Original Article

Cukurova Anestezi ve Cerrahi Bilimler Dergisi

Clinicopathological Factors Associated with Intravesical Recurrence and Survival After Radical Nephroureterectomy for Upper Tract Urothelial Carcinoma

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Abstract

Aim: To evaluate clinicopathological factors and perioperative complications associated with intravesical recurrence-free survival (IVR-FS) and overall survival (OS) after radical nephroureterectomy (RNU) for upper urinary tract urothelial carcinoma (UTUC). **Materials and Methods:** We retrospectively analyzed 99 patients who underwent RNU for UTUC at Çukurova University between 2005 and 2024. Survival outcomes were evaluated using Kaplan–Meier and log-rank analyses, with exploratory multivariable Cox regression for OS. **Results:** The mean age was 64.6±10.3 years, and 80.8% of patients were male. During a mean follow-up of 54.8±49.5 months, intravesical recurrence occurred in 31 patients (31.3%), with a median time to recurrence of 11 months. Higher pathological T stage (p=0.047) and postoperative complications (p<0.001) were associated with worse IVR-FS. Overall, 64 patients (64.6%) died. In the exploratory multivariable analysis, pathological stage ≥pT3 (HR: 2.18, p=0.009), positive surgical margins (HR: 2.41, p=0.020), and postoperative complications (HR: 1.89, p=0.031) were independently associated with worse OS. **Conclusion:** Intravesical recurrence affected approximately one-third of patients, typically within the first year after RNU. Advanced pathological stage, positive surgical margins, and postoperative complications were independently associated with worse OS in the exploratory model. IVR-FS findings remain univariable and require cautious interpretation because death is a substantial competing event, particularly in advanced disease. These findings support close cystoscopic surveillance and require prospective validation.

Keywords: Urinary bladder neoplasms; carcinoma; transitional cell; neoplasms; upper urinary tract; nephroureterectomy

1. Introduction

Upper tract urothelial carcinoma (UTUC) has long been treated with radical nephroureterectomy (RNU) and bladder cuff excision as the standard surgical approach. Nevertheless, despite successful surgery, a substantial proportion of patients develop intravesical recurrence (IVR) during follow-up, imposing additional endoscopic interventions and clinical burden[1]. In the literature, IVR rates after RNU have been reported in the range of approximately 22–47%[2,3]. Therefore, delineating recurrence patterns after RNU and the potential associated factors is important for shaping surveillance and treatment strategies[1,2].

The development of IVR after RNU is related not only to patient- and tumor-related characteristics but also to diagnostic and perioperative practices[2,3]. Specifically, the literature has yielded varying results on the relationship between preoperative diagnostic ureteroscopy (URS) and IVR; some meta-analyses have suggested that URS may increase IVR risk, with a more pronounced effect in cases where a biopsy was performed[4–6]. On the other hand, guidelines from the European Association of Urology strongly recommend single-dose intravesical chemotherapy after RNU to prevent IVR[7]. While certain surgical approaches and procedural steps have been reported to influence IVR, findings across studies remain variable[8–11].

Furthermore, the impact of surgical morbidity on oncological outcomes has increasingly become a subject of interest. It is hypothesized that postoperative complications may trigger a systemic immunosuppressive and inflammatory response, or potentially delay the administration of adjuvant therapies, thereby negatively influencing disease recurrence and survival. However, the exact relationship between surgical morbidity and IVR dynamics following RNU remains underexplored.

In this study, we aimed to evaluate clinical, pathological, diagnostic, and treatment-related variables to explore the dynamics of recurrence after RNU in patients with UTUC. The primary endpoint of our study was intravesical recurrence-free survival (IVR-FS), defined as the interval from RNU to IVR; the secondary endpoint was overall survival (OS).

2. Materials and Methods

Patients who underwent radical nephroureterectomy (RNU) for upper urinary tract urothelial carcinoma (UTUC) at the Department of Urology, Çukurova University Faculty of Medicine between 2005 and 2024 were retrospectively evaluated. Demographic, clinical, perioperative, and pathological data were obtained from patient records and the hospital information system.

The recorded variables included age, sex, body mass index (BMI), history of malignancy and cancer type, preoperative and postoperative creatinine levels, tumor laterality (right/left), presence and grade of preoperative dilation/hydronephrosis, presence and grade of preoperative pelvicaliectasis, preoperative lymph node involvement, performance of preoperative ureterorenoscopy (URS), URS biopsy status, type of forceps used, URS biopsy malignancy result, history of bladder tumor and TUR-M pathology and grade, time interval between diagnostic URS and RNU (months), type of operation (open/laparoscopic), type of bladder cuff excision (open/clip/unknown), administration and type of intravesical therapy after RNU, operation time (minutes), specimen size, presence of postoperative complications, pathological T and N stage (including Nx), histopathology (low grade/high grade/variant), tumor size, surgical margin positivity, neoadjuvant therapy, adjuvant therapy, development of bladder tumor after primary UTUC, and TUR-M pathology and grade of the developed bladder tumor. Intraoperative, early perioperative, and postoperative complications occurring within 30 days of surgery were comprehensively reviewed from patient records and graded according to the standardized Clavien-Dindo classification system.

Table 1. Distribution of missing data for key variables

Variable	N Available	N Missing	% Missing
Preoperative clinical T stage	57	42	42.4%
Pathological N stage (pNx excluded)	53	46	46.5%
Bladder cuff excision technique	97	2	2.0%
Preoperative URS biopsy	98	1	1.0%
Intravesical chemotherapy after RNU	98	1	1.0%
Neoadjuvant therapy	98	1	1.0%
Adjuvant therapy	98	1	1.0%

N available represents patients with documented data for each variable. Patients with missing data for a specific variable were excluded only from the respective subgroup analyses. No imputation methods were used. pNx: pathologically unsampled lymph nodes; URS: ureterorenoscopy; RNU: radical nephroureterectomy.

Postoperative surveillance generally included cystoscopy and cross-sectional imaging every 3–4 months for the first year, semi-annually for the second year, and annually thereafter, in accordance with institutional guidelines. Patients with missing critical data for specific variables were excluded only from the respective subgroup analyses; no statistical imputation methods were used. The distribution of missing data across key variables is summarized in Table 1. Regarding lymph node status, patients were categorized into two groups for survival comparisons: pathologically node-negative (pN0) and others (pNx and pN+). While combining patients with unsampled (Nx) and involved (N+) nodes may introduce clinical heterogeneity, this grouping was necessitated by the high rate of unsampled nodes and the limited number of pathologically confirmed pN+ cases in our cohort, reflecting a non-pN0 group for statistical risk stratification.

The primary endpoint of the study was intravesical recurrence (IVR). Intravesical recurrence-free survival (IVR-FS) was defined as the time from the date of RNU to the date of documented IVR. Overall survival (OS) was defined as the time from the date of RNU to death from any cause.

All statistical analyses were performed using IBM SPSS Statistics. Continuous variables with normal distribution were summarized as mean ± standard deviation, whereas non-normally distributed variables were expressed as median (minimum–maximum). Categorical variables were presented as number (percentage). For comparisons between groups, Student's t-test or the Mann–Whitney U test was used for continuous variables depending on distribution. For comparisons involving more than two groups, one-way ANOVA or the Kruskal–Wallis test was applied as appropriate. Categorical variables were compared using the chi-square test or Fisher's exact test when expected cell counts were insufficient. IVR-FS and OS curves were generated using the Kaplan–Meier method, and differences between groups were compared using the log-rank test. Patients without recurrence or death were censored at the date of the last follow-up.

To address potential confounding while minimizing the risk of model overfitting, an exploratory multivariable Cox proportional hazards regression analysis was performed for overall survival. Because 64 deaths were observed during follow-up, the multivariable model was intentionally restricted to three clinically relevant covariates selected a priori based on their established prognostic relevance and significance in univariable analyses: pathological T stage, surgical margin status, and postoperative complications. This corresponded to approximately 21 events per variable, which was considered acceptable for an exploratory model.

A multivariable model was not constructed for IVR-FS because only 31 intravesical recurrence events were observed, and death represented a substantial competing event, particularly among patients with advanced-stage disease. Therefore, IVR-FS analyses were interpreted as univariable and hypothesis-generating. Hazard ratios were reported with 95% confidence intervals. A two-sided p-value <0.05 was considered statistically significant. Given the exploratory nature of this study and the large number of univariable comparisons performed, no formal correction for multiple testing was applied. Accordingly, all p-values should be interpreted as hypothesis-generating rather than confirmatory, and statistically significant findings must be interpreted with caution in the context of multiple comparisons.

3. Results

A total of 99 patients were included in the study. The mean age was 64.6±10.3 years, and 80.8% of the patients (n=80) were male. The mean follow-up duration was 54.8±49.5 months. During follow-up, intravesical recurrence (IVR) was detected in 31 patients (31.3%); the mean time to recurrence was 21.9±27.5 months (median 11.0 months, range 3.0–116.0).

In univariate survival analyses, pathological T stage ($p=0.047$) and the presence of postoperative complications ($p<0.001$) were significantly associated with intravesical recurrence-free survival (IVR-FS); the median IVR-FS was 78.5 months in pT1 patients and 23.3 months in pT2 patients, with the lowest IVR-FS observed in the pT2 group (Table 2). It is important to note that the seemingly lower intravesical recurrence rate in more advanced stages (pT3–pT4) should be interpreted with caution, as it is likely influenced by competing risks, whereby patients with advanced disease may

experience early mortality before an IVR can manifest. During the study period, 64 patients (64.6%) died.

In terms of overall survival (OS), a significant association was found with a history of cancer/bladder cancer (p=0.001), perioperative clinical stage (T1–2 vs T3–4) (p=0.004), pathological T stage (pT1–2 vs pT3–4) (p=0.003), and positive surgical margins (p=0.030). Additionally, OS was lower in patients who received neoadjuvant therapy (p=0.021) (Table 2). However, this negative association is presumably attributable to indication bias, as neoadjuvant regimens are primarily administered to patients with higher-risk or more advanced disease profiles.

Furthermore, postoperative complications were significantly associated with worse OS (p=0.023) and IVR-FS (p<0.001); perioperative complications were also significantly associated with poorer IVR-FS (p<0.001). The detailed mean and median OS and IVR-FS values according to patient and tumor characteristics are presented in Table 2.

Table 2. Results of survival analyses according to clinical factors

	OS (month)			IVR-FS (month)		
	Total N/N Events	Mean/Median	p	Total N/N Events	Mean/Median	p
Gender						
Male	79/53	80.6/31.0	0.279	79/27	70.3/70.0	0.115
Female	19/11	93.5/62.0		19/4	147.3/—	
Operation type						
Open	41/29	77.4/51.0	0.871	41/13	120.3/—	0.542
Laparoscopic	57/35	78.2/42.0		57/18	73.8/91.0	
Preoperative hydronephrosis						
No	53/34	73.3/42.0	0.905	53/17	104.1/116.0	0.870
Yes	45/30	88.0/47.0		45/14	79.9/91.0	
Prior bladder cancer						
No	78/46	95.3/66.0	0.001	78/20	101.6/91.0	0.849
Yes	20/18	25.2/15.0		20/4	58.7/—	
Preoperative clinical T stage						
T1	21/7	152.1/152.0	0.004	21/14	58.9/36.0	0.280
T2	15/9	60.1/56.0		15/10	20.5/19.0	
T3+4	21/14	40.8/27.0		21/7	53.2/—	
Preoperative URS						
No	40/27	66.5/47.0	0.551	40/9	123.2/—	0.146
Yes	58/37	83.3/44.0		58/22	77.3/70.0	
IVC after RNU						
No	91/60	79.7/46.0	0.778	91/29	103.2/91.0	0.885
Yes	7/4	85.9/17.0		7/2	34.3/12.0	
Perioperative complication						
No	90/60	68.8/44.0	0.138	90/23	117.6/116.0	<0.001
Yes	8/4	131.6/62.0		8/8	22.0/11.0	
Postoperative complication						
No	83/57	63.4/37.0	0.023	83/16	133.6/—	<0.001
Yes	15/7	138.0/—		15/15	22.5/12.0	
Pathological T stage (pT1-2 vs pT3-4)						
pT1	30/15	122.1/112.0	0.003	30/14	78.5/91.0	0.047
pT2	23/18	41.7/26.0		23/10	23.3/21.0	
pT3+4	44/31	58.4/17.0		44/7	148.8/—	
Histopathology						
Low grade	15/8	96.7/56.0	0.620	15/5	102.8/116.0	0.263
High grade	72/48	61.9/44.0		72/24	75.9/91.0	
Variant histology	10/8	57.7/28.0		10/1	137.1/—	

	OS (month) Total N/N Events	Mean/Median	p	IVR-FS (month) Total N/N Events	Mean/Median	p
Positive surgical margin						
No	87/55	87.0/49.0	0.030	87/30	97.3/91.0	0.271
Yes	11/9	32.9/12.0		11/1	117.4/—	
Pathological N stage						
pN0	36/22	87.6/44.0	0.346	36/13	97.5/70.0	0.989
Non-pN0	62/42	69.9/46.0		62/18	87.1/116.0	
Neoadjuvant therapy						
No	84/52	89.1/51.0	0.021	84/30	94.7/91.0	0.103
Yes	14/12	33.1/15.0		14/1	124.9/—	
Adjuvant therapy						
No	90/58	84.8/46.0	0.330	90/30	100.5/91.0	0.421
Yes	8/6	35.9/19.0		8/1	45.2/—	

Variations in the total number of patients across subgroups are due to missing data. IVR-FS: Intravesical recurrence-free survival; OS: Overall survival; IVC: Intravesical chemotherapy; URS: Ureterorenoscopy; RNU: Radical nephroureterectomy. Bold p-values indicate statistical significance (p<0.05).

An exploratory multivariable Cox regression analysis was performed for OS using three prespecified covariates: pathological T stage, surgical margin status, and postoperative complications. All three prespecified covariates were independently associated with worse OS. Pathological stage ≥pT3 was associated with an increased risk of death compared with ≤pT2 disease (HR: 2.18, 95% CI: 1.21–3.92, p=0.009), positive surgical margins were associated with worse OS (HR: 2.41, 95% CI: 1.15–5.04, p=0.020), and postoperative complications were also independently associated with poorer OS (HR: 1.89, 95% CI: 1.06–3.37, p=0.031).(Table 3)(Fig 1)

Table 3. Exploratory multivariable Cox regression analysis for overall survival

Variable	HR	95% CI	p-value
Pathological T stage ≥pT3 vs ≤pT2	2.18	1.21–3.92	0.009
Positive surgical margin	2.41	1.15–5.04	0.020
Postoperative complications	1.89	1.06–3.37	0.031

HR: hazard ratio; CI: confidence interval; OS: overall survival. The model was restricted to three clinically relevant variables to reduce the risk of overfitting (approximately 21 events per variable).

The overall incidence and severity of surgical morbidity were evaluated using the Clavien-Dindo classification system. (Table 4)

Table 4. Postoperative complications according to the Clavien-Dindo classification system

Clavien-Dindo Grade	Complication	Clinical Management and Outcome
Grade I (n=6)	Prolonged Postoperative Ileus	Return of bowel function >4 days; managed with conservative treatment and nasogastric decompression.
Grade II (n=4)	Urinary Tract Infection / Urosepsis	Febrile infection requiring targeted intravenous antibiotic therapy.
Grade II (n=2)	Deep Vein Thrombosis (DVT)	Diagnosed via Doppler US; managed with therapeutic anticoagulation due to prolonged immobilization.
Grade IIIa (n=2)	Symptomatic Lymphocele	Perinephric/pelvic fluid collection requiring ultrasound-guided percutaneous drainage.
Grade IVa (n=1)	Acute Kidney Injury (AKI)	Perfusion failure of the solitary kidney requiring temporary renal replacement therapy (hemodialysis).

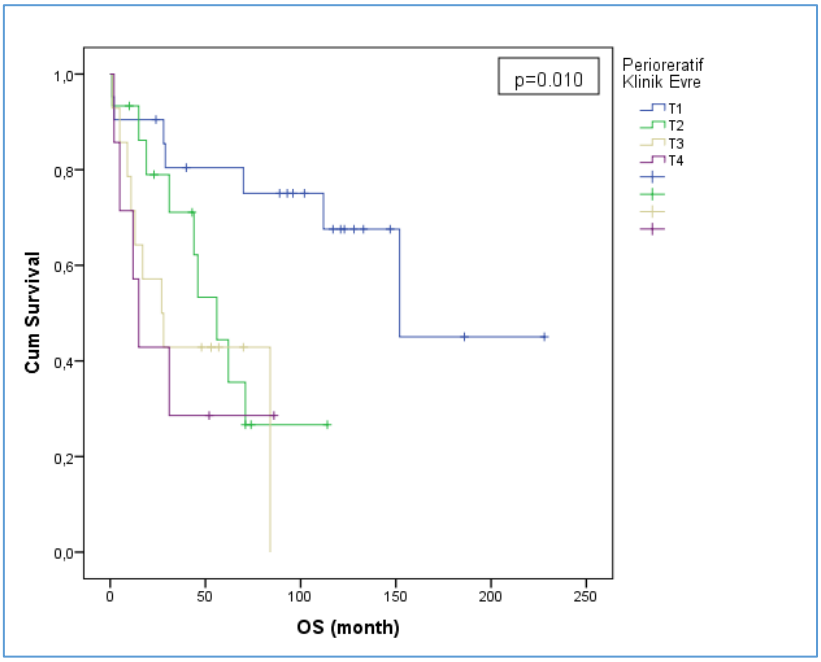

Figure 1. Kaplan–Meier Curve for Overall Survival According to Pathological T Stage.

4. Discussion

In this series, the intravesical recurrence (IVR) rate of 31.3% following RNU and the mean time to recurrence of approximately 22 months are consistent with contemporary reviews and meta-analyses reporting a post-RNU IVR incidence ranging from 22% to 47%[1,2]. The systematic review and meta-analysis by Seisen et al., reporting an IVR rate of 29% and a median time to IVR of 22.2 months, supports the frequency and timing observed in our cohort[2]. In terms of the pathogenesis of IVR, two main mechanisms have been proposed in the literature: intraluminal tumor cell seeding and pan-urothelial field cancerization. Evidence supporting the seeding hypothesis has been strengthened by the multifocal nature of urothelial disease, the potential impact of surgical and endoscopic manipulations, and findings of clonal relationships reported in some series[1,2]. This biological framework also explains why, in our study, many patient-, tumor-, and treatment-related variables may not exhibit effects of the same direction or magnitude on IVR-FS and OS.

In our study, since IVR-FS was defined as the time from RNU to intravesical recurrence, it essentially reflects the "timing of bladder recurrence." In this context, the finding that only pathological T stage was significantly associated with IVR-FS (p=0.047) supports the decisive role of tumor biology in the timing of IVR. Meta-analytic data have shown that invasive pathological stage may be associated with IVR; therefore, the significance of pT in our analysis is consistent with the overall body of evidence[2,3]. However, the observation that the lowest IVR-FS was seen in the pT2 group, while pT3–4 cases demonstrated better-than-expected IVR-FS, suggests that IVR cannot be explained solely by anatomical stage. This pattern is most likely related to "competing risks": in advanced stages, systemic progression and death may occur before intravesical recurrence is observed; thus, IVR may appear less frequent, and IVR-FS curves may seem paradoxically more favorable in these patients.

In the OS analysis, a history of bladder cancer (p=0.001), higher clinical T stage (p=0.004), pT4 disease (p=0.002), positive surgical margins (p=0.030), and receipt of neoadjuvant therapy (p=0.021) were associated with worse survival. The finding that clinical T stage was significantly associated with OS but not with IVR-FS (p=0.402) is consistent with the notion that clinical staging primarily reflects overall disease burden and risk of progression; moreover, the well-recognized discordance

between clinical and pathological staging in UTUC likely contributes to the weaker association observed with IVR-FS[2]. The association between positive surgical margins and OS is an expected finding, as it indicates residual disease and reflects aggressive tumor biology. The observed negative association between neoadjuvant therapy and OS should be interpreted in line with "indication bias" rather than as a harmful effect of the treatment itself: neoadjuvant therapy is typically administered to patients with more advanced or high-risk disease, which may inherently lead to poorer OS outcomes.

The lack of a significant association between sex and both IVR-FS (p=0.115) and OS (p=0.279) may not be fully consistent with the findings of the Seisen meta-analysis, which reported an association between male sex and IVR[2]. However, the relatively low number of female patients (n=19) and the limited number of IVR events (n=31) suggest that this variable may be underpowered. Moreover, given that the direction of the sex effect and inter-study heterogeneity remain controversial in some meta-analyses, the attenuation of a sex-based association in a single-center cohort may be expected[3,12]. Similarly, the lack of significant associations of preoperative dilatation/hydronephrosis and pelvicaliectasis with both IVR-FS and OS is consistent with the literature, where these imaging findings have not been consistently identified as predictors of IVR[2].

The inclusion of pNx patients within the non-pN0 group reflects a real-world scenario in which lymph node dissection was not performed uniformly across the study period. The lack of significant associations between pathological N status and IVR-FS or OS likely reflects the high proportion of unsampled nodes (pNx: 46.5%), heterogeneity in lymph node assessment, and the biological fact that nodal involvement is more closely related to systemic progression than to intravesical recurrence. These findings should be interpreted accordingly and validated in cohorts with standardized template-based lymphadenectomy[2].

In this study, the impact of perioperative and postoperative complications on oncological outcomes was also evaluated. In univariable analyses, postoperative complications were significantly associated with both OS (p=0.023) and IVR-FS (p<0.001). Importantly, in the exploratory multivariable Cox model, postoperative complications remained independently associated with worse OS after adjustment for pathological T stage and surgical margin status (HR: 1.89, 95% CI: 1.06–3.37, p=0.031), suggesting that surgical morbidity may exert a prognostic effect beyond its association with disease severity alone. Biologically, surgical trauma and complications may trigger a systemic inflammatory response and suppress immune function, thereby creating a favorable microenvironment for residual tumor cell proliferation or implantation. Clinically, postoperative morbidity may compromise patients' performance status and delay or preclude adjuvant therapy administration, which could adversely affect long-term oncological control. Perioperative complications were not significantly associated with OS but were associated with IVR-FS, suggesting that early adverse events may specifically influence local recurrence dynamics through perioperative inflammatory mechanisms. However, this finding should be interpreted cautiously given the small number of perioperative complication events (n=8) and the univariable nature of this analysis.

Neither preoperative URS nor URS biopsy was significantly associated with IVR-FS or OS in our cohort, consistent with studies suggesting that appropriately performed diagnostic ureteroscopy does not substantially alter long-term oncological outcomes[1,2]. Nevertheless, given the conflicting evidence in the literature, careful patient selection and minimal intraluminal manipulation remain advisable[4].

The lack of significant associations between surgical approach (open vs. laparoscopic) or bladder cuff technique and IVR-FS/OS may reflect the heterogeneity inherent to a 19-year retrospective series. Our findings should not be interpreted as evidence that surgical technique is unimportant; rather, its effect may not be demonstrable under conditions where specific technical details are not sufficiently captured[8,11].

In our series, postoperative intravesical chemotherapy (IVC) following RNU was administered at a low rate and was not found to be significantly associated with IVR-FS or OS. However, meta-analyses and review studies have demonstrated that a single early postoperative dose of intravesical

chemotherapy (mitomycin C or pirarubicin) can reduce the risk of intravesical recurrence (IVR)[1,13]. The inability to demonstrate an effect in our series is most likely attributable to the low rate of application, heterogeneity in agents and timing, selection bias, and the lack of clearly documented timing data in retrospective records.

Study Limitations

The findings of this study must be interpreted in the context of several important limitations. The retrospective, single-center design is inherently prone to selection and information bias. The long study period (2005–2024) introduced unavoidable heterogeneity in follow-up, surgical techniques, and surveillance practices. Furthermore, nephron-sparing approaches were not included due to their limited numbers in our cohort, so the results strictly reflect the RNU population. Although an exploratory multivariable Cox regression model was constructed for OS incorporating three prespecified covariates, the number of IVR events (n=31) precluded multivariable modeling for IVR-FS. Furthermore, important prognostic variables such as lymph node status, history of bladder cancer, adjuvant treatment, and comorbidity could not be simultaneously included in the OS model due to sample size constraints, and residual confounding cannot be excluded. Competing-risk analyses were also not performed; therefore, IVR-FS results — particularly the paradoxically favorable curves observed in advanced-stage patients — should be interpreted in the context of death as a competing event.

Furthermore, defining IVR-FS as strictly the time to intravesical recurrence without adjusting for competing risks may have obscured certain associations. The lack of complete data on key variables significantly hindered deeper analysis. Notably, the rate of unsampled lymph nodes (pNx) was high (46.5%), and critical surgical quality indicators were not adequately captured in the dataset. Additionally, no correction for multiple testing was applied across the large number of univariable comparisons. Given the exploratory design, the risk of type I error inflation cannot be excluded, and all statistically significant univariable findings should be regarded as hypothesis-generating.

Despite these limitations, our series delineates the burden and timing of intravesical recurrence after RNU in a manner consistent with the literature and successfully supports the strong association between overall survival, markers of advanced disease, and surgical morbidity.

5. Conclusion

In conclusion, this single-center retrospective series demonstrated that intravesical recurrence following radical nephroureterectomy is common, occurring in approximately one-third of patients, with a substantial proportion of recurrences developing within the first year.

While pathological T stage was the primary determinant of IVR-FS, OS was more strongly associated with indicators of advanced disease, positive surgical margins, and a history of bladder cancer. In the exploratory multivariable analysis, pathological stage ≥pT3, positive surgical margins, and postoperative complications were all independently associated with worse OS, suggesting that surgical morbidity carries prognostic relevance beyond disease stage alone. Critically, IVR-FS analyses must be interpreted in the context of death as a substantial competing event: in advanced-stage patients, early mortality may preclude the clinical manifestation of intravesical recurrence, potentially leading to an artifactual underestimation of IVR rates and a paradoxically favorable appearance of IVR-FS curves in this subgroup.

These findings support the importance of close cystoscopic surveillance, especially within the first 12 months after RNU, and highlight the need for improved treatment strategies and prospective studies with larger cohorts to optimize oncological outcomes in patients with advanced-stage and high-risk disease.

genAI: No artificial intelligence-based tools or generative AI technologies were used in this study. The entire content of the manuscript was originally prepared, reviewed, and approved by all authors.

Statement of Ethics: According to decision number 88 of meeting number 166 dated 13.03.2026, approval has been obtained from the Research Ethics Committee of Çukurova University Faculty of Medicine. Due to the retrospective nature of the study, the ethics committee waived the requirement for informed consent.

Data Availability: The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Conflict of Interest: The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

Author Contributions: Conceptualization, writing, and editing: M.G.A. Data collection and writing: İ.O.Y.

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