Original Article

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The Role of Neoadjuvant Chemotherapy in the Pathological T-staging of Patients Undergoing Radical Cystectomy

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Abstract

Objective: For eligible patients with muscle-invasive bladder cancer, the current standard of care is neoadjuvant chemotherapy (NAC) using cisplatin-based regimens followed by radical cystectomy (RC) with pelvic lymph node dissection. We evaluated the role of NAC in the pathological T-staging of tumors in patients who underwent RC and the effect of pathological T-stage regression on disease-free survival (DFS) and overall survival (OS).
Materials and Methods: We evaluated 29 patients who underwent RC following NAC between 2015 and 2023 at our hospital. Eligible participants had histologically confirmed urothelial carcinoma of the bladder with stage cT2-T4a N0-N2 M0 disease and had received cisplatin-based NAC. The primary endpoint was the effect of NAC on pathological T-stage regression, DFS, and OS. The secondary endpoint was to determine the factors affecting DFS following RC.
Results: Cystectomy pN0 rate, in patients with T regression, was significantly higher than that in the other group (86.7% vs. 42.9%, p=0.021). The rate of lymphovascular invasion following cystectomy was significantly lower in the T regression group (57.1%) compared to the non-T regression group (93.3%; p=0.023). T2 pathology to RC time (hazard ratio=1.620, 95% confidence interval: 1.004-2.613, p<0.048) was the only independent predictor for DFS following RC in the multivariate analysis.
Conclusion: Detection of pathological tumor regression in cystectomy pathology after NAC is associated with better DFS and OS. T2 pathology to RC time was an independent predictor of DFS.
Keywords: Neoadjuvant chemotherapy, radical cystectomy, muscle-invasive bladder cancer

Introduction

For eligible patients with muscle-invasive bladder cancer (MIBC), the current standard of care is neoadjuvant chemotherapy (NAC) using cisplatin-based regimens followed by radical cystectomy (RC) with pelvic lymph node dissection (1). This treatment schedule, which includes cisplatin-based NAC, has demonstrated improved oncological outcomes, with an 8% increase in 5-year overall survival (OS) after RC. Further research is needed to identify the most effective regimen of NAC (2,3).

The most frequently employed regimens for NAC treatment are methotrexate, vinblastine, doxorubicin, cisplatin, and gemcitabine-cisplatin (GC). While both regimens demonstrate comparable levels of tumor reduction, the GC regimen has been associated with lower OS rates following RC (4). Some studies have examined how NAC affects the T-stage of MIBC in RC patients. These studies, including both phase 2 and phase 3 trials, have demonstrated that certain NAC regimens can significantly contribute to the pathological downstaging of the tumor (5)

Our study evaluated the influence of NAC on the pathological T-staging of patients with MIBC who underwent RC. Furthermore, the study investigated the correlation between NAC-induced pathological T-stage regression and subsequent disease-free survival (DFS) and OS.

Materials and Methods

Ethics committee approval, numbered 2025/0081, was secured on 31.07.2025 from İstanbul Provincial Health Directorate, Göztepe Prof. Dr. Süleyman Yalçın City Hospital. For this retrospective case-control study. We analyzed data from patients who were treated with NAC before undergoing

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RC at our hospital between 2015 and 2023. Eligible participants had histologically confirmed urothelial carcinoma of the bladder with stage cT2-T4a N0-N2 M0 disease and had received cisplatin-based NAC. We collected data on patient demographics, comorbidities, smoking status, length of hospitalization, antiaggregant/anticoagulant therapy use, the time interval between bladder cancer diagnosis and RC, the interval between muscle-invasive pathology diagnosis and cystectomy, pathological T-stage and grade determined by primary transurethral resection of the bladder tumor (TUR-BT), presence of carcinoma *in situ*, lymphovascular invasion and post-TUR-BT intravesical therapy. Additionally, cystectomy pathological T-stage and grade, as well as the presence of carcinoma in situ and lymphovascular invasion, were evaluated.

Patients were ineligible for inclusion in the study if they had evidence of metastatic disease, non-urothelial tumors, a history of pelvic radiation, or incomplete medical records.

The primary endpoint was the effect of NAC on pathological T-stage regression and its effect on DFS and OS. The secondary endpoint was determining the factors affecting DFS following RC.

Statistical Analysis

Statistical analyses were conducted using SPSS software, version 22. (IBM Corp, Armonk, NY). Continuous normally distributed variables were summarized as mean ± standard deviation. The t-test was used for group comparisons. The chi-square test was used for categorical variables, with a significance level of α =0.05 for all tests. Multivariate logistic regression analyses were conducted to determine independent prognostic factors influencing treatment decisions, using variables that had shown statistical significance in univariate analyses. Univariate and multivariate logistic regression analyses were performed to determine the odds ratios and 95% confidence intervals (CI) of risk factors predicting T-stage regression. A p-value threshold of less than 0.005 was considered statistically significant.

Results

Twenty-nine patients met the inclusion criteria, comprising 20.6% women (n=6) and 79.4% men (n=23). There were 15 people in the T regression group and 14 people in the non-T regression group. No statistically significant differences were observed between groups regarding age, gender, smoking status, comorbidities, and family history. The pN0 rate following cystectomy was significantly higher in the T regression group compared to the other group (86.7% vs. 42.9%, p=0.021). Additionally, lymphovascular invasion in cystectomy specimens was significantly lower in the T regression group (57.1% vs. 93.3%, p=0.023). Operation time was longer in patients with non-T regression (218.5±44.7 vs. 202.67±28.6 min., p=0.035). In contrast, blood loss (217.8±72.3 vs. 306.6±174.1 mL, p=0.014) was significantly lower in this group. The demographic characteristics and pathological results of the patients are summarized in Table 1. Median follow-up was 41.6 months [interquartile range (IQR: 6-76)] in the T regression group; 29.7 months (IQR: 3-97) in the other group.

Table 1. Patient characteristics and pathological outcomes

	pT regression (no) (n=14)	pT regression (yes) (n=15)	p-value
Gender, n (%)			0.411[c]
Female	2 (14.3)	4 (26.7)	
Male	12 (85.7)	11 (73.3)	
Age (years), mean ± SD	64.2±6.7	61.4±8.9	0.954[T]
Operation time (minute), mean ± SD	218.5±44.7	202.67±28.6	**0.035**[T]
Blood loss (mL), mean ± SD	217.8±72.3	306.6±174.1	**0.014**[T]
Removed lymph node number, mean ± SD	9.64±4.9	13.6±8.1	0.154[T]
Number of positive lymph nodes, mean ± SD	0.8±0.8	0.4±1.1	0.860[T]
Smoking interval, median (min-max)	37.5 (20-45)	40 (20-200)	0.399[M]
Diagnosis of bladder cancer to radical cystectomy time, mo, median (min-max)	6.5 (3-78)	5 (3-72)	0.115[M]
T2 pathology - radical cystectomy time, mo, median (min-max)	6 (3-13)	5 (3-7)	0.319[M]
Length of hospitalization, day, median (min-max)	11.5 (7-31)	10 (8-11)	0.128[M]
Family history, n (%)			0.227[c]
No	13 (92.9)	13 (86.7)	
Yes	1 (7.1)	2 (13.3)	
Hypertension, n (%)			0.077[c]
No	11 (78.6)	7 (46.7)	
Yes	3 (21.4)	8 (53.3)	
Coronary artery disease, n (%)			0.311[c]
No	10 (71.4)	13 (86.7)	
Yes	4 (28.6)	2 (13.3)	
Diabetes mellitus, n (%)			0.909[c]
No	10 (71.4)	11(73.3)	
Yes	4 (28.6)	4 (26.7)	
Pulmonary comorbidities, n (%)			0.924[c]
No	11 (78.6)	12 (80.0)	
Yes	3 (21.4)	3 (20.0)	
Reason of hospitilization, n (%)			0.997[c]
Asymptomatic	1 (7.1)	1 (6.7)	
Hematuria	12 (5.7)	13 (86.7)	
LUTS	1 (7.1)	1 (6.7)	

Table 1. Continued

	pT regression (no) (n=14)	pT regression (yes) (n=15)	p-value
Primary T-staging, n (%)			0.567[c]
Ta	1 (7.1)	0 (0.0)	
T1	2 (14.3)	2 (13.3)	
T2	11 (78.6)	13 (89.7)	
Primary grade, n (%)			0.292[c]
Low grade	1 (7.1)	0 (0.0)	
High grade	13 (92.7)	15 (100.0)	
Primary carcinoma *in situ*, n (%)			0.941[c]
No	12 (85.7)	13 (86.7)	
Yes	2 (14.3)	2 (13.3)	
Primary lenfovascular invasion, n (%)			0.960[c]
No	13 (92.9)	14 (93.3)	
Yes	1 (7.1)	1 (6.7)	
Tumor size, n (%)			0.060[c]
<3 cm	2 (14.3)	7 (46.7)	
>3 cm	12 (85.7)	8 (53.3)	
Intravesical Bacillus Calmette-Guérin (BCG) therapy, n (%)			0.858[c]
No	7 (50.0)	8 (53.3)	
Yes	7 (50.0)	7 (46.7)	
Intravesical mitomycin-c (MMC) therapy, n (%)			0.837[c]
No	8 (57.1)	8 (53.3)	
Yes	6 (42.9)	7 (46.7)	
Pre-cystectomy T-staging, n (%)			0.367[c]
Ta	1 (7.1)	0 (0.0)	
T1	0 (0.0)	1 (6.7)	
T2	13 (92.9)	14 (93.3)	
Pre-cystectomy carcinoma *in situ*, n (%)			0.249[c]
No	11 (78.6)	14 (93.3)	
Yes	3 (21.4)	1 (6.7)	
Pre-cystectomy lymphovascular invasion, n (%)			0.960[c]
No	13 (92.9)	14 (93.3)	
Yes	1 (7.1)	1 (6.7)	
Pre-cystectomy clinical T-staging, n (%)			0.287[c]
0	9 (64.3)	13 (86.7)	
1	1 (7.1)	1 (6.7)	
2	4 (28.6)	1 (6.7)	

Table 1. Continued

	pT regression (no) (n=14)	pT regression (yes) (n=15)	p-value
Pre-cystectomy clinical N staging, n (%)			0.374[c]
N0	12 (85.7)	12 (80.0)	
N1	1 (7.1)	3 (20.0)	
N2	1 (7.1)	0 (0.0)	
Urinary diversion type, n (%)			0.367[c]
Ureterocutaneostomy	1 (7.1)	0 (0.0)	
Ileal Loop	13 (92.9)	14 (93.3)	
Ileal Neobladder	0 (0.0)	1 (6.7)	
Cystectomy T-staging, n (%)			**0.002**
pT0	2 (14.3)[a]	13 (86.7)[b]	
pT1	1 (7.1)[a]	2 (13.3)[a]	
pT2	1(7.1)[a]	0	
pT3	7 (50.0)[a]	0	
pT4	3 (21.4)[a]	0	
Cystectomy pN stage, n (%)			**0.021**
pN0	6 (42.9)[a]	13 (86.7)[b]	
pN1	5 (35.7)[a]	0 (0.0)[b]	
pN2	3 (21.4)[a]	2 (13.3)[a]	
Cystectomy lymphovascular invasion, n (%)			**0.023**
No	8 (57.1)	14 (93.3)	
Yes	6 (42.9)	1 (6.7)	
Ureteral positive surgical margin, n (%)			0.292[c]
No	13 (92.9)	15 (100)	
Yes	1 (7.1)	0	

[a,b]: Bonferroni adjustment, [c]: Chi-square analysis, [T]: Student's t-test, [M]: Mann-Whitney U test, SD: Standard deviation, pT: Pathological tumor, pN: Pathological node

Univariate and Multivariate Analysis of the Factors Influencing Survival of Patients

Both DFS and OS were worse in the non-T-regressed group (Figures 1 and 2). Length of hospitalization, smoking status, T2 pathology to RC time, cystectomy pathological tumor (pT) stage, cystectomy pathological node (pN) stage, cystectomy lymphovascular invasion, and number of positive lymph nodes were the factors affecting DFS in the univariate analysis. T2 pathology to RC time (hazard ratio=1.620, 95% CI, 1.004-2.613, p<0.048) was the only independent predictor for DFS following RC in the multivariate analysis, as shown in Table 2.

Kaplan-Meier analysis showed better DFS in the T regression group at 5 years (100% vs. 64.3%, p=0.019) (Figure 1). Also, Kaplan-Meier analysis showed better OS in the T regression group at 5 years (100% vs. 59.1%, p=0.008) (Figure 2).

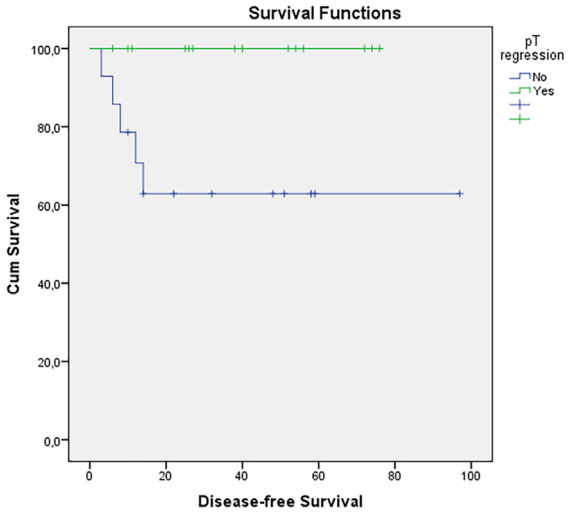

Figure 1. Kaplan-Meier curve for disease-free survival according to presence of pathological T-stage regression. The p-value of the log-rank method was 0.019 and the chi-square value was 5.487
pT: Pathological tumor

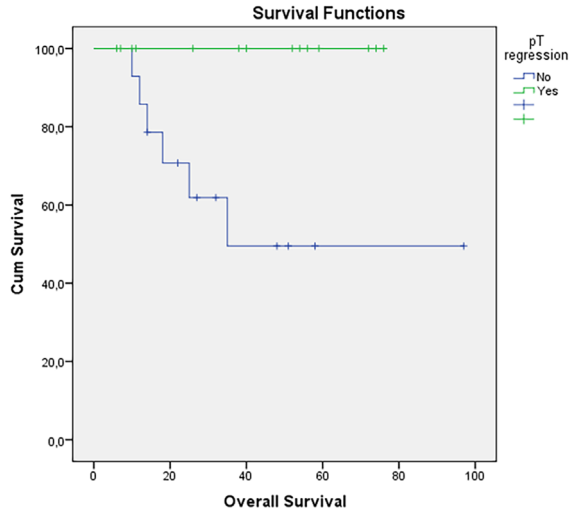

Figure 2. Kaplan-Meier curve for overall survival according to presence of pathological T-stage regression. The p-value of the log-rank method was 0.008 and the chi-square value was 6.945
pT: Pathological tumor

Table 2. Univariate and multivariate cox proportional hazards regression models for patient survival

Variable	Univariate model		Multivariate model	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Diagnosis-radical cystectomy time (years)	1.029 (0.998-1.061)	0.070		
T2 pathology-radical cystectomy time	1.522 (1.061-2.182)	**0.022**	1.620 (1.004-2.613)	**0.048**
Age at RC	1.009 (0.892-1.142)	0.886		
Gender	29.82 (0.004-243.3)	0.460		
Smoking	7.512 (1.360-41.476)	**0.021**		
Charlson comorbidity index	0.033 (<0.1-1220.4)	0.526		
Primary pT-staging	0.570 (0.154-2.109)	0.400		
Primary carcinoma *in situ*	0.038 (<0.1-1168.3)	0.535		
Tumor size (Ref:<3cm)	36.991 (0.14-99784.0)	0.370		
Bacillus Calmette-Guérin (BCG)	5.368 (0.596-48.36)	0.134		
Mitomycin-C (MMC)	7.311 (0.802-66.61)	0.078		
Pre-cystectomy carcinoma in situ status	0.038 (<0.1-1168.3)	0.535		
Pre-cystectomy lymphovascular invasion	4.776 (0.492-46.32)	0.177		
Operation time (min.)	1.006 (0.983-1.029)	0.612		
Peroperative blood loss (mL)	0.999 (0.991-1.006)	0.704		
Length of hospitalization	1.218 (1.062-1.396)	**0.005**		
Cystectomy pT-staging	1.953 (1.071-3.564)	**0.029**		
Cystectomy pN staging	4.344 (1.378-13.688)	**0.012**		
Cystectomy lymphovascular Invasion	15.732 (1.735-142.6)	**0.014**	9.243 (0.862-99.094)	0.066
Removed lymph node number	0.865 (0.691-1.084)	0.208		
Number of positive lymph nodes	2.319 (1.026-5.237)	**0.043**		

pT: Pathological tumor, pN: Pathological node, HR: Hazard ratio, CI: Confidence interval

Discussion

Yin et al. (4) showed an 8% absolute improvement in 5-year survival with NAC. Also, our study found that, following NAC, detecting a pT regression in cystectomy pathology is associated with better DFS and OS.

Our study findings indicate that the cystectomy pT0 and pN0 rate in patients with T regression were significantly higher than those in the other group. Similar findings were observed in the previous study. Møller et al. (6) found that NAC increased pathological downstaging of the tumor and was indirectly associated with OS benefit. Grossman et al. (2) found that pathological downstaging and response was detected in patients who received NAC treatment (21.7%). When our study findings were compared with those in the literature, similar outcomes were observed. NAC prior to RC demonstrated a significant survival benefit. These studies have shown an additional 5% improvement in OS when NAC is administered before RC (7-8). Furthermore, a study reported a 5% increase in OS and a 9% increase in DFS when RC was preceded by platinum-based NAC compared to RC alone (9). Mazza et al. (10) observed 5-year DFS and OS rates of 90% and 86%, respectively, following NAC. Our study findings are that DFS and OS in the T regression group at 5-years are 64.3% and 59.1%, respectively. Compared to the literature, the lower rate of DFS and OS in our study is a result of the delay in RC time.

Some factors may affect the RC time: patient's comorbidities, tumor and surgeon-related factors. The time from the decision to undergo surgery to the actual procedure is a crucial factor. Delaying RC for more than 12 weeks is associated with advanced cancer stage and reduced survival (11-14). Also, our study found that length of hospitalization, smoking status, T2 pathology to RC time, cystectomy pT stage, cystectomy pN stage, and cystectomy lymphovascular invasion were factors affecting DFS in the univariate analysis. On the other hand, multivariate analysis showed that time from T2 pathology to RC was the only independent predictor for DFS. Kulkarni et al. (15) reported a significant increase in mortality risk: a surgical delay of more than 40 days between TUR-BT and RC, and an increased risk of mortality. Additionally, a moderate delay in RC does not compromise patient outcomes. Nielsen et al. (16) found that a moderate delay between the last TUR-BT and RC did not independently impact disease progression or patient survival outcomes. Similarly, Bruins et al. (17) reported that a surgical delay exceeding 3 months had no effect on tumor stage or OS. As a result, our study found that T2 pathology to RC is an important predictor for DFS. On the other hand, our study results show that the time between T2 pathology and RC has no impact on pT regression.

Fleischmann et al. (18) demonstrated the importance of integrating tumor regression grade with TNM classification. The objective of this research was to verify the influence of tumor regression grade, when integrated with TNM classification, on survival rates within an independent patient cohort with MIBC, all of whom underwent NAC and RC.

Study Limitations

This study was limited by its retrospective design, non-randomized nature, incomplete data on treatment-related side effects, and a relatively small sample size. On the other hand, usage of only one NAC regimen, a homogeneous group, and inclusion of only urothelial carcinoma were the strengths of the study.

Conclusion

Detection of pT regression in cystectomy pathology after NAC is associated with better DFS and OS. T2 pathology to RC time was an independent predictor of DFS.

Ethics

Ethics Committee Approval: Ethics committee approval, numbered 2025/0081, was secured on 31.07.2025 from İstanbul provincial health directorate, Göztepe Prof. Dr. Süleyman Yalçın City Hospital.

Informed Consent: This study retrospective case-control study.

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Publication: The results of the study were not published in full or in part in form of abstracts.

Contribution: There is not any contributors who may not be listed as authors.

Footnotes

Authorship Contributions

Surgical and Medical Practices İ.H.Z., Ö.A., Ö.K., M.Ç.Ç., A.Y., Concept: İ.H.Z., Ö.A., Ö.K., M.Ç.Ç., A.Y., Design: Ö.A., Ö.K., M.Ç.Ç., Data Collection or Processing: İ.H.Z., Ö.A., Ö.K., Analysis or Interpretation: İ.H.Z., A.Y., Literature Search: İ.H.Z., Ö.K., M.Ç.Ç., Writing: İ.H.Z., M.Ç.Ç., A.Y.

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