DOI: 10.4081/aiua.2025.14264

ORIGINAL PAPER

# Prognostic value of combined tumor regression grade and TNM stage in muscle-invasive bladder cancer treated with neoadjuvant chemotherapy and radical cystectomy

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**Summary** ***Introduction: Tumor regression grade (TRG) is a recognized prognostic marker in several solid tumors treated with neoadjuvant therapy, but its clinical relevance in muscle-invasive bladder cancer (MIBC) remains under investigation. This study aimed to evaluate the prognostic value of TRG and its integration with pathological TNM staging in patients with MIBC treated with neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC).***

***Materials and methods: We conducted a retrospective analysis of 51 patients with MIBC who received platinum-based NAC followed by RC and lymphadenectomy between 2013 and 2024. TRG was assessed according to the Fleischmann classification and combined with ypTNM stage to categorize patients as complete, partial or non-responders. Overall survival (OS) and disease-free survival (DFS) were estimated using Kaplan–Meier analysis, and independent prognostic factors were identified through Cox regression models.***

***Results: Complete response (ypT≤1, ypN0, TRG1) was observed in 43.1% of patients. Median OS was 19 months, with 3- and 5-year OS rates of 28.6% and 14.3%, respectively. Complete responders demonstrated significantly improved OS and DFS ($p < 0.001$). On multivariable analysis, absence of nodal involvement ($p = 0.047$) and complete response ($p = 0.012$) were independently associated with better OS. Negative surgical margins showed a trend toward improved survival ($p = 0.064$).***

***Conclusions: TRG is a reproducible and clinically meaningful histopathologic scoring system that enhances prognostic stratification when combined with pathological TNM staging. Its integration into routine post-NAC assessment may improve postoperative decision-making and help identify patients who could benefit from tailored surveillance or adjuvant strategies.***

*KEY WORDS: Tumor regression grade; Muscular-invasive bladder cancer; Neoadjuvant chemotherapy; Radical cystectomy.*

Submitted 20 August 2025; Accepted 30 August 2025

## INTRODUCTION

Patients with *muscle-invasive bladder cancer* (MIBC) have a 5-year *overall survival* (OS) of 40-60% after *radical cystectomy* (RC) with lymph node dissection, that is the cornerstone of curative treatment (1). To improve oncological outcomes, *neoadjuvant chemotherapy* (NAC) has become the standard of care for eligible patients, providing a 5-8% increase in survival benefit at five years (2, 3). Beside this, before surgery, more patients can receive chemotherapy, as post-operative status and complications may preclude adjuvant chemotherapy (4).

However, not all patients respond to neoadjuvant treatment. Identifying those most likely to benefit remains a critical challenge, as no validated score currently exists to accurately predict response (5).

It is estimated that following NAC, 20-40% of patients have no residual tumor on histological examination of the RC specimen representing a pathologically complete response (2, 6, 7). These patients tend to have excellent outcomes with reported 5-year OS rates of 80-85% (7). It is even hypothesized that patients with a pathologically complete response after NAC might not benefit from concurrent RC. This hypothesis is being tested in the ongoing PRE-PREVENCYS trial (8).

*Tumor regression grade* (TRG) aims to quantify the extent of histological response to chemotherapy by assessing the relative proportion of residual viable tumor cells and treatment-related changes, such as fibrosis or necrosis. Although its importance has been well established for other malignancies, like rectal and esophago-gastric cancers (9-11), no standardized grading system has been created for bladder cancer. Research has been conducted to validate TRG-based classifications and to demonstrate their association with oncologic outcomes, showing additional prognostic value when combined with standard TNM staging (12-14).

*Fleischmann et al.* introduced a TRG classification and concluded that TRG determination in neoadjuvant treated bladder cancer predicts survival independently and better than ypT and ypN stages (12). Since then, other studies have evoked the role of TRG predicting oncological outcomes in MIBC treated with NAC followed by surgery, and its additional value when combined with standard TNM staging (13-15).

We thus aim to evaluate TRG of patients with MIBC who underwent NAC before RC and lymphadenectomy and to assess its prognostic role in combination with TNM staging classification as predictors of OS and *disease-free survival* (DFS).

## Material and methods

### *Study design*

This is a retrospective cohort study conducted in a tertiary hospital. From a total of 307 patients who underwent RC for bladder cancer between January 2013 and December 2024, the study included a consecutive series of 51 patients with MIBC treated with platinum-based NAC followed by RC with lymphadenectomy.

Inclusion criteria were (1) histologically confirmed *urothelial carcinoma* (UC) of the bladder (pure or predominant histology); (2) clinical stage T2-T4a, N0-3, M0 prior to NAC; (3) completion of at least two cycles of chemotherapy; and (4) availability of full pathological specimens for review. Patients were excluded if they had (1) pure non-urothelial histology, (2) ≤pT1/Tis stage disease on initial histology, (3) completed less than two cycles of NAC, or (4) missing clinical or histopathological data.

Initial diagnosis and staging were established after *transurethral resection of the bladder* (TURB) and chest, abdominal and pelvic *computed tomography* (CT). Follow-up after surgery was based on chest, abdominal and pelvic CT or 18F-FDG (fluordesoxiglicose) Positron Emission Tomography/CT. Last follow-up was performed in July 2025.

### *Neoadjuvant chemotherapy*

The decision of NAC was made after discussion at a multidisciplinary tumor board involving urologists and oncologists. Standard treatment included a platin-based combination of drugs [*gemcitabine and cisplatin* (GemCis); *gemcitabine and carboplatin* (GemCarbo), *methotrexate, vinblastine, doxorubicin and cisplatin* (MVAC); or *cisplatin and etoposide* (CisEto)] depending on patient and tumor features.

### *Surgical procedure*

After NAC all patients were submitted to open RC and bilateral lymphadenectomy in the same procedure. Standard lymph node dissection was generally carried out. Extended or super-extended templates were used depending on preoperative staging results (16). In two cases, lymphadenectomy could not be performed due to intraoperative or anatomical limitations. Intraoperative frozen section analysis of the urethra and ureters was routinely performed.

### *Histopathological analysis*

TURB and RC specimens were analyzed by two dedicated genitourinary pathologists blinded to outcomes. TRG was evaluated in the primary tumor site using the system proposed by *Fleischmann et al.* (12), described in Table 1. If multiple areas with varying response were present, the dominant TRG pattern was recorded. Discrepancies between reviewers were resolved by joint consensus.

***Table 1.***
*Tumor regression grade classification.*

| | |
|---|---|
| TRG1 | Complete regression (no viable tumor) |
| TRG2 | > 50% regression (predominantly therapy-induced changes, sparse viable tumor) |
| TRG3 | ≤ 50% regression (predominantly viable tumor with limited regression) |

*TRG: Tumor Regression Grade.*

***Table 2.***
*Patients classification according to neoadjuvant chemotherapy response.*

| | |
|---|---|
| Complete Responder | ypT≤1 and ypN0 and TRG1 |
| Partial Responder | ypT≥2 or ypN1-3 and TRG1 or TRG2 |
| Non-responder | ypT≥2 or ypN1-3 and TRG3 |

*TRG: Tumor Regression Grade.*

Residual pathological staging (ypTNM) was assigned according to AJCC 8$^{th}$ edition criteria (17). Lymph nodes were examined separately and classified as invaded (pN≥1) or not (pN0). TRG classification and ypTNM stage were combined in treatment response evaluation categories, adapted from the criteria introduced by *Voskuilen C. et al.* (13). Patients were classified as complete, partial or non-responders (Table 2).

### *Data collection and statistical analysis*

Data was analyzed with Stata (*StataCorp LP® version 16.0*). Descriptive statistics were used for clinical and analytical data description. Continuous variables were described with median and *interquartile range* (IQR) and categorical variables with frequencies. OS was defined as the time from RC to death from any cause or last known follow-up. DFS was measured from the date of RC to the first evidence of recurrence, disease progression, or death.

Kaplan-Meier analysis was used to estimate OS and DFS, with group comparisons performed using the log-rank test. Independent predictors of survival were assessed through multivariate Cox proportional hazards regression, with backward selection. Variables with a p-value $< 0.1$ in the univariate analysis were included in the multivariable model. A p-value of $< 0.05$ was considered statistically significant.

### *Ethical considerations*

The project was conducted in accordance with good clinical practice and adhered to the ethical principles of the Declaration of Helsinki. Informed consent was obtained prior to inclusion in the study. All data were anonymized before the analysis.

## Results

### *Study's population characteristics*

A total of 51 patients were included, the majority of whom (76.5%) were male. The median age at diagnosis was 66 years (IQR 60-76) and 42 patients (82.3%) had previous or concurrent history of smoking. Demographic, clinical and histopathological characteristics are detailed

| Parameter | N (%) |
|---|---|
| Age, median (IQR) | 66 (60-76) |
| Gender | |
| Male | 39 (76.5) |
| Female | 12 (23.5) |
| Smoking history | |
| Yes | 42 (83.4) |
| No | 9 (17.6) |
| cT stage | |
| T2 | 39 (76.5) |
| T3 | 5 (9.8) |
| T4 | 7 (13.7) |
| cN stage | |
| N0 | 38 (74.5) |
| N+ | 13 (25.5) |
| NAC scheme | |
| GemCis | 44 (86.3) |
| MVAC | 4 (7.8) |
| CisEto | 2 (3.9) |
| GemCarbo | 1 (2.0) |
| No. of NAC cycles, median (IQR) | 4 (3-4) |
| 2 | 10 (19.6) |
| 3 | 13 (25.5) |
| 4 | 24 (47.1) |
| 6 | 4 (7.8) |
| Radical cystectomy specimen | |
| No tumor present | 12 (23.5) |
| Tumor present | 39 (76.5) |
| Pure urothelial carcinoma/CIS | 25 (64.1) |
| Variant histology | 14 (35.9) |
| Squamous cell | 4 (7.8) |
| Micropapillary | 4 (7.8) |
| Adenocarcinoma | 2 (3.9) |
| Neuroendocrine | 2 (3.9) |
| Sarcomatoid | 2 (3.9) |
| pT Stage | |
| T0 | 12 (23.5) |
| Tis | 11 (21.6) |
| T1 | 3 (5.9) |
| T2 | 3 (5.9) |
| T3 | 14 (27.5) |
| T4 | 8 (15.7) |
| Residual tumor dimension (cm), median (IQR) | 3.25 (2.0-5.5) |
| pN stage | |
| Nx | 2 (3.9) |
| N0 | 36 (70.6) |
| N1 | 1 (2.0) |
| N2 | 12 (23.5) |
| No. of positive lymph nodes if N1-3, median (IQR) | 4.5 (2-8) |
| Surgical margins | |
| Negative | 41 (80.4) |
| Positive | 10 (19.6) |
| Tumor regression grade | |
| TRG1 | 23 (45.1) |
| TRG2 | 9 (17.7) |
| TRG3 | 19 (37.2) |
| Type of responder | |
| Complete responder | 22 (43.1) |
| Partial responder | 10 (19.6) |
| Non-responder | 19 (37.2) |

*GemCis: Gemcitabine/Cisplatin; GemCarbo: Gemcitabine/Carboplatin; CIS: Carcinoma in situ; CisEto: Cisplatin/Etoposide; MVAC: Methotrexate/Vinblastine/Doxorubicin/Cisplatin; NAC: Neoadjuvant Chemotherapy; TRG: Tumor Regression Grade.*

***Table 3.***
*Clinicopathologic data of the study population (N = 51 patients undergoing neoadjuvant chemotherapy followed by radical cystectomy).*

in Table 3. Figure 1 illustrates Tumor Regression Grades. Median time from TURB to NAC and from NAC to RC were 55 days (IQR 35-78) and 100 days (IQR 80-142), respectively.

Majority of patients (86.3%) received GemCis, 4 patients had dense-dose MVAC, 1 patient had GemCarbo due to renal function impairment and 2 patients received CisEto

***Figure 1.***
*Tumor Regression Grade (TRG) (hematoxylin and eosin).*
*A – TRG1, no histologically detectable residual cancer cells, with extensive fibrosis present in the tumor bed.*
*B – TRG2, the tumor bed is predominantly fibrotic, with residual cancer cells comprising less than 50% of the area.*
*C – TRG3, residual cancer cells dominate over fibrosis, occupying 50% or more of the tumor bed area, or there are no signs of regression.*

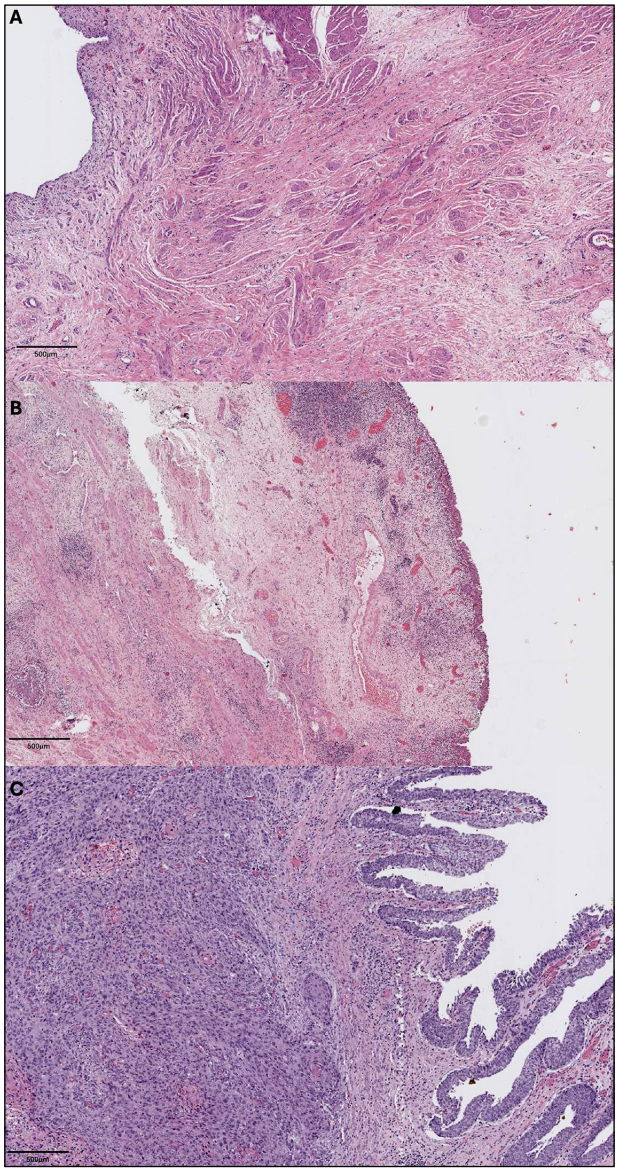
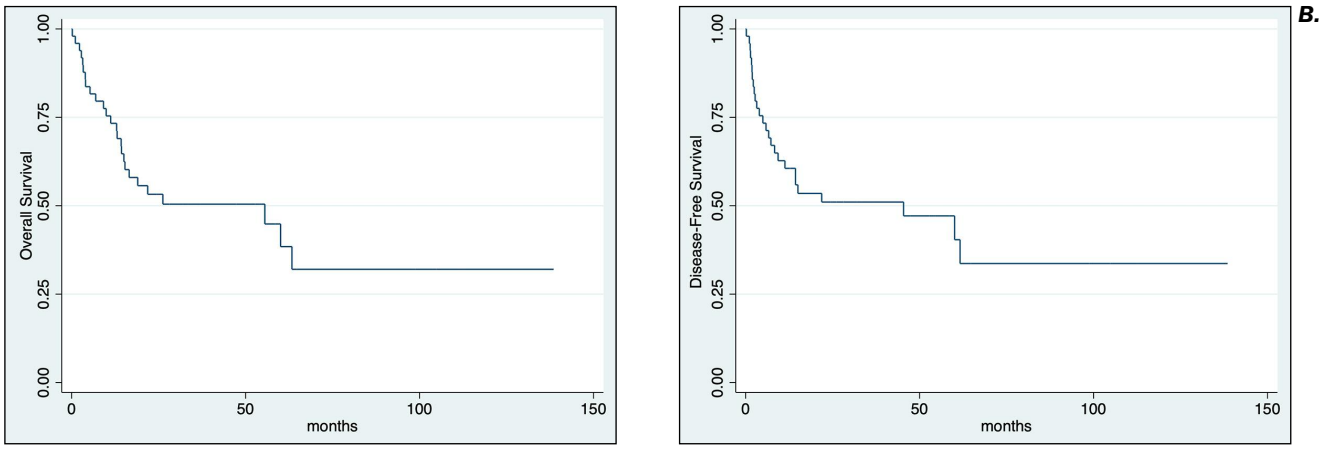


***Figure 2.***
*Kaplan-Meier curves of overall survival (A) and disease-free survival (B) in 51 patients undergoing neoadjuvant chemotherapy followed by radical cystectomy.*



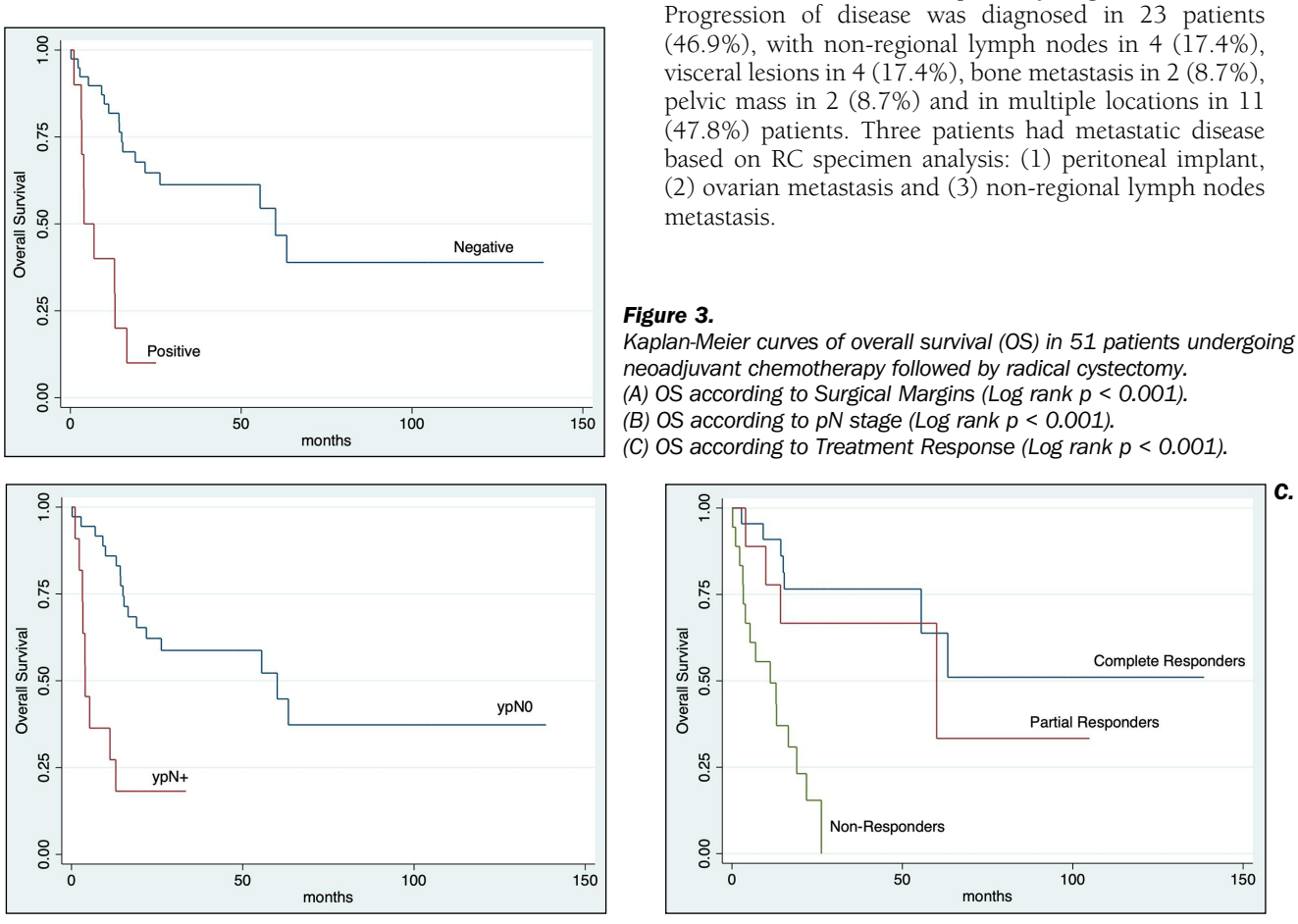

because of poorly differentiated neuroendocrine variant present in > 10% of TURB specimen. Regarding response to neoadjuvant treatment, TRG was closely correlated with response classification. All non-responders (n = 19) exhibited TRG3. Among the 23 patients with TRG1, 22 were classified as complete responders, while one was a partial responder. In this particular case, complete tumor regression was observed in the bladder, but residual UC was identified in the prostate (pT4a, N0, TRG1).

Finally, nine patients were assigned TRG2, contributing to a total of 10 patients categorized as partial responders.

### *Overall and disease-free survivals*

The median follow-up period was 16.7 months (IQR 9.9-47.3), and the 3- and 5-year OS rates were 28.6% and 14.3%, respectively (Figure 2A). The median OS was 19 months (IQR 9.9-47.3). Four patients survived for more than eight years after RC. The 3- and 5-year DFS rates were 28.6% and 14.3%, respectively (Figure 2B).
Progression of disease was diagnosed in 23 patients (46.9%), with non-regional lymph nodes in 4 (17.4%), visceral lesions in 4 (17.4%), bone metastasis in 2 (8.7%), pelvic mass in 2 (8.7%) and in multiple locations in 11 (47.8%) patients. Three patients had metastatic disease based on RC specimen analysis: (1) peritoneal implant, (2) ovarian metastasis and (3) non-regional lymph nodes metastasis.

***Figure 3.***
*Kaplan-Meier curves of overall survival (OS) in 51 patients undergoing neoadjuvant chemotherapy followed by radical cystectomy.*
*(A) OS according to Surgical Margins (Log rank p < 0.001).*
*(B) OS according to pN stage (Log rank p < 0.001).*
*(C) OS according to Treatment Response (Log rank p < 0.001).*



### *Impact of clinical and histopathological factors in the disease-free and overall survival*

Univariate analysis identified several predictors of longer OS, including tumor type in the RC specimen (p = 0.04), with pure UC showing better outcomes compared to variant histology (p = 0.008), as well as pathological stage ypT≤1 (p < 0.001), node-negative status (p < 0.001), negative margins (p < 0.001), lower TRG (p < 0.001), and complete response (p < 0.001) (Figure 3 and Supplementary Table).

These same predictors were also associated with improved DFS (p < 0.05) (Supplementary Table).

### *Independent predictive factors of survival*

On multivariable analysis, the absence of nodal involvement and complete response (defined as ypT≤1, ypN0, TRG1) were identified as independent predictors of improved OS (p = 0.047 and p = 0.012, respectively). Negative surgical margins demonstrated a trend toward significance as an independent prognostic factor for OS (p = 0.064) (Table 4).

***Supplementary Table.***

*Clinical and pathological characteristics of the study population (N = 51 patients undergoing neoadjuvant chemotherapy followed by radical cystectomy) and predictors of overall and disease-free survival (Log rank) (p < 0.05).*

| Parameters | No. of patients (%) | Overall survival | Disease-free survival |
|---|---|---|---|
| Gender | | | |
| Male | 39 (76.5%) | 0.436 | 0.5 |
| Female | 12 (23.5%) | | |
| Age | | | |
| ≤ 65 | 14 (73.7%) | 0.61 | 0.65 |
| > 65 | 5 (26.3%) | | |
| History of smoking | | | |
| Yes | 42 (82.4%) | 0.333 | 0.587 |
| No | 9 (17.7%) | | |
| RC Specimen | | | |
| No tumor present | 12 (23.5%) | 0.04 | 0.026 |
| Tumor present | 39 (76.5%) | | |
| RC specimen with tumor | | | |
| Pure urothelial carcinoma/CIS | 25 (64.1%) | 0.008 | 0.004 |
| Variant histology | 14 (35.9%) | | |
| ypT | | | |
| T≤1 | 7 (36.8%) | < 0.001 | < 0.001 |
| T≥2 | 12 (63.2%) | | |
| ypN | | | |
| N0 | 16 (84.2%) | < 0.001 | < 0.001 |
| N1-3 | 3 (15.8%) | | |
| Surgical margins | | | |
| Negative | 41 (80.4%) | < 0.001 | < 0.001 |
| Positive | 10 (19.6%) | | |
| Tumor regression grade | | | |
| TRG 1 | 23 (45.1%) | < 0.001 | < 0.001 |
| TRG 2 | 9 (17.7%) | | |
| TRG 3 | 19 (37.2%) | | |
| Type of responder | | | |
| Complete | 22 (43.1%) | < 0.001 | < 0.001 |
| Partial | 9 (17.7%) | | |
| Non-responder | 20 (39.2%) | | |

*HR: Hazard Ratio; 95% CI: 95% Confidence Interval.*

***Table 4.***

*Independent predictors of overall survival (Cox Regression).*

| | HR | 95% CI | p value |
|---|---|---|---|
| Surgical margins (negative) | 2.72 | 0.94-7.84 | 0.064 |
| pN stage (N0) | 2.59 | 1.01-6.62 | 0.047 |
| Type of responder (complete responder) | 2.19 | 1.18-4.06 | 0.012 |

*HR: Hazard Ratio; 95% CI: 95% Confidence Interval.*

## Discussion

In this retrospective cohort of 51 patients with MIBC treated with NAC followed by RC, we observed that TRG was significantly associated with both OS and DFS. The median OS in our cohort was 19 months, with 3- and 5-year OS rates of 28.6% and 14.3%, respectively. These are lower rates than those reported in large multicenter trials (2, 3), likely reflecting differences in patient selection, disease burden, and histological subtypes. Despite this, a small subset of patients achieved long-term survival beyond eight years, reinforcing the potential of NAC followed by RC to provide durable benefit in well-selected individuals.

Consistent with prior studies (12, 13, 18) we found that better TRG scores (TRG1-2), node-negative status, and lower pathological stage (ypT≤1) were associated with prolonged survival. Importantly, being a complete responder emerged as a strong prognostic factor on both univariate and multivariate analyses, supporting TRG classification utility in stratifying patients beyond conventional TNM staging. While pathologic complete response (pT0N0) is the most widely used surrogate endpoint in NAC trials, our findings are aligned with the literature in showing that patients with near-complete response (TRG1 and pT≤1N0) also derive substantial benefit (13).

Variant histology was significantly associated with worse survival, consistent with previous evidence suggesting that non-pure UC is less responsive to NAC and associated with more aggressive behavior (19). Additionally, positive surgical margins – despite of not being independently predictive in multivariable analysis – were associated with decreased OS on univariate analysis, highlighting the importance of surgical quality and local tumor control (1).

Nearly half of the cohort (46.9%) experienced disease progression, with distant metastases to lymph nodes, viscera, and bone as the most common. The detection of metastatic disease in three patients at the time of cystectomy highlights limitations in current preoperative staging and supports the need for better diagnostic tools to identify occult disease prior to surgery.

Our results reinforce the prognostic value of TRG after NAC in MIBC and the importance of its integration with standard TNM classification to improve postoperative risk stratification. Patients with poor TRG scores, positive nodes, or incomplete response may benefit from more intensive surveillance or consideration for adjuvant therapies, including immune checkpoint inhibitors, as it is being practiced (20). Conversely, identification of complete or partial responders may support the emerging

bladder-sparing approaches in carefully selected cases. On the behalf of this, the PRE-PREVENCYS trial showed that the absence of residual disease after NAC in patients with MIBC is accurately predicted, and so a randomized controlled trial is scheduled for comparing OS after NAC plus RC versus NAC and close surveillance in patients with a clinically complete response (8). Additionally, the value of circulating tumor DNA holds promise as a biomarker in the perioperative treatment of MIBC and the integration of both markers may be an enthusiastic area of research in the upcoming years (21).

This study is limited by its retrospective, single-center design and relatively small sample size, which may impact statistical power and generalizability. In addition, variations in chemotherapy regimens and timing between TURB, NAC, and RC may introduce heterogeneity.

Nevertheless, the strong association observed between response categories and survival outcomes adds a robust role for TRG as a clinically meaningful criterion.

## Conclusions

TRG system is a reproducible and clinically relevant method for assessing histological response to NAC in bladder cancer. When combined with ypTNM staging, it enhances prognostic stratification and may inform post-operative management decisions. Future studies should focus on standardizing these scoring systems and evaluating their role in prospective treatment algorithms.

## Declarations

***Ethical approval and consent for participate:*** *Ethics approval statement was waived. Informed consent was obtained from all patients, or a representant in case of incapability or death, prior to inclusion in this study.*

***Consent for publication:*** *Not applicable.*

***Availability of data and material:*** *The datasets used and/or analyzed during the current study are available upon reasonable request from the corresponding author.*

***Competing interests:*** *The authors declare that they have no competing interests.*

***Funding:*** *No funding was necessary for this study.*

***Authors' contributions:*** *ML, study concepts, methodology, data acquisition, analysis and interpretation, manuscript original drafting and edition; JP, manuscript drafting and review; MJT, data analysis and interpretation and manuscript review; JG, histopathological analysis and manuscript review; ES, study concepts and manuscript review; VQ, manuscript edition and review; JL, manuscript review; RP, manuscript review; JPL, manuscript review; HD, manuscript review; LM, manuscript review; VS, histopathological analysis and manuscript review; AF, manuscript review and supervision. All the authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.*

***Acknowledgments:*** *the authors are grateful to the staff of Urology and Renal Transplantation Department and Pathology Department of Coimbra University Hospital for their support in data collection and specimen processing.*

## References

*1. Stein J, Lieskovsky G, Cote R, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. Clin Oncol. 2001; 19:666-675.*

*2. Grossman H, Natale R, Tangen C, et al. Neoadjuvant Chemotherapy Plus Cystectomy Compared With Cystectomy Alone for Locally Advanced Bladder Cancer. N Engl J Med. 2003; 349:859-66.*

*3. Collaboration. ABCM. Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. Lancet. 2003; 361:1927-1934.*

*4. Van Der Heijden A, Bruins H, Carrion A, et al. European Association of Urology Guidelines on Muscle-invasive and Metastatic Bladder Cancer. Eur Assoc Urol. 2025; 87:582-600.*

*5. Motterle G, Andrews JR, Morlacco A, Karnes RJ. Predicting Response to Neoadjuvant Chemotherapy in Bladder Cancer. Eur Urol Focus. 2020; 6:642-649.*

*6. Yuh B, Ruel N, Wilson T, et al. Pooled analysis of clinical outcomes with neoadjuvant cisplatin and gemcitabine chemotherapy for muscle invasive bladder cancer. J Urol. 2013; 189:1682-1686.*

*7. Rosenblatt R, Sherif A, Rintala E, et al. Pathologic downstaging is a surrogate marker for efficacy and increased survival following neoadjuvant chemotherapy and radical cystectomy for muscle-invasive urothelial bladder cancer. Eur Urol. 2012; 61:1229-1238.*

*8. Hinsenveld FJ, Noordman BJ, Boormans JL, et al. Prediction of pathological response following neoadjuvant chemotherapy in patients with muscle-invasive bladder cancer: the PRE-PREVENCYS trial. BMC Cancer. 2021; 21:1-11.*

*9. Morgan M, Koorey D, Painter D, et al. Histological tumour response to pre-operative combined modality therapy in locally advanced rectal cancer. Color Dis. 2002; 4:177-183.*

*10. Becker K, Langer R, Reim D, et al. Significance of histopathological tumor regression after neoadjuvant chemotherapy in gastric adenocarcinomas: A summary of 480 cases. Ann Surg. 2011; 253:934-939.*

*11. Fareed K, Ilyas M, Kaye P, et al. Tumour regression grade (TRG) analyses in patients with resectable gastro-oesophageal adenocarcinomas treated with platinum-based neoadjuvant chemotherapy. Histopathology. 2009; 55:399-406.*

*12. Fleischmann A, Thalmann GN, Perren A, Seiler R. Tumor Regression Grade of Urothelial Bladder Cancer After Neoadjuvant Chemotherapy. A novel and successful strategy to predict survival. Am J Surg Pathol. 2014; 38:325-332.*

*13. Voskuilen CS, Oo HZ, Genitsch V, et al. Multicenter Validation of Histopathologic Tumor Regression Grade after Neoadjuvant Chemotherapy in Muscle-invasive Bladder Carcinoma. Am J Surg Pathol. 2019; 43:1600-1610.*

*14. Gronostaj K, Czech AK, Fronczek J, et al. The Prognostic Value of Tumor Regression Grades Combined With TNM Classification in Patients With Muscle-Invasive Bladder Cancer Who Underwent Neoadjuvant Chemotherapy Followed by Radical Cystectomy. Clin Genitourin Cancer. 2019; 17:e1203-e1211.*

*15. Seiler R, Oo HZ, Todenhöfer T, et al. Tumor regression grading after neoadjuvant chemotherapy in bladder cancer: Validation in an independent cohort. Eur Urol Suppl. 2017; 16:e685.*

*16. Nakagawa T. Lymph node dissection for bladder cancer: Current standards and the latest evidence. Int J Urol. 2021; 28:7-15.*

*17. Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin. 2017; 67:93-99.*

*18. Zargar H, Espiritu PN, Fairey AS, et al. Multicenter assessment of neoadjuvant chemotherapy for muscle-invasive bladder cancer. Eur Urol. 2015; 67:241-249.*

*19. Veskimäe E, Espinos EL, Bruins HM, et al. What Is the Prognostic and Clinical Importance of Urothelial and Nonurothelial Histological Variants of Bladder Cancer in Predicting Oncological Outcomes in Patients with Muscle-invasive and Metastatic Bladder Cancer? A European Association of Urology Mus. Eur Urol Oncol. 2019; 2:625-642.*

*20. Mamede I, Silva C, Alves AC, et al. Adjuvant Immunotherapy in High-Risk Muscle-Invasive Urothelial Cancer: An Updated Meta-Analysis of Randomized Controlled Trials. Clin Genitourin Cancer 2025; 23:102288.*

*21. Crupi E, de Padua TC, Marandino L, et al. Circulating tumor DNA as a Predictive and Prognostic Biomarker in the Perioperative Treatment of Muscle-invasive Bladder Cancer: A Systematic Review. Eur Urol Oncol. 2024; 7:44-52.*

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