Original Article

Oncological outcomes and complications following radical cystectomy with or without neoadjuvant chemotherapy – A retrospective comparative cohort study from a single-center in South India

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ABSTRACT

Introduction: Neoadjuvant chemotherapy (NAC) in the management of muscle-invasive bladder carcinoma has not been adopted universally. We studied the oncological outcomes and complications in patients who underwent radical cystectomy (RC) with or without NAC.

Methods: A retrospective review of patients who underwent RC with or without NAC from June 2009 to June 2020 was conducted. Oncological outcomes, overall survival (OS) and recurrence-free survival (RFS), complications, and prognostic factors were analyzed.

Results: Of the 314 patients who underwent RC, 83 patients received NAC (Group A), and 231 underwent RC alone (Group B). The median age was 58 years. The median follow-up duration was 22 (3–64) and 24 (3–62) months, respectively. The median OS in Group A was significantly higher than Group B (38 months [confidence interval (CI): 34–42] and 32 [CI: 29–35], respectively, [$P = 0.033$]). The RFS in Groups A and B was 34 (CI: 30–39) and 31 (CI: 28–34) months, respectively ($P = 0.47$). Higher pathological T stage (T3/4), node positivity and lymphovascular invasion (LVI) were predictors of poor OS and RFS ($P < 0.0001$). Clavien grades 3/4 complications were comparable (8% vs. 15%; $P = 0.19$). Glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 was associated with higher postoperative complications in both groups ($P = 0.012$).

Conclusion: The OS with NAC was superior to upfront RC. RFS was, however, comparable. NAC was safe and well-tolerated. Pathologically, higher T stage, node positivity, and LVI were associated with poorer OS and RFS. Low GFR negatively influenced postoperative complications.

INTRODUCTION

Radical cystectomy (RC) is the treatment of choice for muscle-invasive bladder carcinoma (MIBC). However, the 5-year recurrence-free survival (RFS) is only ~60%, with most of the recurrence occurring within 3 years.[1,2] In general, neoadjuvant chemotherapy (NAC) is used to eradicate micro-metastatic disease, downsize tumors for surgery, and assess survival predictors based on pathologic response. NAC for MIBC has shown benefits in

Access this article online	
Quick Response Code:	Website: www.indianjurol.com
	DOI: 10.4103/iju.iju_214_24

Received: 30.05.2024, **Revised:** 16.08.2024,

Accepted: 19.08.2024, **Published:** 01.01.2025

Financial support and sponsorship: Nil.

Conflicts of interest: There are no conflicts of interest.

various retrospective and randomized control trials.[3-12] Two meta-analyses reveal a 5%–8% overall survival (OS) benefit in clinically node-negative patients.[13,14] This survival benefit has been seen predominantly when cisplatin-based regimen was used.[14-16,17] There has been limited data from the Indian subcontinent with a few retrospective reviews.[1] Adoption of NAC is poor due to concerns of increased complications and the belief that it is only modestly beneficial. Hence, we conducted a comparative retrospective review in patients undergoing RC for MIBC with or without NAC. The study's objective was to compare the oncological outcomes (RFS and OS) and complication rates and to evaluate the risk factors that predict poor prognosis.

METHODS

Study design

This was a retrospective comparative cohort study comparing the outcomes of patients undergoing RC with or without NAC. Data of patients who underwent RC was obtained from our institution's electronic database from June 2009 to June 2020. The patients were divided into two groups. Group A received NAC, and Group B underwent RC with or without adjuvant chemotherapy.

This study was approved by the Institutional Review Board (IRB no: 12736 [retro], dated March 25, 2020). It adhered to the ethical guidelines of the Declaration of Helsinki. The authors confirm the availability of and access to all original data reported in this study.

The primary outcome was to study the OS in patients undergoing RC with or without NAC. The secondary outcomes were to analyze the RFS and complications and the factors that predict recurrence, mortality, and complications.

Patient population

All patients who were diagnosed with MIBC and underwent RC were included in the study; the patients who underwent RC with or without NAC were categorized as Groups A and B, respectively.

Treatment

Neoadjuvant chemotherapy protocol

All patients with good performance status and glomerular filtration rate (GFR) >60 mL/m^2 and satisfying the Galsky *et al.* criteria[18] received cisplatin-based chemotherapy whereas patients with GFR <60 mL/m^2 received oxaliplatin and gemcitabine.

Patients diagnosed with T2a–T4a, N0, and M0 were eligible for NAC. However, even node-positive patients were offered NAC to downstage the disease.

The following chemotherapeutic protocols were used: methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC), dose-dense MVAC, gemcitabine and cisplatin and gemcitabine and oxaliplatin, and pembrolizumab in one patient.

Following the completion of NAC, axial imaging in the form of magnetic resonance imaging (MRI) or contrast-enhanced computed tomogram (CECT) of the abdomen and pelvis was done to assess the response to chemotherapy. Subsequently, after 3 weeks, RC was performed.

Radical cystectomy and bilateral pelvic lymph node dissection

RC was performed in patients with MIBC (≥T2 stage). Patients who were diagnosed to have multifocal T1, high-grade urothelial carcinoma, or who had BCG failure underwent early cystectomy. Patients were preoperatively staged by transurethral resection of the bladder tumor and a cross-sectional imaging (CECT or an MRI) of the abdomen and pelvis. All patients who underwent RC with curative intent underwent bilateral pelvic lymph node dissection. Patients who underwent a palliative cystectomy underwent only a sampling of the lymph nodes.

Pathology

The RC specimen was sent to a uropathologist. Multiple sections were obtained from the tumor, the bladder wall, and mucosa adjacent to and distant from the tumor, along with the ureters and regional lymph nodes. In men, tissue was obtained from the seminal vesicles and prostate. In women, sections were obtained from ovaries, uterus, and vagina when appropriate. Histologic grading was performed according to WHO/ISUP grading. Pathologic staging of the primary bladder tumor and lymph nodes was performed according to the tumor–node–metastasis (TNM) classification (AJCC 8th Edition, 2018).[19] The final pathology after RC was used for all analyses.

Adjuvant therapy

All patients diagnosed with extravesical disease (>T3a) or node positive on the final histopathology were advised to receive adjuvant chemotherapy.

Follow-up

Patients were followed for 2–4 weeks in the immediate postoperative period. Subsequently, they were followed up at 6-monthly intervals for 2 years and yearly thereafter. They underwent serum creatinine, urea, electrolytes including chloride, liver function tests, chest X-ray, and a CECT abdomen and pelvis. Those patients who did not come for follow-up beyond 12 months were contacted telephonically or through mail to assess their survival status. The recurrence status was determined by evaluation in the majority by cross-sectional imaging (CECT or MRI) and ultrasound of the abdomen in a few patients. If reports from regional hospitals were available, they were also reviewed to increase the accuracy of the cause of death/recurrence.

Statistical analysis

Data were summarized as mean (standard deviation [SD])/median (interquartile range) for continuous variables depending on normality, and the categorical data were expressed as *n* (%). Kaplan–Meier survival estimates were calculated, and the graphs along with mean/median survival time with a 95% confidence interval (CI). The equity of survivors was compared using Wilcoxon (Breslow) test for categorical prediction. Satisfying the assumptions, the Cox PH model was used to present the adjusted and unadjusted hazard ratios of OS and RFS. All the variables predicting survival (RFS and OS) and complication were compared using Chi-square statistics, and logistic regression was performed to present the adjusted and unadjusted effect sizes using odds ratio (OR) (95% CI). The analysis was performed using STATA IC/16, Stata Corp LLC, Texas, USA.

RESULTS

The patient characteristics are summarized in Table 1. The median ages were 58 and 56 years in Groups A and B, respectively, with a male predominance (9:1). Among the patients who underwent RC in the review period (June 2009–June 2020), 14% ($n = 83$) received NAC. The baseline characteristics of age, gender, tobacco use, and performance status (the American Society of Anesthesiologists) were similar between the two groups. However, the patients in the NAC arm had better preoperative albumin, GFR, and hematocrit. Adjuvant chemotherapy was given to 17% ($n = 14$) of patients in Group A and 29% ($n = 68$) of patients in the group. The median follow-up was 22 (3–64) months and 24 (3–62) months, respectively. Four (12%) patients in Group A and 24 (11%) in Group B were lost to follow-up [Supplementary Figure 1].

Table 1: Patient characteristics

Patient characteristics (n=314)	Group A (n=83), n (%)	Group B (n=231), n (%)
Median age (years)	58	56
Gender (male/female)	31/6	183/26
Tobacco use	16	22
BMI		
Underweight (≤18.5)	5 (6)	18 (8)
Normal weight (18.5–24.9)	44 (53)	142 (61)
Overweight (25–29.9)	24 (29)	59 (26)
Obesity (BMI of 30 or greater)	10 (12)	11 (5)
ASA		
1	23 (28)	90 (39)
2	56 (67)	137 (59)
3	4 (5)	4 (2)
GFR		
Stage 1 (≥90)	30 (36)	56 (25)
Stage 2 (60–89)	94 (45)	94 (40)
Stage 3 (30–59)	12 (14)	77 (33)
Stage 4 (15–29)	4 (5)	4 (2)
Albumin		
<3.5	18 (24)	30 (14)
≥3.5	65 (76)	1 (86)
HCT		
<30	10 (30)	34 (15)
≥30	23 (70)	197 (85)
Median follow-up (months) (range)	22 (3–64)	24 (3–62)

BMI=Body mass index, ASA=American Society of Anesthesiology physical status grading, GFR=Glomerular filtration rate, HCT=Hematocrit

Operative and pathological characteristics

Most of the patients underwent an RC with an ileal conduit (77% in Group A and 79% in Group B), while 13% ($n = 16$) in Group A and 11% ($n = 10$) in Group B underwent orthotopic neobladder reconstruction. The majority of the patients underwent standard pelvic lymph node dissection (>90%).

The TNM characteristics were comparable between the groups. However, Group B had more patients with atypical histology (0% vs. 20%), and the margin positivity rate was higher (0% vs. 5%) [Supplementary Tables 1 and 2].

The overall lymph nodal yield was 16 nodes in Group B (SD: 9.2) versus 10 nodes in Group A (SD: 7.2). The inadequate lymph-nodal yield (<10 nodes) was higher in the group that received NAC (lymph nodes <10: 43% [Group A] vs. 18% [Group B], $P = 0.00001$) [Supplementary Table 3]. It must be remembered that inaccurate restaging approaches after NAC are related to discrepancies between clinical complete response and pathologic complete response, especially regarding nodal staging.[20]

Primary outcome: Overall survival

OS in Group A was significantly better than in Group B (OS at 3 years was 75% vs. 55% and at 5 years was 60% and 45%). The estimated median OS in Group A was 6 months more than Group B (38 months [CI: 34–42] and 32 [CI: 29–35], $P = 0.033$). Higher the nodal status, poorer the OS [Figure 1]. The patient's survival was poorer as the T stage increased. This was statistically significant ($P < 0.001$) [Figure 1].

The OS in patients with a complete pathological response (cPR) was greater than that in patients who had a partial response, indicating that the subgroup of patients responding to NAC had better patient outcomes. The subgroup with cPR had no mortality at a median follow-up of 24 months versus 30% in those who had a partial response ($P = 0.01$) [Figure 1].

Secondary outcome: Recurrence-free survival

The RFS between Group A and Group B was 34 (CI: 30–39) and 31 (CI: 28–34) months, respectively ($P = 0.47$), which was statistically similar. The recurrences were predominantly in the first 2 years after RC and were mainly distant in both groups [Figure 2].

However, the RFS stratified based on the T stage and nodal status showed that the higher the T stage or nodal

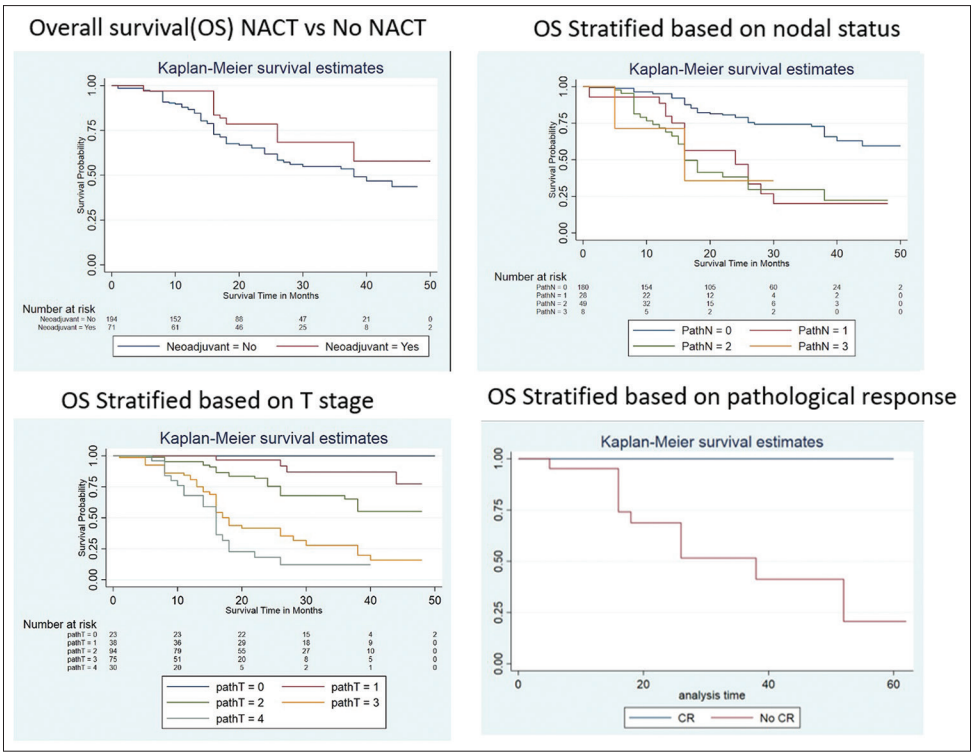

Figure 1: The overall survival following radical cystectomy with or without neoadjuvant chemotherapy: (stratified based on T stage, nodal status, and pathological response). OS = Overall survival, NACT – Neoadjuvant Chemotherapy

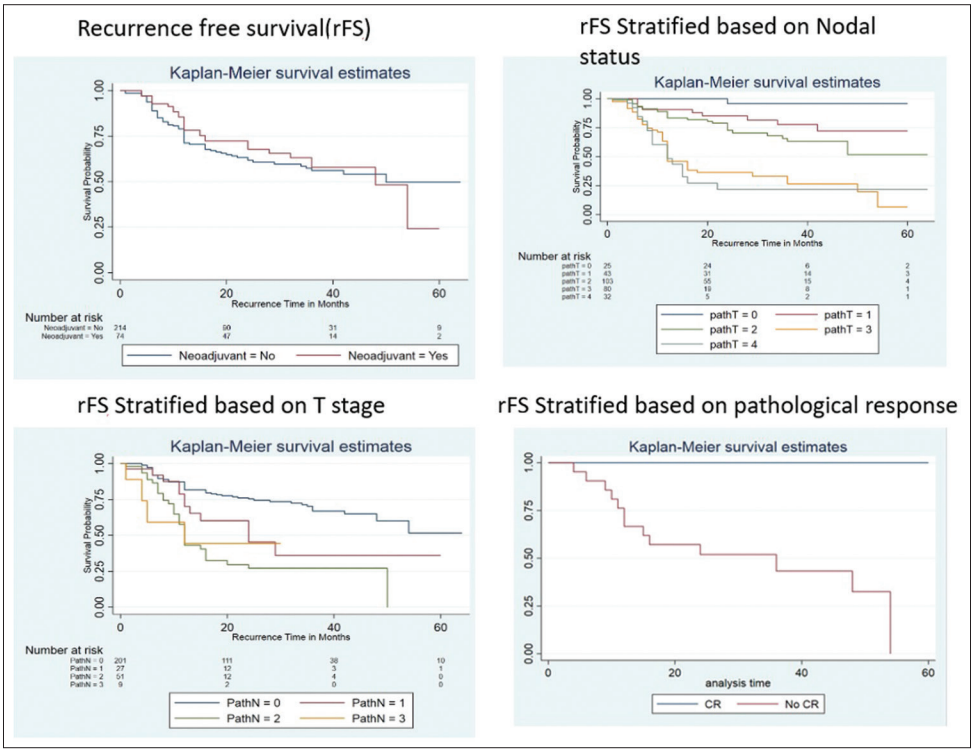

Figure 2: Recurrence-free survival following radical cystectomy with or without neoadjuvant chemotherapy: (stratified based on T stage, nodal status, and pathological response). rFS = Recurrence-free survival

status, the earlier the recurrence [Figure 2]. Those who had a cPR had no recurrence at a median follow-up of 24 months ($P < 0.001$).

Neoadjuvant chemotherapy – Patient characteristics

The most common chemotherapy regimen was MVAC in 60% of patients. The majority (94%) of the patients completed

the NAC regimen with minimal morbidity. cPR was seen in 23% (19/83) of the patients (patients who had cPR received MVAC). Cisplatin-ineligible patients received gemcitabine, oxaliplatin, and immunotherapy in one patient [Table 2]. This heterogenicity in the regimens can affect the outcomes; however, the observation was that MVAC was well-tolerated and had a good pathological response.

Predictors of overall survival

Multivariate analysis revealed that NAC, GFR <60, pT stage, nodal status, and lymphovascular invasion (LVI) were strong predictors of OS [Table 3]. Those who received adjuvant chemotherapy were the ones with more advanced malignancy and had poorer outcomes.

Predictors of recurrence-free survival

Multivariate analysis revealed that higher pT stage, nodal status, and LVI were strong predictors of RFS [Supplementary Table 4]. Adjuvant chemotherapy did not benefit in reducing recurrences.

Postoperative complications

Intraoperative and early postoperative complications were compared (day 30). The Clavien grade > III/IV complications in Group A was 7% versus 14% in Group B. However, this was not statistically significant ($P = 0.19$). Hence, NAC did not increase the surgical morbidity. The 30-day mortality rate was also similar between the two groups (1% in both groups) [Supplementary Table 5].

Predictors of complication

Among the various factors that were analyzed to predict the complications following RC (diabetes, low GFR <60 mL/min/1.73 m^2, higher body mass index, hypoalbuminemia and a low hemoglobin [Haematocrit (HCT)<30]), GFR <60 was the only significant risk factor found in univariate analysis ($P = 0.048$), but the multivariate analysis did not show significance (OR of 3.1 [standard error - 0.26] and $P = 0.078$ [CI: 0.37–1.35]) [Supplementary Table 6].

Table 2: Patient characteristics in the Group A-neoadjuvant chemotherapy

Characteristics (NAC) (*n*=83)	*n* (%)
Chemotherapy regimen	
MVAC	50 (60)
GC	16 (19)
Others	17 (21)
Completed	78 (94)
ADR to chemotherapy	
Clavien ½	8 (10)
Clavien ¾	2 (2)
Partial response	29 (35)
cPR	19 (23)
Progression	35 (42)

cPR=Complete pathological response, MVAC=Methotrexate, vinblastine, doxorubicin, and cisplatin, GC=Gemcitabine, NAC=Neoadjuvant chemotherapy, ADR=Adverse drug Reaction

DISCUSSION

NAC confers an OS benefit of 5%–8% in clinically node-negative patients.[11,12] However, it is being underutilized globally[21] and is not being offered universally to patients in the Indian subcontinent due to costs, unacceptance of chemotherapy, fear of complications, and apprehension of delay in the definitive procedure (RC). There has been limited data from the Indian subcontinent.[1,22,23] NAC has been increasingly offered in our institution in the past few years, and we present our early experience. To our knowledge, this is the first retrospective comparative cohort study depicting the outcomes following RC with or without NAC in India.

In the present study, the OS was significantly longer at 5 years (60% vs. 45%) in the neoadjuvant arm, which is promising in the Indian context where there has been a reluctance to use the same. Grossman *et al.*[6] have shown superior results with MVAC as NAC in patients undergoing RC. The median survival was 77 months compared to 46 months in the RC cohort. Earlier reports have shown a moderate to no benefit with NAC compared to adjuvant chemotherapy.[24] However, a recent meta-analysis shows that there is an OS benefit in giving NAC, and is adopted as the standard of care by the European and American societies.[13,14] There have been some contrasting reports from a Japanese cohort of patients showing equivalent outcomes with or without NAC where the 5-year OS was 58% and 61% in the NAC and non-NAC groups, respectively.[25]

The T stage, nodal status, and the presence of LVI were independent risk factors for OS in the multivariate analysis done in this study. This is in corroboration with prior studies.[2,26] GFR < 60 mL/min/1.73 m^2 was a risk factor for OS and RFS. This indicated the need to preserve renal function due to obstructive uropathy secondary to tumor by urinary diversion, if feasible. This can aid in giving appropriate NAC and can also improve patient survival. Previous studies have shown that the OS was lower in patients with preoperative estimated GFR <60 mL/s.[27,28] The RFS was similar between the groups, suggesting that the T stage, nodal status, and LVI remain independent factors predicting recurrence.

Following NAC, 23% of patients achieved cPR with varying regimens as described due to patient-related factors. This was higher than seen in other series from Asia. In a study by Cajipe *et al.*, pathological downstaging was seen in 4% of patients.[17] However, Peyton *et al.*[29] showed a cPR of 41% with dose-dense MVAC and 27% for gemcitabine–cisplatin-based NAC.

In the subgroup of patients who had a cPR, there was no recurrence, and all the patients survived at a median

Table 3: Predictors of overall survival (univariate and multivariate analysis)

Predictors	Median OS (CI)	Mean OS (SE)	*P*	Multivariate analysis hazard ratio (SE)	*P*	CI
NAC	38 (34–42)	38 (2.1)	0.033	0.58 (0.15)	0.04	0.35–0.97
No NAC	32 (29–35)	32 (1.3)				
DM	NA	34 (2.0)	0.66	NA	NA	NA
No DM	38 (24–NA)	34 (1.5)				
GFR						
<30	24 (15–NA)	28 (2.2)	0.012	0.65 (0.11)	0.016	0.46–0.92
30–60	26 (16–52)	34 (6.5)				
>60	-	37				
ASA						
1	38 (26–NA)	31 (1.9)	0.36	NA	NA	NA
2	NA	36 (1.5)				
3	16 (8–NA)	35 (1.2)				
Path						
T0	NA	41 (1.2)	<0.0001	2.57 (0.29)	<0.0001	2.0–3.2
T1	NA	28 (3.3)				
T2	NA	23 (2.6)				
T3	17 (15–28)	17 (2.9)				
T4	16 (11–18)	15 (2.3)				
N0	NA	40 (1.3)	<0.0001	1.82 (0.18)	<0.0001	1.4–2.22
N1	16 (13–26)	24 (3.0)				
N2	16 (13–38)	23 (2.5)				
N3	16 (5–NA)	17 (3.9)				
LVI						
Present	16 (13–24)	20 (1.7)	<0.0001	3.6	<0.001	2.3–5.7
Absent	NA	38 (1.3)				
Margin						
Negativity	40 (34–NA)	22 (5.2)	0.12	NA	NA	NA
Positivity	26 (5–NA)	35 (1.2)				
Adjuvant chemo						
No	38 (34–NA)	39 (1.3)	<0.0001	2.8 (0.63)	<0.0001	1.85–4.41
Yes	26 (17–38)	26 (2.01)				

LVI=Lymphovascular invasion, NAC=Neoadjuvant chemotherapy, NA=Not available, GFR=Glomerular filtration rate, DM=Diabetes mellitus, CI=Confidence interval, SE=Standard error, OS=Overall survival, ASA=American society of anaesthesiology

follow-up of 24 months. Prior studies have shown improved OS and RFS in patients achieving cPR.[6,29,30,31]

Morgan *et al*. have shown that the lymph nodal yield is a prognostic factor for OS and disease-specific survival in patients undergoing RC.[31] Adequate lymph nodal yield was defined by the EAU guidelines 2021[32] as 10 or more lymph nodes removed during RC. The overall adequate lymph nodal yield was seen in 75% of the patients. Although different templates were used, all patients underwent a minimum of standard pelvic lymph node dissection. We found that the lymph nodal yield in the patients' receiving NAC was significantly lower (10 vs. 16) as the lymph node planes were difficult to dissect in some cases. This could reflect a response to chemotherapy. Kaczmarek *et al*.[33] have shown that persistent nodal disease after NAC correlates with a worse prognosis. This is in concordance with the findings in this study as well.

Patients with good performance status and normal renal functions (GFR >60 mL/min/1.73 m^2) were selected to have NAC. Patients undergoing cystectomy for locally advanced disease and those with altered renal functions were offered upfront RC. Hence, there may be poorer survival outcomes in the group that underwent RC without NAC. This suggests an inherent selection bias.

The complications between the groups were comparable which is similar to the published literature;[6,10,12,30,34] though there were more patients with lower hemoglobin (<10 g%) and preoperative albumin (<3.5 g%) in the NAC arm. Hence, the apprehension of increased surgical morbidity using NAC in the developing world can be erased and it can be offered as a standard of care. The GFR <60 mL/min/1.73 m^2 was found to be a risk factor for the development of postoperative complications in our study. However, it was not significant in multivariate analysis.

There is a paucity of data in the Indian subcontinent regarding the experience of NAC before RC. There are a few retrospective studies[1,22,23] reviewing the outcomes of RC but no patient received NAC. This is one of the first few studies comparing the outcomes of patients undergoing RC with or without chemotherapy and deriving prognostic factors for the same. This study shows superior outcomes with NAC in terms of OS, reduced margin positivity, and low morbidity.

The inherent limitations of a retrospective study exist. The NAC regimens used were not similar in all the patients as they were tailored according to their performance status and renal functions. Although the predominant

regimen used was the MVAC (60%), there was a significant heterogenicity in the NAC group. However, subgroup analysis revealed a higher complete response in those who received MVAC. A high number of patients were lost to follow-up (10%). Although most of the patients were contactable through mail or telephone to know their survival status, the recurrence status may not be accurate. The lymph node yield in the NAC group was significantly lower, which may affect the staging accuracy and, consequently, the survival outcomes. However, similar findings have been reported by Lee *et al.*[35]

In the Indian scenario, NAC before RC is a viable option with no additional morbidity and should be adopted as the standard of care. Patients who show cPR have better OS and RFS. Response to NAC also aids in assessing the biological behavior of the tumor and helps in prognostication.

CONCLUSION

OS with NAC followed by RC is superior, with greater benefit in the subgroup with cPR when compared to upfront RC in patients with MIBC. NAC did not increase surgical morbidity. Pathologically, higher T stage, node positivity, and LVI were associated with poorer outcomes.

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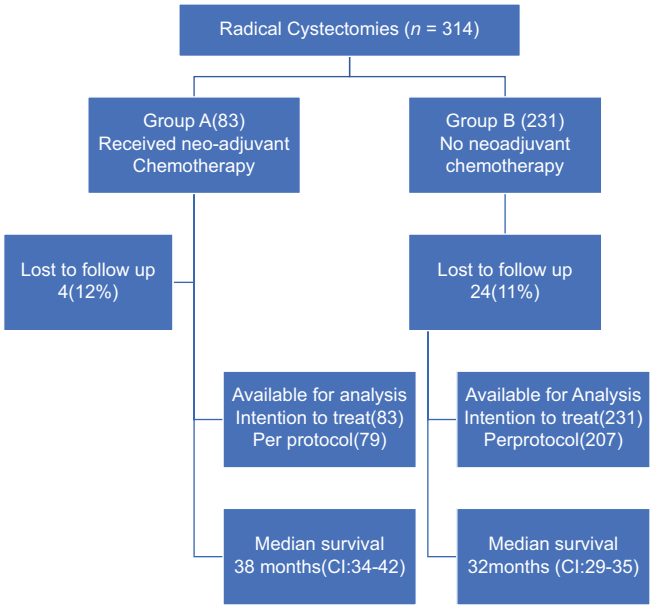
How to cite this article: Jayanth ES, Jat SL, Samuel BP, Singh A, John NT, Joel A, *et al*. Oncological outcomes and complications following radical cystectomy with or without neoadjuvant chemotherapy – A retrospective comparative cohort study from a single-center in South India. Indian J Urol 2025;41:20-7.



Supplementary Figure 1: Study flowchart. CI=Confidence interval

Supplementary Table 1: Operative characteristics

Operative characteristics	Group A (*n*=83), *n* (%)	Group B (*n*=231), *n* (%)
RC RC and ileal conduit	64 (77)	183 (79)
RC + ONB	13 (16)	22 (10)
Anterior exenteration	6 (7)	26 (11)
PND		
Nil	4 (5)	14 (6)
Standard	79 (95)	212 (92)
Extended	0	5 (2)
Blood loss (mL), median (range)	700 (200–3000)	800 (200–3000)
Duration of surgery (h)		
<4	9 (27)	31 (13)
4–6	13 (40)	104 (45)
>6	9 (27)	68 (30)
Missing data	2 (6)	28 (12)

ONB=Orthotopic neo bladder, RC=Radical cystectomy, PND=Pelvic Node Dissection

Supplementary Table 2: Pathological characteristics between Groups A and B

Pathological characteristics (final histopathology after RC)	Group A (*n*=83), *n* (%)	Group B (*n*=231), *n* (%)
T stage		
Tis	4 (5)	1 (0.5)
T0	19 (23)	7 (3)
T1	7 (8)	38 (16.5)
T2	21 (25)	94 (41)
T3	24 (29)	65 (28)
T4	8 (10)	26 (11)
Nodes		
N0	55 (66)	163 (70)
N1	10 (12)	22 (10)
N2	13 (16)	41 (18)
N3	5 (6)	5 (2)
Metastasis		
M0	63 (76)	197 (86)
M1	16 (19)	10 (4)
LTFU	4 (5)	24 (10)
Histology		
Urothelial	83 (100)	189 (82)
Nonurothelial	Nil	42 (18)
Perineural invasion	14 (17)	72 (31)
LVI	16 (19)	48 (21)
Associated CIS	16 (19)	53 (23)
Number of nodes		
<10	36 (43)	41 (18)
≥10	47 (57)	190 (82)
Lymph node yield, mean (SD)	10 (7)	16 (9)
Margin positivity	0	12 (5)

RC=Radical cystectomy, SD=Standard deviation, LVI=Lymphovascular invasion, LTFU=Lost to Follow up, CIS=Carcinoma Insitu

Supplementary Table 3: Lymph nodal yield between the two groups

Lymph Nodal Yield	Group A - NAC (*n*=83)	Group B - no NAC (*n*=231)	*P*
Lymph nodal yield <10	36	41	<0.00001
Lymph nodal yield ≥10	47	190	

NAC: Neoadjuvant Chemotherapy

Supplementary Table 4: Predictors of recurrence-free survival (univariate and multivariate analysis)

Predictors	Median RFS (CI)	Mean RFS (SE)	*P*	Multivariate analysis, hazard ratio	*P*	CI
NAC	48 (8–12)	34 (2.3)	0.47	NA	NA	NA
No NAC	50 (9–36)	31 (1.5)				
T stage						
Path T0	NA	48 (1.1)	<0.0001			
Path T1	NA	40 (2.4)		5.9 (6.2)	0.092	0.7–46
Path T2	NA	36 (1.9)		10.0 (10.5)	0.022	1.4–76
Path T3	12 (8–14)	19 (2.2)		32 (32.8)	0.001	4.4–236
Path T4	12 (7–13)	16 (2.6)		36 (38.9)	<0.0001	4.9–278
Nodal status						
Path N0	NA	37 (1.4)	<0.0001			
Path N1	24 (8–28)	26 (3.7)		2.16 (0.67)	0.012	1.18–3.9
Path N2	12 (7–12)	20 (2.6)		3.64 (0.83)	<0.0001	2.3–5.6
Path N3	12 (1–NA)	16 (4.7)		3.56 (1.8)	0.015	1.2–9.8
LVI						
Present	12 (10–16)	19 (2.1)	<0.0001	3.34 (0.72)	<0.0001	2.1–5.1
Absent	54 (40–58)	36 (1.4)				
Margin						
Negative	54 (46–58)	20 (5.5)	0.29	NA	NA	NA
Positivity	22 (18–26)	33 (1.33)				
Adjuvant chemo						
Yes	16 (9–18)	37 (1.4)	<0.001	2.8 (0.56)	<0.0001	1.9–4.1
No	NA	23 (2.3)				

LVI=Lymphovascular invasion, NA=Not available, RFS=Recurrence-free survival, CI=Confidence interval, SE=Standard error, NAC=Neoadjuvant Chemotherapy

Supplementary Table 5: Postoperative complications

Complication	Group A (*n*=83), *n* (%)	Group B (*n*=231), *n* (%)
0	52 (63)	116 (50)
I	14 (17)	56 (24)
II	6 (7)	20 (9)
IIIa	1 (1)	3 (1)
IIIb	2 (2)	17 (7)
IVa	3 (4)	11 (5)
IVb	0	1 (0.5)
V	1 (1)	2 (1)

Supplementary Table 6: Predictors of complication (univariate and multivariate analysis)

Predictors	Complications	*P*	Multivariate analysis OR (SE)	*P*	CI
DM	31/104	0.229	2.3 (0.3)	0.126	0.33–1.125
No DM	77/210				
GFR					
<30	1/9	0.048	3.1 (0.266)	0.078	0.37–1.05
30–60	39/91				
>60	68/214				
BMI					
<30	95/270	0.22	0.5 (0.51)	0.47	0.25–1.87
≥30	6/21				
HCT		0.103	2.6 (0.36)	0.20	0.30–1.29
<30	15/59				
>30	93/254				
Albumin					
<3.5	15/50	0.83	0.77 (0.25)	0.22	0.28–1.33
≥3.5	92/263				

BMI=Body mass index, GFR=Glomerular filtration rate, HCT=Hematocrit, DM=Diabetes mellitus, CI=Confidence interval, SE=Standard error, OR=Odds ratio