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RESEARCH ARTICLE

Effects of Neoadjuvant Chemotherapy Treatment on Perioperative Outcomes Following Radical Cystectomy

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Abstract

Objective: This study aimed to assess the impact of neoadjuvant chemotherapy (NAC) on perioperative outcomes in patients undergoing radical cystectomy (RC) for urothelial carcinoma.

Materials and Methods: We retrospectively analyzed the clinical records of 317 patients who underwent RC and ileal loop diversion between February 2019 and May 2025. Patients were categorized into NAC+RC and RC-only groups. Demographic, preoperative, intraoperative, and postoperative variables were evaluated. Propensity score matching (PSM) was conducted to match the groups in a 1:1 ratio using the nearest-neighbor matching algorithm in terms of age, body mass index (BMI), previous surgery history, American Society of Anesthesiologists (ASA) score, preoperative T stage, hemoglobin, white blood cell (WBC), incision length and urinary diversion technique.

Results: Among the 317 patients, 60 (18.9%) received NAC+RC and 257 (81.1%) underwent RC alone. Preoperative T2 stage was more prevalent in the NAC group compared with the RC-only group (85% vs. 68.5%, p=0.024). Preoperative hemoglobin (12.6 vs. 11.9 g/dL, p=0.006) and white blood cell levels (8886.9 vs. 7416.8/μL, p<0.001) were significantly higher in the RC-only group. Postoperative complications were more frequent among RC-only patients (47.5% vs. 31.7%, p=0.027). After PSM, 57 matched pairs were obtained. The RC-only group demonstrated higher blood transfusion requirements (1 vs. 0 units, p = 0.048), longer hospitalization (17 vs. 15 days, p=0.015), and delayed return to oral intake (3 vs. 3 days, p=0.028) compared with the matched NAC+RC group. Although complications were more common in the RC-only group, the difference was not statistically significant (29% vs. 19%, p=0.058).

Conclusion: NAC does not adversely affect perioperative morbidity following RC and may enhance specific postoperative recovery parameters. These findings support the safety and clinical value of NAC in appropriately selected patients with muscle-invasive bladder cancer.

Keywords: complication, neoadjuvant chemotherapy, radical cystectomy, treatment

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INTRODUCTION

Bladder cancer (BCa) is the tenth most common cancer among adults and the sixth most frequent cancer among males, as more than 75% of cases occur in men. (1). Similar to most other cancers, BCa is considered treatable when it remains confined to the bladder. Once the disease extends to distant organs, treatment is generally limited to life-prolonging approaches, such as chemotherapy or immunotherapy. The therapeutic approach of non-metastatic BCa is mainly operative and depends on the stage/ local extension of the disease. More precisely, the infiltration of detrusor muscle is applied as the limit between patients eligible for superficial tumor excision (transurethral resection of bladder tumor, TURBT for non-muscle invasive bladder cancer, NMIBC) and patients eligible for radical bladder excision (radical cystectomy [RC] for muscle invasive bladder cancer [MIBC]) (2). Nevertheless, in the recent years, the role of detrusor infiltration as sole criterion for deciding between superficial and radical excision has been reconsidered since a patient subset with NMIBC seems to benefit from undergoing an early cystectomy (aggressive histological subtypes, multiple TURBTs, unresponsiveness to intravesical therapy), while other meticulously selected MIBC patients are managed by multimodal approaches (radiochemotherapy plus radical TURBT) in the context of a bladder- preserving treatment strategy (3).

In parallel to the surgical methods, which comprise the main approach of localized BCa management, systemic therapy, in the form of chemotherapy or other newer pharmaceutical agents, represents a basic component of the management in a continuously increasing number of specific clinical scenarios. Initially, chemotherapy was primarily used in metastatic BCa; however, it has now become an established component of perioperative treatment (before or after RC) or in MIBC patients that opt for bladder-preserving management. The rationale for this expanded indication is to enhance the effectiveness of local treatment by reducing tumor burden and increasing the likelihood of achieving negative surgical margins. Moreover, chemotherapy can eradicate micrometastases that are not detectable by the available diagnostic methods (3).

Regarding the perioperative chemotherapy, there is strong evidence supporting its administration before (neoadjuvant chemotherapy, NAC) rather than after RC (adjuvant chemotherapy, AC). In addition to the advantages of NAC, the latter can bring upon serious morbidity, insufficient tumor response, and prolongation of time to RC, which may affect the patient's oncological course. Up to the present, there are no criteria to delineate the patients who are eligible for NAC and are bearing the highest possibility for increased clinical benefit-to-cost ratio. Nevertheless, available data suggest that NAC may be more effective in patients with genomically unstable and urothelial-like tumors (4), while the presence of advanced nodal disease seems to be a negative predictor of NAC effectiveness (5). Moreover, female patients seem to perform better in terms of survival after NAC+RC than the respective male patients (6), while the NAC regimen may also be of clinical significance since dose-dense methotrexate/ vinblastine/ adriamycin/ cisplatin (ddMVAC) induces longer survival prolongation than the gemcitabine/ cisplatin (GC) regimen (7). In conclusion, despite the wide indication for NAC administration, there are many issues that should be further investigated to maximize the clinical benefit in the MIBC patient population.

In the current study, we aimed to examine another aspect of NAC administration, which is the perioperative events of the subsequent RC in the respective patient cohort. Our aim was to unveil or to exclude any detrimental effect of NAC on the patients during the RC procedure and their postoperative course, and to confirm the safety of NAC in combination with the RC.

MATERIAL AND METHODS

Data from 386 patients who underwent RC and ileal loop diversion for urothelial carcinoma between February 2019 and May 2025 were retrospectively analyzed. All procedures were performed by urooncologists with at least 10 years of experience in major oncologic surgery and a minimum annual volume of ten radical cystectomies at a high-volume tertiary cancer center, with the choice of surgical technique left to the discretion of the operating surgeon. Each patient underwent an extended pelvic lymph node dissection.

Sixty-nine patients with insufficient data or a diagnosis of non-urothelial bladder cancer were excluded from the study. The data of 317 patients were included in the study. The Institutional Review Board of Ankara Bilkent City Hospital

approved this study (TABED1/1513/2025, Date: 2025-10-22).

Before undergoing RC, every patient received a preoperative TURBT. Subsequently, comprehensive staging with total-body computed tomography (CT) was carried out for staging. Following diagnostic evaluation, patients were referred to a medical oncologist for cisplatin-based NAC. Eligibility for NAC was determined by a multidisciplinary team including urooncologists and medical oncologists according to contemporary guideline recommendations. Patients were considered eligible for cisplatin-based NAC if they had muscle-invasive bladder cancer, adequate renal function (estimated glomerular filtration rate ≥60 mL/min/1.73 m^2), acceptable functional capacity, and no contraindications such as severe cardiac dysfunction, uncontrolled infection, or significant hearing impairment. Patients who were medically unfit, who did not want to wait more for RC because of NAC (declined chemotherapy), or had contraindications to cisplatin were assigned to the RC alone group (3). Those in the NAC cohort were treated with either the GC regimen or the MVAC regimen (methotrexate, vinblastine, adriamycin, and cisplatin), each administered for four cycles prior to surgery. The interval between the completion of chemotherapy and RC did not exceed six weeks for any patient.

The demographic (age, gender and body mass index [BMI], preoperative (previous surgery history, intravesical treatment history, neoadjuvant chemotherapy history, concomitant malignancy, presence of ascites, presence of hydronephrosis, smoking status, American Society of Anesthesiologists classification [ASA] score, functional capacity, T stage, grade, clinical lymph node positivity, hemoglobin, white blood cell [WBC], serum creatinine, blood nitrogen urea, serum albumin, sodium and potassium levels, comorbidities), intraoperative (operation duration, incision length, urinary diversion technique, length of bowel segment used in urinary diversion, amount of bleeding,) and postoperative (amount of blood transfusion, duration of total parenteral nutrition administration, hospitalization, time to oral nutrition, ureteral catheterization duration, complications, pathological T stage, pathological N stage) characteristics of patients were collected from hospital database. The patients were divided into two groups according to the administration of neoadjuvant chemotherapy. The comparison was made between the two groups in terms of perioperative outcomes.

Postoperative complications were evaluated according to the Clavien–Dindo classification system (8). Preoperative T stage was determined based on the pathological findings of TURBT in conjunction with preoperative imaging. Tumor grade was assessed exclusively according to TURBT pathology (9). Postoperative complications were evaluated within 30 days after surgery according to the Clavien–Dindo classification system (8). Tumor staging was determined based on the current TNM classification of bladder cancer (9).

Statistical Analysis

Data coding and statistical analyses were performed on the computer using the SPSS 22 software package program (IBM SPSS Statistics, IBM Corporation, Chicago, IL). The normality of the variables was assessed using the Shapiro–Wilk test. Variables with a normal distribution were expressed as mean ± standard deviation, while non-normally distributed variables were expressed as median (interquartile range). For non-categorical variables, the independent samples t-test or Mann–Whitney U test was used. For categorical variables, the Chi-square test or Fisher's exact test was used. To address potential baseline disparities arising from the non-randomized study design, propensity score matching (PSM) was employed. Based on the calculated propensity scores, patients undergoing radical cystectomy (RC) alone were paired with those receiving RC plus NAC in a 1:1 ratio using the nearest-neighbor matching algorithm in terms of age, BMI, previous surgery history, ASA score, preoperative T stage, hemoglobin, WBC, incision length and urinary diversion technique. The balance of matched covariates was evaluated through standardized mean differences (SMDs), with an SMD below 0.10 considered to indicate adequate balance between groups. Cases with a p-value below 0.05 were considered statistically significant.

RESULTS

The mean age of the 317 patients who underwent RC was 65.8 ± 7.8 years. NAC plus RC was administered to 60 patients (18.9%) (n=51 for GC and n=9 for MVAC) and among patients receiving NAC, the median interval between completion of NAC and RC was 31 (IQR: 22–39) days. RC alone was performed in 257 patients (81.1%). In RC alone group, 151 (58.8%) patients who were considered eligible for NAC but declined treatment or proceeded directly to surgery due to

patient preference or logistical reasons while 106 patients were not eligible for NAC. Among the patients who received NAC plus RC, 51 (85%) were at preoperative stage T2, compared to 176 (68.5%) in the RC alone group (p = 0.024). In the RC alone group, preoperative serum hemoglobin and WBC levels were significantly higher compared to the NAC plus RC group (12.6 vs. 11.9 g/dL, p = 0.006; 8886.9 vs. 7416.8/μL, p < 0.001, respectively). The postoperative complication rate was significantly higher in the RC alone group compared to the NAC plus RC group (47.5% vs. 31.7%, p = 0.027). Detailed demographic, preoperative, intraoperative and postoperative characteristics of patients who underwent RC for urothelial carcinoma and comparative analysis according to the administration of neoadjuvant chemotherapy were shown in Table 1.

Table 1. Demographic, preoperative, intraoperative and postoperative characteristics of patients who underwent radical cystoprostatectomy for urothelial carcinoma and comparative analysis according to the administration of neoadjuvant chemotherapy

	Total (n=317)	**NAC plus RC (n=60, 18.9%)**	**RC alone (n=257, 81.1%)**	**p**
Demographic characteristics				
Age (year) (Mean ± SD)	65.8±7.8	64±8.7	66.2±7.6	0.115[m]
Male gender, n (%)	279 (88)	52 (86.7)	227 (88.3)	0.721[c]
BMI (kg/m²) (Mean ± SD)	26.2±3.8	26.1±3.4	26.2±3.9	0.837[m]
Preoperative characteristics				
Previous surgery history, n (%)	54 (17)	9 (15)	45 (17.5)	0.641[c]
Intravesical treatment history, n (%)	34 (10.7)	7 (11.7)	27 (10.5)	0.794[c]
Concomitant malignancy, n (%)	13 (4.1)	3 (5)	10 (3.9)	0.718[f]
Presence of ascites, n (%)	1 (0.3)	0 (0)	1 (0.4)	0.811[f]
Presence of hydronephrosis, n (%)	138 (43.5)	21 (35)	117 (45.5)	0.139[c]
Smoking status, n (%)	285 (89.9)	54 (90)	231 (89.9)	0.978[c]
ASA score				
1, n (%)	6 (1.9)	3 (5)	3 (1.2)	0.235[f]
2, n (%)	162 (51.1)	28 (46.7)	134 (52.1)	
3, n (%)	142 (44.8)	28 (46.7)	114 (44.4)	
4, n (%)	7 (2.2)	1 (1.6)	6 (2.3)	
Functional capacity				
Independent, n(%)	310 (97.8)	59 (98.3)	251 (97.7)	0.606[f]
Partially-dependent, n (%)	7 (2.2)	1 (1.7)	6 (2.3)	
Dependent, n (%)	0 (0)	0 (0)	0 (0)	
Preoperative T stage				
Ta, n (%)	16 (5)	3 (5)	13 (5.1)	**0.024[c]**
T1, n (%)	74 (23.4)	6 (10)	68 (26.4)	
T2, n (%)	222 (70)	51 (85)	176 (68.5)	
Preoperative grade				

Grade 1, n (%)	12 (3.8)	4 (6.7)	8 (3.1)	0.251[f]
Grade 2, n (%)	0 (0)	0 (0)	0 (0)	
Grade 3, n (%)	305 (96.2)	56 (93.3)	249 (96.9)	
Clinical lymph node positivity, n (%)	74 (23.3)	19 (31.7)	55 (21.4)	0.091[c]
Hemoglobin (g/dl) (Mean ± SD)	12.5±1.9	11.9±1.4	12.6±2	**0.006[m]**
WBC (g/dl) (Mean ± SD)	8608.6±3368.8	7416.8±4408.5	8886.9±3019.7	**<0.001[m]**
Serum Creatinine (mg/dl) (Mean ± SD)	1.1±0.4	1±0.3	1.1±0.4	0.301[m]
Blood nitrogen urea (mg/dl) (Mean ± SD)	19.6±7	18.1±6.7	19.9±7.1	0.081[m]
Serum albumin (gr/l) ((Mean ± SD)	41.5±4.8	41.6±4.6	41.4±4.9	0.922[m]
Sodium (mEq/l) (Mean ± SD)	139.6±2.7	139.7±2.8	139.6±2.7	0.813[m]
Potassium (mEq/l) (Mean ± SD)	4.4±0.4	4.4±0.4	4.4±0.5	0.938[t]
Comorbidities				
Coronary artery disease, n (%)	47 (14.8)	12 (20)	35 (13.6)	0.21[c]
Heart failure, n (%)	15 (4.7)	1 (1.7)	14 (5.4)	0.319[f]
HT, n (%)	137 (43.2)	27 (45)	110 (42.8)	0.757[c]
DM, n (%)	75 (23.7)	15 (25)	60 (23.3)	0.786[c]
Thyroid disease, n (%)	13 (4.1)	0 (0)	13 (5.1)	0.138[f]
CKD, n(%)	138 (43.5)	24 (40)	114 (44.4)	0.54[c]
CVD, n(%)	15 (4.7)	2 (3.3)	13 (5.1)	0.745[f]
COPD, n(%)	37 (11.7)	6 (10)	31 (12.1)	0.654[c]
Intraoperative characteristics				
Operation duration (minutes) (Mean ± SD)	366.3±85.8	356.7±83.8	368.6±86.3	0.281[m]
Incision length				
Infraumbilical midline, n (%)	142 (44.8)	25 (41.7)	117 (45.5)	0.588[c]
Supra and infraumbilical midline, n (%)	175 (55.2)	35 (58.3)	140 (54.5)	
Urinary diversion technique				
Bricker, n (%)	188 (59.3)	34 (56.7)	154 (59.9)	0.644[c]
Wallace, n (%)	129 (40.7)	26 (43.3)	103 (40.1)	
Length of bowel segment used in urinary diversion (cm) (Mean ± SD)	19.9±4.7	20.4±6.7	19.8±4.2	0.879[m]
Amount of bleeding (mL) (Median) (IQR)	800 (500-1275)	750 (425-1240)	800 (500-1300)	0.364[m]
Postoperative characteristics				
Amount of blood transfusion (Unit) (Median) (IQR)	0 (0-1)	0 (0-1)	0 (0-1)	0.22[m]
Duration of TPN administration (days) (Median) (IQR)	0 (0-4)	0 (0-4)	0 (0-5)	0.975[m]
Hospitalization (days) (Median) (IQR)	15 (12-19.5)	15 (13-17)	15 (12-20)	0.582[m]
Time to oral nutrition (days) (Median) (IQR)	3 (2-4)	3 (2-3)	3 (2-4)	0.598[m]
Ureteral catheterization duration (days) (Median) (IQR)	19 (10.5-21)	16 (11-21)	20 (10-21)	0.972[m]
Complications (Clavien-Dindo classification system), n (%)	141 (44.5)	19 (31.7)	122 (47.5)	**0.027[c]**

Grade 1, n (%)	64 (20.2)	11 (18.3)	53 (20.6)	0.429[f]
Grade 2, n (%)	3 (0.9)	0 (0)	3 (1.2)	
Grade 3a, n (%)	43 (13.6)	7 (11.7)	36 (14)	
Grade 3b, n (%)	21 (6.6)	1 (1.7)	20 (7.8)	
Grade 4a, n (%)	2 (0.6)	0 (0)	2 (0.8)	
Grade 4b, n (%)	2 (0.6)	0 (0)	2 (0.8)	
Grade 5, n (%)	6 (1.9)	0 (0)	6 (2.3)	
Pathological T stage				
Tis, n (%)	9 (2.8)	3 (5)	6 (2.3)	**0.003**[f]
T0, n (%)	33 (10.4)	16 (26.7)	17 (6.6)	
Ta, n (%)	8 (2.5)	1 (1.6)	7 (2.7)	
T1, n (%)	21 (6.6)	3 (5)	18 (7)	
T2a, n (%)	20 (6.3)	3 (5)	17 (6.6)	
T2b, n (%)	50 (15.9)	7 (11.7)	43 (16.7)	
T3a, n (%)	58 (18.3)	7 (11.7)	51 (19.9)	
T3b, n (%)	60 (18.9)	12 (20)	48 (18.7)	
T4a, n (%)	55 (17.4)	7 (11.7)	48 (18.7)	
T4b, n (%)	3 (0.9)	1 (1.6)	2 (0.8)	
Pathological N stage				
N0, n (%)	226 (71.3)	49 (81.7)	177 (68.9)	0.147[c]
N1, n (%)	36 (11.3)	6 (10)	30 (11.7)	
N2, n (%)	45 (14.2)	5 (8.3)	40 (15.6)	
N3, n (%)	10 (3.2)	0 (0)	10 (3.8)	

NAC: Neoadjuvant Chemotherapy, **RC:** Radical cystoprostatectomy, **BMI:** Body Mass Index, **IQR:** Interquartile Range, **ASA:** American Society of Anesthesiologists, **WBC:** White Blood Cell, **HT:** Hypertension, **DM:** Diabetes Mellitus, **CKD:** Chronic Kidney Disease, **CVD:** Cerebrovascular Disease, **COPD:** Chronic Obstructive Pulmonary Disease, **TPN:** Total Parenteral Nutrition, [t]: Independent Sample T Test, [m]: Mann Whitney U Test, [k]: Chi-Square Test, [f]: Fisher's Exact Test

Bold p values indicate statistical significance.

Patients undergoing NAC plus RC were paired with patients undergoing RC alone based on the calculated propensity scores in a 1:1 ratio using the nearest-neighbor matching algorithm in terms of age, BMI, previous surgery history, ASA score, preoperative T stage, hemoglobin, WBC, incision length and urinary diversion technique. It was possible to match 57 patients undergoing NAC plus RC with 57 patients undergoing RC alone. According to the comparative analysis, the median amounts of blood transfusion, hospitalization duration, and time to oral nutrition were significantly higher in the RC alone group compared to the NAC plus RC group (1 [IQR: 0–2] vs. 0 [0–1] units, p = 0.048; 17 [IQR: 14–20.5] vs. 15 [IQR: 13–17] days, p = 0.015; 3 [IQR: 3–4] vs. 3 [2–3] days, p = 0.028, respectively). The postoperative complication rate was higher in the RC alone group, although this difference was not statistically significant (29% vs. 19%, p = 0.058). The two groups were similar in terms of operation duration and intraoperative blood loss (p = 0.33 and p = 0.127, respectively) (Table 2).

Table 2. Perioperative outcomes of patients who underwent radical cystoprostatectomy for urothelial carcinoma and comparative analysis according to the administration of neoadjuvant chemotherapy after propensity score matching

	NAC plus RC (n=57)	RC alone (n=57)	p
Intraoperative outcomes			
Operation duration (minutes) (Mean ± SD)	359±84	372±73.4	0.33[m]
Amount of bleeding (mL) (Median) (IQR)	750 (450-1225)	600 (300-1200)	0.127[m]
Postoperative outcomes			
Amount of blood transfusion (Unit) (Median) (IQR)	0 (0-1)	1 (0-2)	**0.048[m]**
Duration of TPN administration (days) (Median) (IQR)	0 (0-4)	0 (0-4.5)	0.848[m]
Hospitalization (days) (Median) (IQR)	15 (13-17)	17 (14-20.5)	**0.015[m]**
Time to oral nutrition (days) (Median) (IQR)	3 (2-3)	3 (3-4)	**0.028[m]**
Ureteral catheterization duration (days) (Median) (IQR)	16 (11-21)	14 (10-21)	0.767[m]
Complications (Clavien-Dindo classification system), n (%)	19 (33.3)	29 (50.9)	0.058[c]
Grade 1, n (%)	11 (19.3)	17 (29.8)	0.187[f]
Grade 2, n (%)	0 (0)	1 (1.8)	
Grade 3a, n (%)	7 (12.3)	6 (10.5)	
Grade 3b, n (%)	1 (1.7)	2 (3.5)	
Grade 4a, n (%)	0 (0)	0 (0)	
Grade 4b, n (%)	0 (0)	0 (0)	
Grade 5, n (%)	0 (0)	3 (5.3)	

NAC: Neoadjuvant Chemotherapy, **RC:** Radical cystoprostatectomy, **IQR:** Interquartile Range, **TPN:** Total Parenteral Nutrition, [m]: Mann Whitney U Test, [k]: Chi-Square Test, [f]: Fisher's Exact Test

Bold p values indicate statistical significance.

DISCUSSION

In the current study, we collected the clinical data of 317 patients who underwent RC as local treatment for BCa, and 18.9% of them received a complete preoperative chemotherapy course, as recommended by the respective guidelines. Regarding the clinical characteristics of the patient subgroups (NAC+RC, RC only), they were comparable in almost every parameter except for the preoperative T stage. The latter was more advanced (higher percentage of MIBC patients) in the NAC+RC subgroup. Postoperatively, the NAC+RC subgroup demonstrated significantly lower percentage of complications. As expected, significantly more NAC+RC patients were found with no residual tumor in their cystectomy histological specimen. To exclude the effect of other factors (preoperative performance status, age, sex, BMI, etc.) and to consolidate the initial finding of reduced complication rate among NAC+RC patients, we performed patient matching based on calculated propensity scores. Subsequently, we compared two similar subgroups in terms of clinical parameters that have a major effect on the postoperative course. The above comparison demonstrated that NAC had no detrimental role in the respective patients after RC. Interestingly, NAC was associated with a significant improvement in specific aspects of the postoperative time period, such as the blood transfusion rate, the length of hospital stay, and the time to adequate gastrointestinal mobilization and return to oral nutrition. The sum of our results demonstrates that NAC administration is a safe measure to enhance the oncological results of RC without risking a prolonged and eventful recovery period.

To compare our results with the respective findings of other researchers, we performed a thorough literature search and found that the available bibliographical data are mostly in line with our conclusions. In 2019, Aldhaam et al. performed an analysis of the data of 298 patients who underwent NAC plus robotic radical cystectomy (RARC), and the respective data

of 858 patients, who received only RARC. The NAC+RARC patients had similar perioperative parameters (operative time, length of stay), yet they had significantly more 90-day readmissions and demonstrated a trend towards more 90-day complications (10). In the same year, Jerlström et al. published the results of the comparison between NAC+RC vs. RC patients after propensity score matching, and found no deterioration of short-term complication and mortality rates for NAC. Interestingly, the latter was associated with a significant reduction of gastrointestinal complications (11). Another report by Riveros et al. demonstrated that, after adjustment for the rest of the affecting factors, NAC is not associated with any difference in 30-day postoperative complications after RC (12). In 2022, Hoeh et al. analyzed the perioperative and postoperative parameters of NAC+RC patients and found that the latter performed better in terms of wound, cardiac, pulmonary and genitourinary complications and demonstrated shorter length of stay and lower in-hospital mortality compared to RC-only patients (13). More recently, the safety of NAC was confirmed by two reports, which demonstrated a lack of association between NAC before RARC and any effect on perioperative complication rates (14, 15).

From the above data can be concluded that patients after NAC+RC perform at least as well as the respective patients who receive only RC, in terms of perioperative events and postoperative morbidity. This conclusion, combined with the perspective of an improved oncological course after NAC, further consolidates the recommendation for NAC administration in MIBC patients who are going to undergo RC. Interestingly, a report by Kitamura et al. explored the life quality deterioration after the NAC procedure compared with the RC-only treatment and found that the respective indices under evaluation (physical well-being, functional well-being, etc.) were indeed lower during the period between NAC and RC, but not after RC (16).

Provided that the current neoadjuvant pharmaceutical regimens were once first-line treatments in the metastatic setting of BCa, it is plausible that the current first-line agents for metastatic patients are evaluated for their effectiveness in patients before RC. According to a review by Suartz et al., immune checkpoint inhibitors (ICI) combined with chemotherapy seem to further improve the rates of pathological complete response and the prolongation of OS at the cost of a manageable complication profile and an increased financial burden (17). Molecular targeted agents (mostly kinase inhibitors) demonstrate also a significant effect on the prolongation of survival, yet ICI-based regimens seem to drive the further evolution of MIBC neoadjuvant therapy (18). Since the emergence of innovative pharmaceutical agents in cancer is continuous, the recommendations of urological societies regarding the proposed pharmaceutical regimens in the various clinical scenarios of BCa are expected to change accordingly. The scientific effort of the researchers should focus not only on the validation of the effectiveness of these innovative drugs but also on the demarcation of predictive biomarkers, which will render the administration of systemic therapy more selective, beneficial for the BCa patients, and financially sustainable.

The present study has several limitations that should be acknowledged. First, its retrospective and single-center design may introduce selection bias and limit the generalizability of the findings. Second, although propensity score matching was applied to reduce baseline imbalances, residual confounding due to unmeasured variables cannot be completely excluded. In addition, the overall sample size and the relatively small number of patients in certain subgroups may have limited the statistical power of some analyses. Specifically, patients received different neoadjuvant chemotherapy regimens (GC vs. MVAC), which may have distinct toxicity profiles and could theoretically influence perioperative outcomes. However, the number of patients in each subgroup was limited, particularly in the MVAC group (n=9), which precluded a statistically reliable subgroup or sensitivity analysis. Performing such analyses with very small sample sizes would substantially reduce statistical power and increase the risk of type II error and overinterpretation. Therefore, potential regimen-specific effects on perioperative outcomes could not be adequately evaluated in this cohort.

CONCLUSIONS

In the current study, we compared the perioperative events and the postoperative course of patients who underwent NAC+RC with the respective data of RC-only patients to examine the safety of NAC in this specific clinical setting of BCa. Our analysis showed that perioperatively and postoperatively, NAC+RC patients perform at least as well

as the RC-only patients. This finding confirms the safety of NAC in combination with RC and further consolidates the recommendation of NAC administration in MIBC patients in order to improve their oncological course.

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Author Contributions:

- Concept and Design: EU, SS
- Supervision: SS, CC, YK
- Data Collection and/or Analysis: SO, SCE
- Analysis and/or Interpretation: SS, AK
- Literature Search: EU, HBA
- Writing: EU, AK
- Critical Review: CO

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