	142 (45)	
LN metastases	114 (20)	64 (24)	50 (16)	0.025
Pathological LVI	142 (33)	121 (41)	21 (16)	<0.001
Positive surgical margins	48 (8)	26 (9)	22 (7)	0.5

associated with recurrence-free survival (HR 1.03, 95% CI 0.61–1.73, $P = 0.9$) or with cancer-specific survival (HR 1.08, 95% CI 0.61–1.94, $P = 0.8$).

Discussion

In the present multicentre propensity score-based study, we found that patients with cT2 BCa without hydronephrosis treated with NAC before RC had a significantly higher rate of pathological response at RC compared to patients who underwent upfront RC. Moreover, NAC was the only independent predictor of pathological response. These findings provide additional corroborating evidence to support the role of NAC in this favourable subgroup of patients and reinforce the current recommendations regarding NAC in cT2–T4a MIBC. The lack of significant OS benefit in the present 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 randomised controlled trials (Southwest Oncology Group [SWOG]-8710, BA06 30894, Nordic I–II) and systematic meta-analyses have confirmed the ability of NAC to downstage tumours 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 pathological 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 favourable risk MIBC. Culp *et al.* [7] proposed a preoperative risk stratification model based on

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Fig. 3 Pathological response at RC among the study population (%).

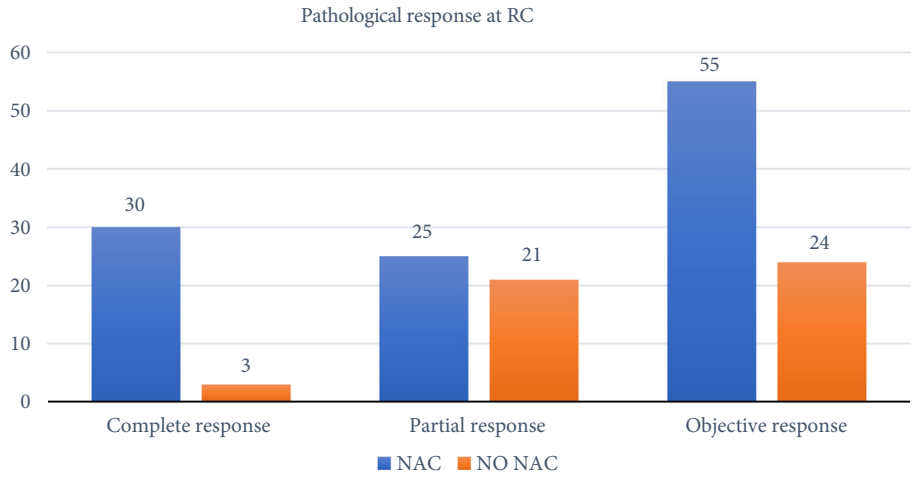

Table 3 Multivariable logistic regression analysis for prediction of complete (pT0N0M0), partial (pTa–Tis–T1N0M0) and objective (pT0–Tis–Ta–T1N0M0) response among the study population

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 TURBT	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 TURBT	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 TURBT	0.72 (0.31–1.67)	0.7	0.78 (0.35–1.75)	0.5	0.66 (0.33–1.34)	0.3

Abbreviations: BCa, bladder cancer; BMI, body mass index; CCI, Charlson Comorbidity Index; CIS, carcinoma in situ; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; IPTW, inverse probability of treatment weighting; IQR, interquartile range; LN(D), lymph node (dissection); LVI, lymphovascular invasion; (N)MIBC (non-)muscle-invasive BCa; NAC, neoadjuvant chemotherapy; OR, odds ratio; OS, overall survival; RC, radical cystectomy; SWOG, Southwest Oncology Group; TURBT, transurethral resection of bladder.

clinical stage, presence of hydronephrosis, LVI, and histological variants. The patients with 'low risk' had 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 that trial, 50% of 'low-risk' patients were upstaged to pT3–4 or pN+ at RC, with shorter OS rates compared to the 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 amongst 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 present propensity-based study, we found 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 nine-fold increased probability of being cancer-free at the time of RC. These findings have several practical implications and reinforce the role of NAC even in patients with more favourable features. It has been extensively demonstrated that pathological downstaging at RC can be used as surrogate endpoint for OS [15]. By analysing patients enrolled in the Nordic Cystectomy Trials I and II, Rosenblatt *et al.* [16] showed that survival benefits of NAC are reflected in

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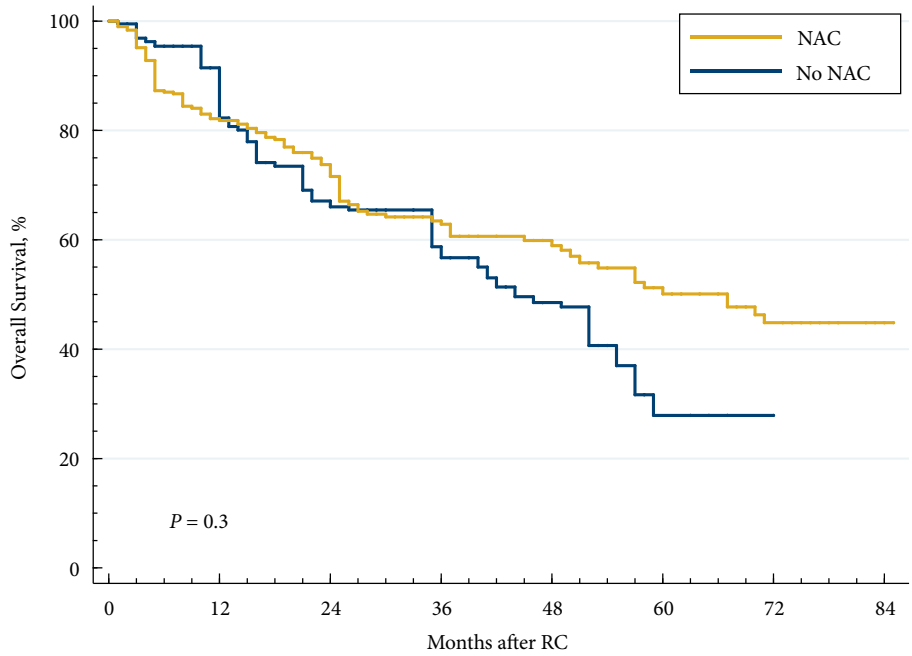
Fig. 4 IPTW-adjusted Kaplan–Meier analysis of OS for patients who received NAC+RC vs those treated with RC upfront for cT2N0M0 BCa without preoperative hydronephrosis.



downstaging of the primary tumour at RC: the combination of NAC and complete downstaging revealed a HR for overall mortality of 0.32 compared with 1.0 for the combination of no NAC and no downstaging. In our present 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 pathological downstaging should be taken as a proxy of the benefit of NAC in cT2 Stage without hydronephrosis.

Our present 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 pathological review of the specimens was not provided. Pathological response rate may depend upon tumour volume and completeness of TURBT (other than NAC), factors that may also influence treatment choice that could not be recorded in the present 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 present 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 multicentre retrospective propensity score-based analysis, NAC was associated with pathological complete and objective response in patients with cT2N0 BCa without preoperative hydronephrosis, further supporting the role of NAC in this subset.

Conflict of Interest

Petros Grivas (all unrelated to this project in the last 3 years): consulting for AstraZeneca, Bayer, Bristol-Myers Squibb, Clovis Oncology, Driver, EMD Serono, Exelixis, Foundation Medicine, Genentech, Genzyme, GlaxoSmithKline, Heron Therapeutics, Janssen, Merck, Mirati Therapeutics, Pfizer, Roche, Seattle Genetics, QED Therapeutics; prior participation in educational programs for Bristol-Myers Squibb; institutional research funding from AstraZeneca, Bayer, Genentech, Kure It Cancer Research, Merck, Mirati Therapeutics, Oncogenex, Pfizer, Clovis Oncology, Bavarian Nordic, Immunomedics, Debiopharm, Bristol-Myers Squibb, QED Therapeutics. The other authors have no conflict of interest to declare.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Kernel density plots showing the distribution of propensity scores in the NAC+RC vs RC alone groups before and after IPTW adjustment.
Table S1. Multivariable Cox regression analysis for prediction of OS among the study population.

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