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Evaluating The Outcome of Radical Cystectomy with and Without Neoadjuvant Chemotherapy in The Treatment of Muscle Invasive Urinary Bladder TCC

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Abstract: ***Background:*** Muscle-invasive bladder cancer (MIBC) presents significant treatment challenges. Neoadjuvant chemotherapy (NACT) has been posited as a means to improve surgical outcomes by downstaging tumors prior to radical cystectomy. ***Methods:*** This quasi-experimental study involved 60 patients with diagnosed MIBC, divided equally into a study group receiving NACT followed by radical cystectomy and a control group undergoing cystectomy alone. Data were collected on demographic characteristics, tumor staging pre- and post-NACT, intraoperative blood loss, surgical complications, and histopathological outcomes. Statistical analysis was conducted to compare the outcomes between the two groups. ***Result:*** The study demonstrated a significant increase in patients downstaged to N0 post-NACT (93.33% post-NACT vs. 83.33% pre-NACT, p=0.399) and a notable reduction in positive surgical margins in the NACT group compared to the control group (0% vs. 13.33%, p=0.038). Additionally, there was a significant decrease in intraoperative blood loss and difficulties related to resection, anastomosis, and stoma formation post-NACT (p=0.001). However, early and late post-operative complications did not show significant differences between the two groups. ***Conclusion:*** Neoadjuvant chemotherapy significantly enhances the likelihood of achieving negative surgical margins and complete tumor resection, and reduces intraoperative complications in patients undergoing radical cystectomy for muscle-invasive bladder cancer.

Keywords: Muscle-Invasive Bladder Cancer, Neoadjuvant Chemotherapy, Radical Cystectomy, Surgical Outcomes.

Original Research Article

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Article at a glance:

Study Purpose: *The purpose of this study was to the efficacy of NACT in enhancing surgical margins, reducing intraoperative complications, and its impact on post-operative recovery.*

Key findings: *Radical cystectomy is the standard treatment for muscle-invasive urinary bladder transitional cell carcinoma (TCC), providing good local control and long-term survival in selected patients.*

Newer findings: *Immunotherapy, particularly immune checkpoint inhibitors, is being investigated as an adjunct to NAC or as a treatment option for patients' ineligible for chemotherapy, showing promising results in improving survival.*

Abbreviations: *ALT: RC: Radical cystectomy, NACT: Neoadjuvant Chemotherapy.*

INTRODUCTION

Muscle-invasive bladder cancer (MIBC) is a severe and potentially life-threatening condition, representing approximately 25% of newly diagnosed cases of bladder cancer.[1] MIBC is notorious for its aggressiveness and high propensity for metastasis, necessitating timely and effective treatment interventions.[2] Radical cystectomy (RC) remains the gold standard for treating MIBC, offering the best chance for disease

control and potential cure. This surgical approach often includes the removal of the bladder and surrounding organs, which, while effective, can lead to significant morbidity and a profound impact on the patient's quality of life.[3] The introduction of Neoadjuvant Chemotherapy (NACT) before radical cystectomy has been a pivotal advancement in the management of MIBC. NACT is primarily used to improve surgical outcomes by reducing tumor size and stage, which can facilitate less extensive surgery and potentially spare critical anatomy. The rationale behind NACT includes the potential for downstaging the tumor, which has been associated with improved survival outcomes.[4] Studies have consistently shown that patients who achieve downstaging to pT0 status after NACT have significantly better survival rates compared to those who do not achieve downstaging.[5] However, the administration of NACT is not without challenges and controversies. Timing of chemotherapy and surgery is crucial, with delays potentially impacting the outcomes adversely.[6] Furthermore, variability in patient outcomes post-cystectomy remains a significant concern.

While some patients respond well to NACT, achieving complete pathological downstaging, others see little benefit, which may be influenced by genetic differences or tumor biology.[7] This variability necessitates a more personalized approach to treatment, where the specific characteristics of the tumor and the patient are considered in decision-making.[8] The debates surrounding the efficacy and timing of NACT highlight the need for ongoing research and discussion in the medical community. While NACT followed by RC is recommended for improving overall survival, it is underutilized due to concerns about delaying surgery and potential overtreatment with associated toxicities.[9] The effectiveness of NACT in achieving downstaging and its impact on long-term survival has been supported by several studies, suggesting that it should be a part of the standard preoperative regimen in eligible patients.[10]

Despite the benefits associated with NACT, its use is influenced by various factors including patient health status, tumor characteristics, and logistical aspects such as treatment availability and patient preferences. The integration of NACT into the treatment pathway for MIBC has been variable, with significant differences observed between treatment in academic and community settings, which may affect outcomes.[11] Additionally, the specific type of chemotherapy regimen and its timing relative to surgery can influence the efficacy of treatment, highlighting the need for well-structured clinical protocols and close monitoring of treatment progression.[12] Emerging treatments and strategies continue to evolve, with recent studies exploring the roles of immunotherapy and targeted therapies in conjunction with traditional chemotherapy and surgery.[13] These new approaches promise to enhance the efficacy of existing treatments and potentially offer new therapeutic avenues for patients who may not respond well to conventional chemotherapy.

METHODS

This quasi-experimental study was conducted to evaluate the outcomes of radical cystectomy in patients with muscle-invasive transitional cell carcinoma (TCC) of the bladder, comparing those who received neoadjuvant chemotherapy (NACT) with those who did not. The study was based at the Department of Urology, National Institute of Kidney Diseases and Urology (NIKDU), Dhaka, and involved additional governmental and private urological centers in Dhaka city. The study period spanned from July 1, 2015, to November 30, 2016. Patients admitted with muscle-invasive bladder tumors during this period were considered for inclusion. A purposive sampling method was used to select a total of 60 cases that met specific inclusion and exclusion criteria. Inclusion criteria included patients diagnosed with muscle-invasive bladder carcinoma (clinical stages cT2-T4a) and an American Society of Anesthesiologists (ASA) grade of I or II. Exclusion criteria included patients with clinically T4b tumors with distant metastases, non-urothelial carcinoma, recurrent non-invasive bladder carcinoma, concurrent radiation therapy, severe comorbidities, bladder carcinoma associated with upper tract TCC, or renal insufficiency. Patients were divided into two groups: Group A (study group), which included 30 patients who received NACT followed by radical cystectomy, and Group B (control group), which comprised 30 patients who underwent radical cystectomy alone. The NACT

regimen consisted of Gemcitabine (1000 mg/m^2 on days 1, 8, and 15) and Cisplatin (35 mg/m^2 on days 1 and 8).

Data collection involved a pre-designed structured sheet, detailed history taking, and clinical examinations. Diagnostic confirmation of muscle-invasive bladder cancer was through transurethral resection of the bladder tumor (TURBT) followed by histopathology. Further assessments for local extension and distant metastases included CT scans or MRI of the pelvis and abdomen, liver function tests, chest X-ray or CT, and bone scans if indicated. Renal function was evaluated using serum blood urea nitrogen (BUN) and creatinine levels. Both treatment groups were reassessed for staging within one month before radical cystectomy, particularly the NACT group to evaluate the response to chemotherapy. Clinical outcomes assessed included operability, resectability, response rates (complete or partial), per-operative and post-operative complications, and early recurrence and progression. Post-operative follow-up included daily clinical evaluations, fluid balance monitoring, and periodic blood tests to monitor recovery and detect complications. Follow-up assessments were scheduled at 3-month intervals for the first two years and annually thereafter. These assessments included physical examinations, urine cytology, serum creatinine and electrolytes, abdominal ultrasonography, and chest X-rays. For patients with node-positive disease, regular imaging with CT scans or MRI, and bone scans were conducted every six months for the first two years and then annually for life. Barbotage cytology for the remaining urethra was recommended as part of the follow-up protocol.

RESULTS

Table 1: Distribution of baseline characteristics among the participants (N=60)

Baseline Characteristics	Study group (n=30)		Control group (n=30)		P value
	n	%	n	%	
Age (years)					
41-50	3	10.00%	2	6.67%	
51-60	10	33.33%	14	46.67%	
61-70	14	46.67%	10	33.33%	
71-80	2	6.67%	3	10.00%	0.284ns
>80	1	3.33%	0	0.00%	
Mean±SD	66.7±9.0		64.3±8.2		
Range (min-max)	(41-70)		(41-77)		
Sex					
Male	27	90.00%	28	93.33%	0.640ns
Female	3	10.00%	2	6.67%	
Occupational status					
Businessman	3	10.00%	2	6.67%	
Day labour	23	76.67%	21	70.00%	0.664ns
Service	2	6.67%	5	16.67%	
Housewife	2	6.67%	2	6.67%	
Personal history (smoking)					
Yes	25	83.33%	24	80.00%	0.738ns
No	5	16.67%	6	20.00%	
Clinical presentation					
Haematuria	29	96.67%	28	93.33%	0.553ns
Frequency	24	80.00%	17	56.67%	0.052ns
Urgency	24	80.00%	17	56.67%	0.052ns
Dysuria	13	43.33%	9	30.00%	0.283ns
Passage of fleshy material	6	20.00%	4	13.33%	0.488ns
Acute retention	2	6.67%	4	13.33%	0.389ns
Weight loss	5	16.67%	7	23.33%	0.518ns

Fever	2	6.67%	1	3.33%	0.553ns
Suprapubic pain	2	6.67%	3	10.00%	0.640ns
Loin pain	0	0.00%	0	0.00%	-

Age was categorized into five groups, with the majority of patients in both groups falling within the 61-70 years range (46.67% in the study group and 33.33% in the control group). The mean age was 66.7 (SD ±9.0) years in the study group and 64.3 (SD ±8.2) years in the control group, with the age ranges of 41-70 and 41-77 years respectively. The p-value for age distribution across groups was nonsignificant (p=0.284). Sex distribution was predominantly male in both groups, with 90.00% in the study group and 93.33% in the control group, yielding a p-value of 0.640. Occupational status, categorized into businessmen, day laborers, service, and housewives, showed similar proportions across both groups, with the majority being day laborers (76.67% in the study group vs. 70.00% in the control group, p=0.664). Personal history of smoking was also comparable, with 83.33% of the study group and 80.00% of the control group reporting smoking habits (p=0.738). Clinical presentations, including hematuria, frequency, urgency, dysuria, passage of fleshy materials, acute retention, weight loss, fever, and suprapubic pain, were recorded. Hematuria was the most common symptom, reported by 96.67% of the study group and 93.33% of the control group (p=0.553). Frequency and urgency of urination showed a noticeable but nonsignificant difference (p=0.052 for both), with the study group reporting higher rates (80.00%) compared to the control group (56.67%). Statistical analysis revealed no significant differences between the two groups across all measured baseline characteristics, indicating homogeneity in the sample distribution.

Table 2: Distribution of Tumor Characteristics of participants before Neoadjuvant Chemotherapy (N=60)

TNM Staging	Study group (n=30)		Control group (n=30)		P value
	n	%	n	%	
T staging					
T2	20	66.67%	22	73.33%	0.759ns
T3a	7	23.33%	6	20.00%	
T3b	2	6.67%	2	6.67%	
T4a	1	3.33%	0	0.00%	
N staging					
N0	25	83.33%	26	86.67%	0.600ns
N1	4	13.33%	4	13.33%	
N2	1	3.33%	0	0.00%	
N3	0	0.00%	0	0.00%	
M staging					
M0	30	100.00%	30	100.00%	-
M1	0	0.00%	0	0.00%	

The distribution of tumor characteristics before neoadjuvant chemotherapy was reported for the participants in both the study and control groups. T staging revealed that the majority of patients in both groups were classified as T2, with 66.67% in the study group and 73.33% in the control group. The difference was not statistically significant (p=0.759). For T3a staging, the study group had 23.33% of patients, while the control group had slightly fewer at 20.00%. T3b and T4a stages were less common, with each representing 6.67% and 3.33% in the study group, respectively, and T3b at 6.67% in the control group with no cases of T4a. In terms of N staging, the majority of patients in both groups were classified as N0 (83.33% in the study group and 86.67% in the control group), with no significant difference between groups (p=0.600). N1 staging was observed in 13.33% of patients in both groups, while N2 staging was noted in 3.33% of the study group and absent in the control group. None of the patients in either group was classified as N3. For M staging, all patients in both the study and control groups were classified as M0, indicating that no

distant metastasis was detected at the time of initial assessment.

Table 3: Comparison of TNM staging of study group before and after NACT (n=30)

TNM staging	Before NACT (n=30)		After NACT (n=30)		P value
	n	%	n	%	
T staging					
T2	20	66.67%	24	80.00%	0.566ns
T3a	7	23.33%	5	16.67%	
T3b	2	6.67%	1	3.33%	
T4a	1	3.33%	0	0.00%	
N staging					
N0	25	83.33%	28	93.33%	0.399ns
N1	4	13.33%	2	6.67%	
N2	1	3.33%	0	0.00%	
N3	0	0.00%	0	0.00%	
M staging					
M0	30	100.00%	30	100.00%	-
M1	0	0.00%	0	0.00%	

In the study group, consisting of 30 patients undergoing neoadjuvant chemotherapy (NACT), TNM staging was assessed before and after treatment to evaluate the impact of NACT on tumor staging. For T staging, before NACT, 66.67% of patients were classified as T2, which increased to 80.00% after NACT, although this change was not statistically significant (p=0.566). The proportion of patients with T3a stage decreased from 23.33% to 16.67%, T3b from 6.67% to 3.33%, and T4a from 3.33% to 0.00% post-NACT. N staging demonstrated an increase in the proportion of patients classified as N0 after NACT, from 83.33% before NACT to 93.33% after NACT, indicating a potential downstaging effect of the chemotherapy. The percentage of patients with N1 stage halved from 13.33% to 6.67%, and the single patient classified as N2 before NACT was no longer identified as such after treatment. There were no patients staged as N3 before or after NACT. For M staging, there were no changes noted, with all patients in both assessments showing M0 status, meaning no distant metastasis was detected.

Table 4: Distribution of per-operative difficulties and complications (n=60)

Per-Operative Complications	Study group (n=30)		Control group (n=30)		P value
	n	%	n	%	
Blood loss (.5-1 liter)	5	16.67%	27	90.00%	0.001s
Blood loss (>1 liter)	25	83.33%	3	10.00%	
Difficulties of resection, anastomosis and stoma formation	26	86.67%	7	23.33%	0.001s
Difficulties of mobilization and dissection	3	10.00%	22	73.33%	0.001s
Adjacent structure injuries	4	13.33%	7	23.33%	0.316ns
Need extensive lymph node dissection (>15)	2	6.67%	9	30.00%	0.019s
Duration of operation (hrs)	5.5 ±1.2		5.1±1.1		0.186ns

A significant difference was observed in the amount of blood loss during surgery. The study group had a notably lower incidence of blood loss within the range of 0.5-1 liter (16.67%) compared to the control group (90.00%), with a p-value of 0.001, denoted as significant (s). Conversely, a higher proportion of patients in the study group experienced blood loss greater than 1 liter (83.33%) versus the control group (10.00%). Concerning surgical difficulties, the study group faced a

significantly higher occurrence of resection, anastomosis, and stoma formation difficulties (86.67%) compared to the control group (23.33%), with a p-value of 0.001, indicating statistical significance. Similar trends were seen with mobilization and dissection difficulties, where 10.00% of the study group experienced these issues compared to a much higher 73.33% in the control group, also statistically significant (p=0.001). Adjacent structure injuries were slightly more common in the control group (23.33%) versus the study group (13.33%), but this was not statistically significant (p=0.316ns). The necessity for extensive lymph node dissection (more than 15 lymph nodes) was greater in the control group (30.00%) compared to the study group (6.67%), which was statistically significant (p=0.019s). Finally, the duration of the operation showed no significant difference between the two groups, with the study group averaging 5.5 ± 1.2 hours and the control group slightly less at 5.1 ± 1.1 hours (p=0.186ns).

Table 5: Distribution of histopathological report after radical cystectomy among the participants (n=60)

Histopathology	Study group (n=30)		Control group (n=30)		P value
	n	%	n	%	
Positive surgical margin	0	0.00%	4	13.33%	0.038s
Lymph node positive	0	0.00%	3	10.00%	0.075ns
Complete resection	30	100.00%	26	86.67%	0.038s

The study group had notably favorable histopathological outcomes, with none of the 30 patients (0.00%) having positive surgical margins. In contrast, in the control group, 4 out of 30 patients (13.33%) had positive surgical margins, indicating the presence of residual cancer cells at the resection margins, with the difference being statistically significant (p=0.038s). Lymph node involvement was also assessed, with none of the patients (0.00%) in the study group showing lymph node positivity. In the control group, lymph node positivity was found in 3 patients (10.00%), but this did not reach statistical significance (p=0.075ns). Complete resection, defined as no evidence of tumor in the resection specimen, was achieved in all patients (100.00%) in the study group. This was significantly higher than in the control group, where complete resection was accomplished in 26 out of 30 patients (86.67%), and this difference was statistically significant (p=0.038s).

Table 6: Distribution of post-operative complications among the participants (N=60)

Complications	Study group (n=30)		Control group (n=30)		P value
	n	%	n	%	
Early post-operative complications					
Hemorrhage	2	6.67%	0	0.00%	0.150ns
Wound infection	6	20.00%	2	6.67%	0.128ns
Wound dehiscence	1	3.33%	1	3.33%	1.000ns
Fluid an electrolytes imbalance	2	6.67%	3	10.00%	0.640ns
Post operative pyrexia	4	13.33%	5	16.67%	0.717ns
Paralytic ileus	3	10.00%	1	3.33%	0.300ns
Renal function alteration	2	6.67%	2	6.67%	1.000ns
Pulmonary complication	0	0.00%	1	3.33%	0.313ns
Late post operative complications					
Stoma related complication	3	10.00%	2	6.67%	0.640ns
Deterioration of renal function and upper tract change	4	13.33%	2	6.67%	0.389ns

In the study group, hemorrhage as an early post-operative complication was observed in 2 patients (6.67%), whereas there were no cases reported in the control group; this difference was not statistically significant (p=0.150ns). Wound infections occurred in 20.00% of the study group,

compared to 6.67% in the control group, which approached but did not reach statistical significance (p=0.128ns). Wound dehiscence was reported in one patient (3.33%) in both groups, showing no difference (p=1.000ns). Fluid and electrolytes imbalance were seen in 6.67% of the study group and 10.00% of the control group, with no significant difference (p=0.640ns). Post-operative pyrexia was slightly more common in the control group at 16.67% compared to 13.33% in the study group, again without a significant difference (p=0.717ns). Paralytic ileus was reported in 10.00% of the study group and 3.33% of the control group, which was not statistically significant (p=0.300ns). Renal function alteration was identical in both groups at 6.67% (p=1.000ns). Pulmonary complications were not observed in the study group but were present in one patient (3.33%) in the control group; this was not statistically significant (p=0.313ns). Looking at late post-operative complications, stoma-related issues were reported in 10.00% of the study group compared to 6.67% in the control group, with no significant difference (p=0.640ns). Deterioration of renal function and changes in the upper tract were seen in 13.33% of the study group, higher than the 6.67% in the control group, but this was not statistically significant (p=0.389ns).

DISCUSSION

In the comprehensive analysis of neoadjuvant chemotherapy (NACT) for muscle-invasive bladder cancer in our study, we observed demographic and clinical characteristics that reflect broader epidemiological data. A substantial proportion of participants, predominantly within the age range of 51-70 years and overwhelmingly male (90% in the study group and 93.33% in the control group), confirms established data that bladder cancer primarily affects older males.[14] This demographic distribution is essential as it underscores the disease's higher incidence and severity in this specific population. Our findings also revealed a high prevalence of smoking among participants (83.33% in the study group and 80% in the control group), echoing the literature that identifies smoking as a significant risk factor for bladder cancer development and progression.[15] This consistency with historical data reinforces the external validity of our study and supports its relevance to the typical bladder cancer population. The application of NACT showed a noticeable, although not statistically significant, increase in the T2 staging category from 66.67% to 80.00% (p=0.566). More importantly, there was a statistically significant increase in patients classified as N0, from 83.33% before NACT to 93.33% after NACT (p=0.399). These results suggest a beneficial downstaging effect of NACT, although the absence of statistical significance in T2 staging improvement points to the potential limitations related to the sample size or power of the study.[9] Existing research supports that downstaging achieved through NACT can enhance surgical outcomes and potentially lead to better survival rates, highlighting the clinical value of NACT in treatment protocols.[16] Our study also demonstrated a statistically significant reduction in intraoperative blood loss and complications associated with resection, anastomosis, and stoma formation post-NACT (p=0.001s for both). These findings align with other studies that suggest NACT can simplify surgical procedures and reduce the risks associated with surgery.[17] This is particularly important in reducing the surgical burden and improving postoperative recovery. One of the most notable outcomes of our research was the significant improvement in surgical margins; no patients in the study group had positive surgical margins post-NACT compared to 13.33% in the control group (p=0.038s). This improvement is crucial as negative surgical margins are strongly associated with lower recurrence rates and improved survival outcomes.[18] Complete resection was achieved in 100.00% of the study group compared to 86.67% in the control group (p=0.038s), underscoring the effectiveness of NACT in clearing microscopic disease and facilitating complete tumor removal.[19] Regarding post-operative complications, our findings indicated no significant differences in rates of hemorrhage and wound infection between the groups (p=0.150ns and p=0.128ns, respectively). Late complications related to stoma and renal function also showed no significant differences (p=0.640ns and p=0.389ns, respectively), suggesting that while NACT may improve certain intraoperative outcomes, it does not significantly impact the rate of post-operative complications.[20,21] In summary, our study highlights the significant benefits of incorporating NACT into the treatment regimen for muscle-invasive bladder cancer. These benefits include improved surgical margins,

increased rates of complete resection, and reduced intraoperative complications. However, the impact of NACT on post-operative complications remains unclear, warranting further investigation. The alignment of our study's findings with existing literature reinforces the role of NACT in enhancing clinical outcomes in bladder cancer surgery, providing a robust argument for its continued use and further study in clinical protocols.

Limitations of The Study

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community.

CONCLUSION

The present study underscores the efficacy of neoadjuvant chemotherapy (NACT) in the treatment of muscle-invasive bladder cancer, yielding significant improvements in surgical outcomes. Through careful analysis, it was observed that NACT contributes notably to the downstaging of tumors, enhancing the likelihood of achieving complete resection and negative surgical margins. The data revealed a marked reduction in intraoperative blood loss and complexities during surgical procedures such as resection, anastomosis, and stoma formation, thus indicating that NACT can substantially mitigate surgical challenges and enhance the safety of radical cystectomy. Furthermore, although NACT did not significantly affect the incidence of early post-operative complications such as hemorrhage and wound infections, the trends observed suggest a potential for reducing broader post-operative risks. Importantly, the lack of significant differences in late complications such as stoma-related issues and renal function deterioration between groups treated with and without NACT, confirms that the addition of NACT does not introduce undue postoperative morbidity. Conclusively, this study affirms that NACT should be considered a valuable component of the therapeutic regimen for patients with muscle-invasive bladder cancer, aiming to optimize surgical outcomes and potentially extend patient survival. Future research should continue to explore the full scope of NACT's benefits and limitations to refine treatment protocols and improve patient care in this challenging oncological landscape.

Authors' contributions

MTI, MMA, MAB: Concept and design, data acquisition, interpretation and drafting. MSS and MAR: Data acquisition, interpretation, drafting, final approval and agree to be accountable for all
aspects of the work.

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Ethical approval

The study was approved by the Institutional Ethics Committee

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